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Disease Activity Score in 28 Joints Using GGT Permits a Dual Evaluation of Joint Activity and Cardiovascular Risk

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ABSTRACT. ***Objective.*** To identify the factors potentially associated with serum gamma-glutamyltransferase (GGT) elevation in patients with rheumatoid arthritis (RA).

Methods. This is a cross-sectional monocentric study including RA patients over a 12-month period. Data on liver function, RA disease activity, and hepatotoxic and cardiovascular (CV) risk factors were systematically collected. To provide a simple tool to evaluate both joint disease activity and CV risk factors, we constructed the Disease Activity Score in 28 joints (DAS28)-GGT composite index by replacing erythrocyte sedimentation rate (ESR) with GGT.

Results. Among the 129 included patients, 32 (25%) had isolated GGT increase. GGT correlated with age, C-reactive protein (CRP) levels, and body weight and were significantly increased in patients with alcohol intake, type 2 diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome. GGT levels also gradually increased with the number of CV risk factors and correlated with the Framingham CV risk score. The composite index DAS28-GGT remained a reliable marker of RA disease activity and accurately detected patients with CV risk factors. Conversely to the DAS28 and the DAS28-CRP, the DAS28-GGT steadily increased according to the number of CV risk factors and had an increased diagnostic value compared to the DAS28 and DAS28-CRP for the presence of at least 2 CV risk factors and a Framingham CV risk score greater than 10%.

Conclusion. GGT may be considered as a marker of systemic inflammation and CV risk in patients with RA. Based on these findings, we herein propose an original index, the DAS28-GGT, which is able to evaluate both joint disease activity and CV risk. This index will deserve further validation in prospective cohorts.

Key Indexing Terms: cardiovascular risk factors, GGT levels, inflammation, rheumatoid arthritis

Patients with rheumatoid arthritis (RA) experience premature mortality that is largely due to cardiovascular (CV) diseases. Compared to the general population, patients with RA have a 45% to 60% increased risk of CV death[1,2,3], which is even higher when traditional CV risk factors are associated. It is currently accepted that inflammatory processes contribute to the pathogenesis of atherosclerosis and that an aggressive management of joint and systemic inflammation could significantly reduce the number of CV events[4].

Gamma-glutamyltransferase (GGT) is a plasma membrane enzyme that is primarily present in the kidney, liver, and pancreatic cells. GGT levels are elevated, alone or in combination with alkaline phosphatase (ALP), in any and all forms of liver disease, and also in many systemic conditions, including metabolic syndrome, systemic infections, or autoimmune diseases[5,6,7].

Increased GGT levels have been reported in RA with a prevalence ranging from 23% to 73%[8,9]. Preliminary results from a single study with a limited sample size showed a correlation between GGT levels and several RA disease activity markers [i.e., tender joint counts, erythrocyte sedimentation rate (ESR)], suggesting that this biological marker might be helpful to assess disease activity[8]. Further, accumulating evidence supports the association between elevated GGT levels and increased CV risk, and GGT levels are becoming an important addition to the screening strategy of CV diseases (CVD)[5,10,11]. Thus, GGT elevation may represent an integrative biomarker linking inflammation and CV risk in RA.

Our aim was to identify the factors potentially associated with increased GGT levels in patients with RA, with a specific focus on markers of disease activity and CV risk factors.

MATERIAL AND METHODS

Inclusion and exclusion criteria. We included patients with RA, > 18 years of age, fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) classification for RA[12,13], who attended the 1-day hospitalization program of the Department of Rheumatology, Cochin Hospital, over a 12-month period, for the evaluation and/or the treatment of their disease. We excluded patients with unstable hepatic disease associated with biologic signs of liver dysfunction (decreased albumin and procoagulant synthesis, altered bilirubin metabolism) or liver failure. All included patients agreed to participate in the study after informed consent, which was recorded in the medical source file. The protocol and the informed consent document received Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval before initiation of

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Data collection from RA patients. History taking, physical examination, laboratory tests, and review of medical files were systematically performed to collect data from patients with RA.

CV risk factors (high blood pressure, tobacco, diabetes, fasting hyperglycemia, BMI, and metabolic syndrome), hepatotoxic factors [medications like analgesics, nonsteroidal antiinflammatory drugs (NSAID), and alcohol consumption] and current/past medication use were obtained from information provided by patients and based on the review of medical records. RA disease activity was assessed using the Disease Activity Score in 28 joints (DAS28)[14], using ESR and C-reactive protein (CRP)[15]. Health status was measured by the self-administered Health Assessment Questionnaire (HAQ). Systematic hand and foot radiographs were performed to measure joint destruction, defined by the presence of erosions.

