Disease Activity Score-28 using γGT 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 (γGT) elevation in patients with rheumatoid arthritis (RA).

Methods: Cross-sectional monocentric study including RA patients for a 12-month period. Data on liver function, RA disease activity, 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 DAS28-γGT composite index by replacing ESR by γGT.

Results: Among the 129 included patients, 32 (25%) had isolated γGT increase. γGT correlated with age, CRP levels, body weight and were significantly increased in patients with alcohol intake, type 2 diabetes mellitus, blood hypertension, dyslipidemia and metabolic syndrome. γGT levels also gradually increased with the number of CV risk factors and correlated with the Framingham CV risk score. The composite index DAS28-γGT 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-γGT 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 >10%.

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

INTRODUCTION

Patients with rheumatoid arthritis (RA) experience premature mortality that is largely due to cardiovascular (CV) diseases. Compared to the general population, patients with RA had a 45 to 60% increased risk of CV death (1-3), 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 (γGT) is a plasma membrane enzyme that is primarily present in kidney, liver and pancreatic cells. γGT 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 (5-7).

Increased γGT 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 γGT levels and several RA disease activity markers (tender joint counts, Erythrocyte sedimentation rate), suggesting that this biological marker might be helpful to assess disease activity (8). Furthermore, accumulating evidence supports the association between elevated γGT levels and increased CV risk, and γGT levels are becoming an important addition to the screening strategy of CV diseases (5, 10