Laboratory tests. Routine laboratory study tests were obtained in RA patients on the morning of the hospital visit. They included complete blood cell count, Westergren ESR, CRP concentration, serum creatinine concentration, and liver function tests [serum-glutamic-oxaloacetate-transferase (SGOT), serum glutamate-pyruvate transaminase (SGPT), GGT, and ALP]. GGT levels were measured in succession by a standardized enzymatic colorimetric assay (Cobas 8000, Roche) recommended by the International Federation of Clinical Chemistry. Rheumatoid factor and second-generation anticyclic citrullinated peptide (anti-CCP2) antibodies were detected by ELISA.

Definitions. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) classification criteria. Metabolic syndrome was considered as present when patients had 3 of the 5 following criteria: fasting blood glucose of 6.1 mmol/L or greater; triglycerides of 1.7 mmol/L or greater; high-density lipoprotein < 1.04 mmol/L in men and < 1.29 mmol/L in women; high blood pressure with systolic arterial pressure/diastolic arterial pressure of ≥ 135/85 mmHg; and waist circumference of ≥ 102 cm in men and ≥ 88 cm in women. If patients received antihypertensive agents, they were considered to have high blood pressure. When waist circumference was not available, it was replaced by BMI of ≥ 25 kg/m^2 according to the American Association of Clinical Endocrinologists (AACE) criteria[16]. Ten-year risk prediction of CVD was estimated by the algorithm developed by the Framingham Heart Study[17]. Increased GGT levels were defined according to our laboratory standard by a level of > 35 IU/L. ESR and CRP were considered as elevated > 28 mm/h and 10 mg/L, respectively.

Ultrasonography assessment. The equipment used was a 7–15 MHz linear array transducer (Toshiba Aplio). The presence of hypoechoic synovial hyperplasia and joint effusion (both assessed using greyscale), and of synovial vascularization, assessed using power Doppler (PD), was scored using semiquantitative scales. The examination was performed the day of patient hospitalization by an independent investigator, blinded to patient status. The presence of synovitis (synovial hyperplasia and PD, without joint effusion) was scored for each joint according to the semiquantitative Outcome Measures in Rheumatology (OMERACT)-EULAR-US composite PD ultrasonography (PDUS) scale, giving a score of 0–3 for each joint (0 = absence, no synovial hyperemia, 1 = mild, hyperemia in less than one-third of the synovial surface area; 2 = moderate, hyperemia in less than two-thirds of the synovial surface area; and 3 = marked, in more than two-thirds of the synovial surface area). A global synovitis score, derived from the Global OMERACT-EULAR Synovitis Score (GOESS), was calculated for 16 paired joints on both hands (metacarpophalangeal 1–5 and proximal interphalangeal 1–5), both wrists (radio-ulnar, medio-carpal, and radio-carpal), and both forefeet (metatarsophalangeal 1–5), using the sum of the composite PDUS scores for all joints examined, giving a potential score of 0–96 for the 16 paired joints[18].

Statistical analysis. All data were expressed as mean values ± SD or median (range), unless stated otherwise. Statistical analysis was performed using Medcalc (v18.9.1). Correlations between GGT levels and numeric variables were assessed using Spearman rank correlation test.

Given the nonparametric distribution of serum GGT (Kolmogorov-Smirnov distance of 0.226, $P < 0.001$), GGT levels according to binary variables, including markers of disease activity or CV risk factors, were tested using the Kruskal-Wallis test with Dunn correction. Comparisons of mean values were assessed by the unpaired *t* test, and the chi-square test was used for differences in frequency. Multivariate analyses by logistic regression were also performed to determine the factors independently associated with increased GGT levels and moderate/high CV risk. These analyses included GGT levels (> 35 IU/L) and a Framingham risk score > 10% as the dependent variables. All relevant identified covariates with a *P* value < 0.1 in the single variable analysis were then entered in 1 single step in each model. OR and 95% CI were then calculated. In this model, a *P* value < 0.05 was considered statistically significant.

DAS28-GGT calculation. Given the potential association between inflammation and GGT levels and the growing interest of GGT levels for CV evaluation, our aim was to construct a simple screening tool providing the rheumatologist rapid information related to both joint disease activity and CV risk. Thus, we constructed a composite index called DAS28-GGT, obtained by replacing ESR by GGT levels in the following formula: $0.56 * \sqrt{TJ - 28} + 0.28 * \sqrt{SJ - 28} + 2 * \ln(GGT) + 0.14 * GH$. The weight of GGT in this formula was determined by applying different weight coefficients, ranging from 0.7 (original DAS28 formula) to 4. Each formula was then tested by measuring its correlation with markers of RA disease activity, the HAQ, and the Framingham CV risk score (Supplementary Table 1, available with the online version of this article). We retained the formula providing the optimal combination between the evaluation of disease activity and CV risk (weight coefficient of 2).

The diagnostic value of the DAS28-GGT was assessed by receiver-operating characteristic curve analysis. We also constructed a risk matrix to compare the diagnostic values of DAS28 and DAS28-GGT according to CRP levels, the importance of synovial vascularization by PDUS, and the number of CV risk factors.

RESULTS

Study population. A total of 129 patients (111 females, 86%) were included, with a mean age of 58 ± 13 years and a mean disease duration of 14 ± 11 years. Positive rheumatoid factor and anti-CCP antibodies were detected in 102 (79%) and 105 (81%) patients, respectively. Erosions were present in 79 (61%) patients. Detailed characteristics of our study sample are provided in Table 1. GGT levels ranged from 7 to 219 IU/L with a mean value of 32 ± 32 IU/L and a frequency distribution illustrated in Supplementary Figure 1 (available with the online version of this article); 32 (25%) patients had GGT values > 35 IU/L.

GGT and RA disease activity and severity. GGT levels correlated with CRP levels (Rs = 0.30, $P = 0.002$; Figure 1A). GGT levels were significantly higher in patients with CRP levels > 10 mg/L [median 31.5 IU/L (range 9–219) vs 20 IU/L (range 7–126), $P < 0.001$; Figure 1B]. There was no correlation between GGT levels and ESR, nor with composite indices evaluating RA disease activity (DAS28 and DAS28-CRP). No relationship was observed between GGT levels and tender/swollen joint counts, GOESS on PDUS, presence of bone erosions, or HAQ (Supplementary Table 1, available with the online version of this article).

Table 1: Study population.

	Patients With RA and Normal GGT, n = 97	Patients With RA and GGT > 35 IU/L, n = 32	*P*
Demographics			
Age, yrs, mean ± SD	57 ± 14	62 ± 9	0.061
Females	87 (90)	24 (75)	0.043
Disease characteristics			
Disease duration, yrs, mean ± SD	13 ± 11	16 ± 12	0.193
Positive rheumatoid factor	78 (80)	24 (75)	0.550
Positive anti-CCP2 antibodies	78 (80)	27 (84)	0.618
Erosions on hand/foot radiographs	57 (59)	22 (69)	0.315
Disease activity			
DAS28, mean ± SD	3.43 ± 1.35	3.55 ± 1.70	0.684
DAS28 > 3.2	38 (39)	10 (31)	0.418
DAS28-CRP, mean ± SD	2.72 ± 1.15	3.12 ± 1.36	0.106
DAS28-CRP > 3.2	29 (30)	12 (38)	0.402
ESR, mm/h, mean ± SD	20.0 ± 18.5	21.7 ± 19.5	0.657
ESR > 28 mm/h	22 (23)	10 (31)	0.367
CRP, mg/L, mean ± SD	5.6 ± 7.1	17.9 ± 40.6	0.005
CRP > 10 mg/L	16 (16)	13 (41)	0.003
Function			
HAQ, mean ± SD	1.00 ± 0.81	1.18 ± 0.90	0.291
Treatment received			
Current analgesic use	47 (48)	14 (44)	0.695
Current corticosteroid use	64 (66)	22 (69)	0.756
Current corticosteroid use, > 10 mg/day	6 (6)	4 (13)	0.058
Current use of NSAID	19 (20)	7 (22)	0.808
Current conventional DMARD use	90 (93)	28 (88)	0.374
Current anti-TNF-α use	16 (16)	6 (19)	0.695
Current rituximab use	24 (25)	8 (25)	1.000
Current tocilizumab use	10 (10)	2 (6)	0.495
Current abatacept use	7 (7)	2 (6)	0.846
Modifiable cardiovascular risk factors			
Smokers	24 (25)	13 (41)	0.132
High blood pressure	21 (22)	16 (50)	0.007
Diabetes mellitus	8 (8)	7 (22)	0.098
Dyslipidemia	30 (31)	19 (59)	0.020
BMI, kg/m^2, mean ± SD	24 ± 5	28 ± 6	0.003
BMI > 30 kg/m^2	14 (14)	10 (31)	0.097
Patients with ≥ 2 CV risk factors	37 (38)	27 (84)	< 0.001
Mean Framingham risk score, % (range)	9.7 (0.4–30.0)	16.3 (3.7–30.0)	< 0.001
Regular alcohol intake	5 (5)	5 (16)	0.061
Hepatic disorders	16 (16)	4 (13)	0.684
Metabolic syndrome	6 (6)	9 (28)	0.003

Values are n (%) unless otherwise specified. Anti-CCP2: anticyclic citrullinated peptide; CRP: C-reactive protein; CV: cardiovascular; DAS28: Disease Activity Score in 28 joints; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; GGT: gamma-glutamyltransferase; HAQ: Health Assessment Questionnaire; NSAID: nonsteroidal antiinflammatory drug; RA: rheumatoid arthritis; TNF-α: tumor necrosis factor-α.

GGT and CV risk factors. GGT levels correlated with age (Rs = 0.28, *P* = 0.002), fasting glycemia (Rs = 0.20, *P* = 0.027), total cholesterol levels (Rs = 0.20, *P* = 0.033), triglycerides (Rs = 0.31, *P* < 0.001), and body weight (Rs = 0.22, *P* = 0.016). GGT levels were significantly increased in males [median 32 (range 13–144) IU/L vs 21 (range 7–219) IU/L, *P* = 0.021], in patients with type 2 diabetes mellitus [median 35 (range 8–215) IU/L vs 21 (range 7–219) IU/L, *P* = 0.024], high blood pressure [median 31 (range 10–219) IU/L vs 21 (range 7–88) IU/L, *P* < 0.001], dyslipidemia [median 28 (range 7–219) IU/L vs 19 (range 8–215) IU/L, *P* = 0.004], and metabolic syndrome [median 48 (range 14–219) IU/L vs 21 (range 7–144) IU/L, *P* = 0.003]. No link was observed with smoking status. GGT levels were also associated with the number of CV risk factors, with a dose-ranging effect (Figure 2). In addition, GGT levels correlated with the Framingham risk score (Rs = 0.44, *P* < 0.001), evaluating the 10-year CV risk.

GGT, hepatic diseases, and hepatotoxic factors. GGT levels were

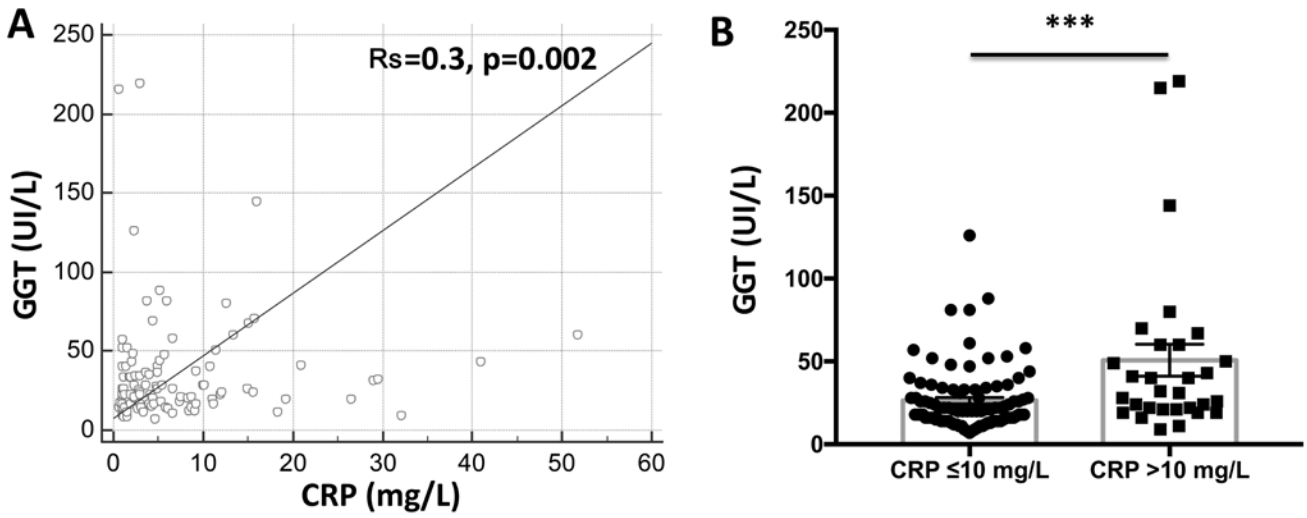

Figure 1. Association between GGT and systemic inflammation. (A) Rank correlation between GGT (IU/L) and C-reactive protein (mg/L); (B) GGT levels (IU/L) according to CRP levels (mg/L). *** $P < 0.001$ by Kruskall-Wallis test with Dunn correction. CRP: C-reactive protein; GGT: gamma-glutamyltransferase.

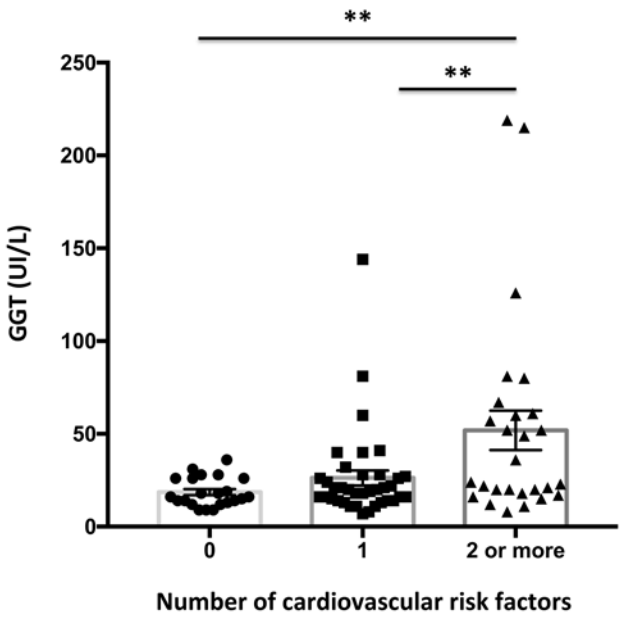

Figure 2. GGT levels (IU/L) according to the number of cardiovascular risk factors (0, 1, or ≥ 2 risk factors). ** $P < 0.01$ by Kruskall-Wallis test with Dunn correction. GGT: gamma-glutamyltransferase.

higher in patients with alcohol consumption [median 35 (range 20–44) IU/L vs 22 (range 7–219) IU/L, $P = 0.012$]. Three patients with RA had associated primary biliary cirrhosis with positive antimitochondrial antibodies; all were treated with ursodeoxycholic acid, and all had normal GGT levels. Fourteen patients had occult hepatitis B (HB) infection [undetectable HB virus DNA, HBsAg-negative, and anti-HBc- and anti-HBs–positive antibodies) requiring no specific treatment, and 3 had isolated GGT elevation. In addition, 3 patients had nonalcoholic fatty liver disease detected by liver US, associated with metabolic syndrome, and 1 had GGT levels > 35 IU/L. GGT was not higher in patients with hepatic disease compared to patients without this condition [4/20 (20%) vs 31/109 (28%)]. We did not detect any association between GGT levels and the use of NSAID, analgesics, corticosteroids (≤ 10 mg/day), conventional synthetic disease-modifying antirheumatic drugs (DMARD) or targeted biologic DMARD. A trend was observed for higher GGT in patients treated with > 10 mg/day of corticosteroids [median 29.5 IU/L (range 17–61) vs 20 IU/L (range 7–219), $P = 0.058$].

Multivariate analyses. A first logistic regression analysis confirmed the independent association between increased GGT levels (> 35 IU/L) and CRP > 10 mg/L (OR 4.42, 95% CI 1.41–13.80; Table 2). A second logistic regression analysis confirmed that increased GGT levels and the presence of metabolic syndrome were independently associated with a Framingham risk score > 10% (OR 3.42, 95% CI 1.27–9.22 and 16.19, 95% CI 1.72–152.80, respectively; Supplementary Table 2, available with the online version of this article).

Value of the DAS28-GGT for RA disease activity and the presence of CV risk factors. Since GGT levels reflected both systemic inflammation and the number of CV risk factors, we hypothesized that GGT may bring additional value to ESR to evaluate both joint disease activity and CV risk. Thus, we constructed a simple screening tool index called DAS28-GGT and tested its merit for the assessment of RA disease activity and the presence of CV risk factors.

DAS28-GGT correlated with ESR (Rs = 0.30, $P < 0.001$), CRP (Rs = 0.48, $P < 0.001$), DAS28 (Rs = 0.57, $P < 0.001$), DAS28-CRP (Rs = 0.70, $P < 0.001$), the GOESS on PDUS (Rs = 0.39, $P = 0.004$), and HAQ (Rs = 0.35, $P < 0.001$).

Table 2. Multivariate logistic regression analysis including increased GGT levels (> 35 IU/L) as the dependent variable.

Variables	Univariate *P*	OR (95% CI)	*P*
Age, yrs	0.061	1.02 (0.98–1.07)	0.337
Female sex	0.043	0.30 (0.07–1.21)	0.091
High blood pressure	0.007	1.58 (0.47–5.29)	0.455
Diabetes mellitus	0.098	1.88 (0.45–7.88)	0.388
Dyslipidemia	0.020	2.27 (0.80–6.46)	0.125
Current alcohol intake	0.061	2.64 (0.46–15.26)	0.277
BMI > 30 kg/m^2	0.097	1.11 (0.29–4.18)	0.875
CRP > 10 mg/L	0.003	4.42 (1.41–13.80)	0.010
Metabolic syndrome	0.003	3.51 (0.65–18.85)	0.143
Treatment with corticosteroids (> 10 mg/day)	0.058	1.23 (0.19–7.70)	0.823

CRP: C-reactive protein; GGT: gamma-glutamyltransferase.

Correlation coefficients were similar between DAS28-GGT, DAS28, and DAS28-CRP for HAQ (0.35 vs 0.39 and 0.31, respectively) and close for the GOESS on PDUS (0.39 vs 0.53 and 0.54). The discriminating capacities of DAS28-GGT and DAS28 to identify patients with active disease (DAS28-CRP > 3.2 or DAS28-CRP > 5.1) were similar (Supplementary Figure 2, available with the online version of this article). For the classification variable DAS28-CRP > 3.2, the areas under the curve (AUC) were 0.88 and 0.90 for the DAS28-GGT and DAS28, respectively. For the classification variable of DAS28-CRP > 5.2, the AUC were 0.95 and 0.96 for the DAS28-GGT and DAS28, respectively.

DAS28-GGT correlated with total cholesterol (Rs = 0.20, P = 0.031) and triglycerides (Rs = 0.24, P = 0.009); it was associated with alcohol consumption [median 8.6 (range 6.98–10.26) vs 7.34 (range 4.80–12.14), P = 0.047], high blood pressure [median 8.16 (range 5.41–12.14) vs 7.26 (range 4.80–11.47), P = 0.012], dyslipidemia [median 8.24 (range 4.80–12.14) vs 7.08 (range 5.04–11.81), P = 0.011], and metabolic syndrome [median 8.47 (range 6.23–12.03) vs 6.40 (range 4.80–12.14), P = 0.045].

DAS28-GGT gradually increased according to the number of CV risk factors (Figure 3A) and correlated with the Framingham risk score (Rs = 0.30, P = 0.001) . DAS28-GGT had a diagnostic value for the presence of at least 2 CV risk factors characterized by an AUC of 0.70 compared to 0.51 for the DAS28 and DAS28-CRP (P < 0.001 for both comparisons; Figure 3B). In addition, the diagnostic value of DAS28-GGT for a Framingham risk score < 10% was characterized by AUC of 0.74 compared to 0.53 for the DAS28 and 0.49 for the DAS28-CRP (P < 0.001 for both comparisons).

Matrix models highlighted the capacity of DAS28-GGT to identify patients with high RA disease activity and CV risk compared to the DAS28, which was only relevant to identify patients with high RA disease activity, but did not bring additional value for the detection of increased CV risk factors (Figures 4A,B).

In our cohort, patients with a DAS28-GGT < 5.5 were all in remission and at low CV risk[2]. A large majority (93%) of patients with a DAS28-GGT between 5.5 and 7.5 were in remission or low disease activity, but 41% were at medium or high CV risk according to the Framingham risk score (Supplementary Table 3, available with the online version of this article), supporting the evaluation of CV risk factors (Supplementary Figure 3). Patients with a DAS28-GGT > 7.5 were at risk of active disease and/or CV risk, supporting the priority evaluation of both joint involvement and CV risk (Supplementary Table 3 and Supplementary Figure 3, available with the online version of this article).

DISCUSSION

GGT is a surface cell enzyme widely distributed in the body tissues, particularly abundant in the proximal convoluted tubules of the kidney, the ciliary body of the eye, the seminal vesicles, the villi of the small intestine, the liver, the pancreas and the mammary glands. This ubiquitous enzyme is involved in glutathione (GSH) salvage, metabolism of endogenous mediators such as prostaglandins or leukotrienes, and detoxification of xenobiotics, thus playing a key role in maintaining GSH homeostasis and defense against oxidative stress[19]. Beyond its physiological functions, isolated elevation of serum GGT levels could reflect hepatic lesions as well as systemic conditions, including hyperthyroidism, metabolic syndrome, increased BMI, and others.

Increased GGT levels in patients with RA have been reported in preliminary ancient studies with limited sample sizes[8,9], without clear pathological explanation. Increased GGT levels were not significantly higher in patients with stable hepatic disease. The likelihood of increased GGT levels was also not increased significantly in patients treated with potentially hepatotoxic drugs, such as analgesics, NSAID, corticosteroids, methotrexate, or biological agents, as previously reported[8].

Increased GGT levels were associated with the presence of CV risk factors and correlated with the Framingham CV risk score. Our findings are consistent with those of previous studies, which reported a correlation between GGT levels and BMI,

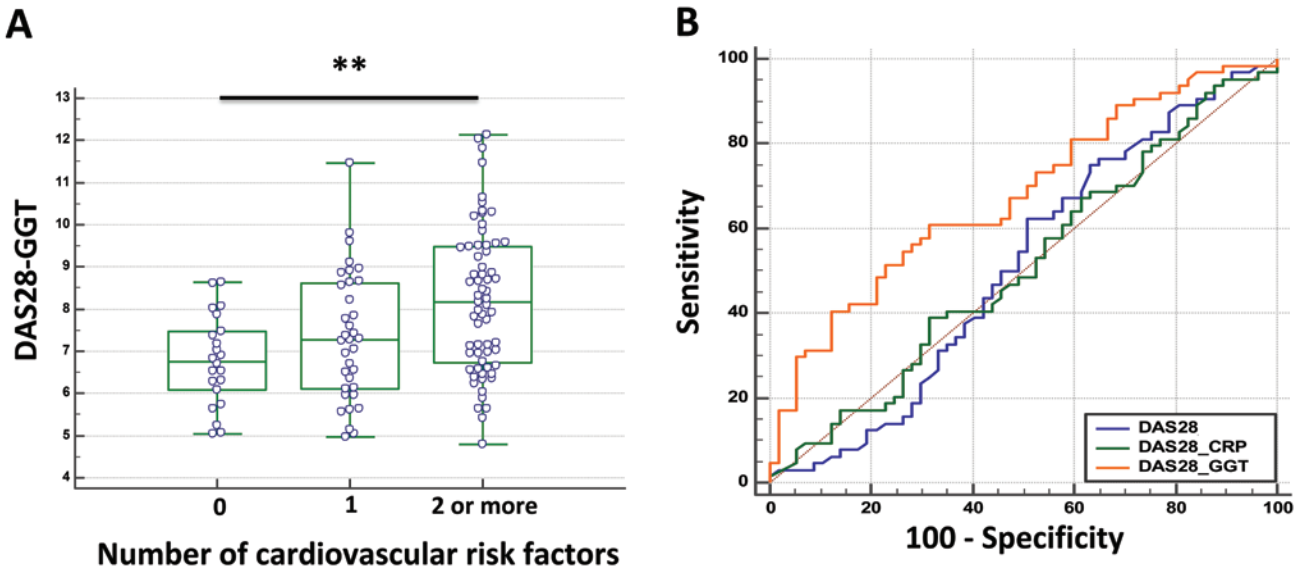

Figure 3. DAS28-GGT levels and cardiovascular risk factors. (A) DAS28-GGT levels according to the number of cardiovascular risk factors (0, 1, or ≥ 2 risk factors). ** $P < 0.01$ by Kruskall-Wallis test with Dunn correction. (B) Comparison of ROC curves of DAS28, DAS28-CRP, and DAS28-GGT. CRP: C-reactive protein; DAS28; Disease Activity Score in 28 joints; GGT: gamma-glutamyltransferase; ROC: receiver-operating characteristic curve.

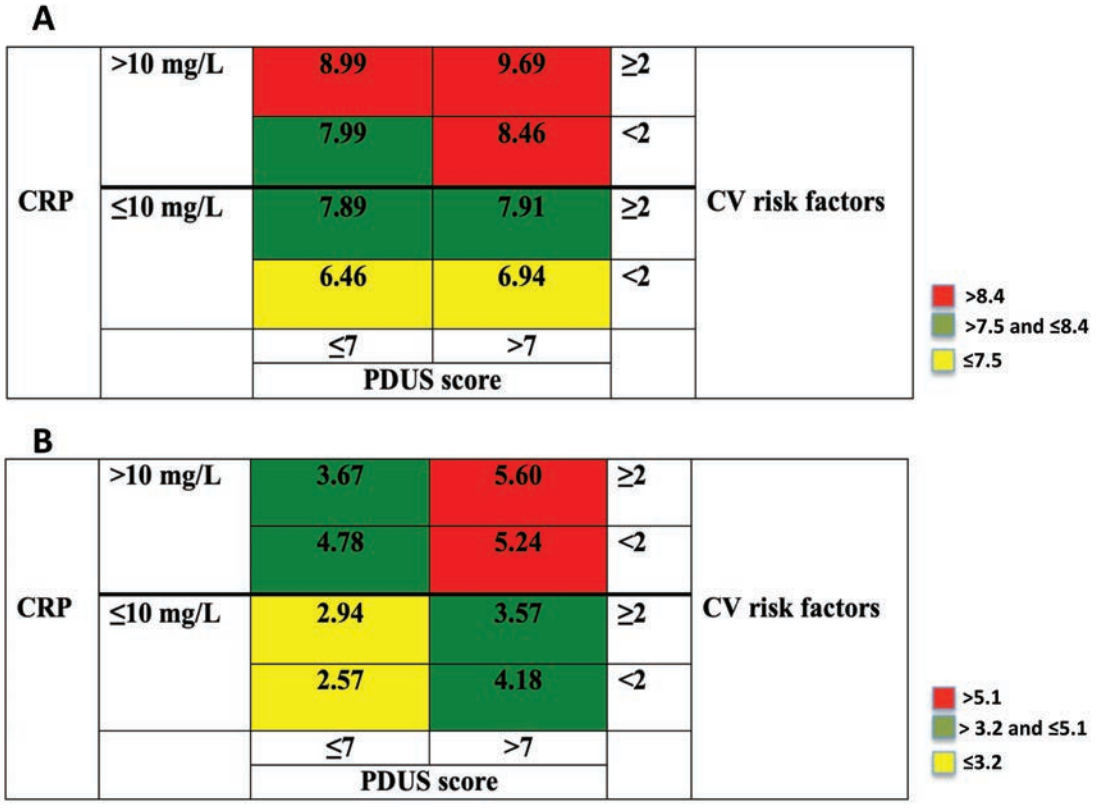

Figure 4. Risk matrix comparing the diagnostic values of the (A) DAS28 and the (B) DAS28-GGT according to CRP levels, the importance of synovial vascularization by PDUS, and the number of CV risk factors. A cutoff of 7 was chosen for the global synovitis score, corresponding to the 75th percentile value. This cutoff provided the best sensitivity (Se) and specificity (Sp) for active disease, defined by a DAS28 > 5.1 (Se 87.5%, Sp 88%, AUC 0.89). The "low-risk" cutoff of 7.5 for DAS28-GGT was chosen since it provided the best AUC to identify patients with CRP < 10 mg/L and PDUS score ≤ 7 (AUC 0.70, Se 68%, Sp 63%). The "high-risk" cutoff of 8.4 for DAS28-GGT was chosen since it provided the best AUC to identify patients with CRP > 10 mg/L and PDUS score > 7 (AUC 0.73, Se 75%, Sp 75%). AUC: area under the ROC curve; CRP: C-reactive protein; CV: cardiovascular; DAS28: Disease Activity Score in 28 joints; GGT: gamma-glutamyltransferase; PDUS: power Doppler ultrasound; ROC: receiver-operating characteristics.

total cholesterol/triglycerides[20], and an association with the risk of diabetes mellitus[21], high blood pressure[22], and metabolic syndrome[10]. Rising evidence has previously suggested that increased GGT levels may predict the occurrence of CVD in the general population[23,24]. Moreover, increased serum GGT levels were reported to be positively associated with increased risk of CV mortality in a dose-response manner[25]. The underlying mechanisms of the association between GGT and increased CVD remain unknown. Increased GGT levels could be a marker of the presence of concomitant CV risk factors. However, some studies suggested a direct involvement of GGT in the pathophysiology of atherosclerosis, especially in the plaque progression and instability[26,27].

Serum GGT levels are also a marker of systemic inflammation. GGT levels correlated with CRP levels and our logistic regression analysis revealed an independent association between increased GGT levels and high CRP levels. A previous study also reported this association in the general population, which persisted after stratification on BMI, ethnic group, and alcohol consumption[28]. Moreover, it is well known that systemic inflammation is implicated in atherosclerosis process. Thus, a continuum seems to exist between GGT elevation, inflammation, and atherosclerosis, but the pathogenic contribution of GGT in this association remains unknown. In addition, although we did not observe any link between GGT levels and the presence of bone erosions, GGT may also display osteoclastogenic activity mediated by Toll-like receptor 4 and directly intervene in RA pathology[29].

Taken together, our data suggest that serum GGT levels may reflect both systemic inflammation and a metabolic condition. In order to provide rheumatologists with a simple tool feasible in clinical practice, we constructed a new composite index called DAS28-GGT, replacing ESR by GGT levels. DAS28-GGT remained a reliable marker of RA disease activity, equivalent to the DAS28 for the assessment of disease activity evaluated by clinical examination or PDUS. This composite index also provided added value to identify the presence of CV risk factors and correlated with the Framingham CV risk score.

The DAS28-GGT has not been designed to be a substitute for the traditional CV risk assessment as it currently stands, given that it does not cover the whole spectrum of CV risk factors (e.g., smoking status). It has been constructed to be an additional tool to warn the clinician about the CV risk burden in patients with RA. It may be used in clinical practice to assess joint disease activity without losing validity compared to the DAS28 and may help rheumatologists decide whether they have to go more in depth regarding CV evaluation, as proposed in the algorithm presented in Supplementary Figure 3 (available with the online version of this article). This CV evaluation is critical in daily practice because CV events are responsible for 10–30% of the deaths in patients with RA and are the leading cause of death in this population[3,30,31]. Although systemic inflammation plays a key role in this increased risk of CV death, the presence of traditional CV risk factors also highly contributes to the CV risk. The 2017 guidelines from EULAR recommend the identification and aggressive management of traditional risk factors in addition to RA disease activity control to decrease the CV risk[32]. The consequence of our results is that, with a simple and common biological marker, we have the possibility to evaluate both disease activity and CV risk that are interrelated and probably linked by common physiopathological mechanisms.

Our study included consecutive longstanding patients who were carefully assessed and phenotyped in a tertiary center with a long-lasting experience in RA evaluation and care. However, our study is limited by its observational design, the relatively small number of patients included in some analyses, and the use of surrogates for CVD risk. The inclusion of RA patients followed in hospital may have resulted in a selection bias. Since this study is cross-sectional, any pathogenic link should be taken very cautiously, with the possibility of confounders and lack of evidence for causal associations. It is also important to note the low strength of the identified correlations between GGT levels and CVD risk factors, inflammatory markers, as well as the Framingham risk score. In addition, our study was underpowered to assess the influence of GGT levels on CV events, which had a low prevalence in our study sample. Prospective studies are requested to determine the validity of DAS28-GGT levels and its predictive value for the occurrence of CV events in RA populations.

In conclusion, GGT levels are associated in RA patients with systemic inflammation and several CV risk factors. DAS28-GGT might be a simple and useful tool to evaluate disease activity and identify associated CV risk factors.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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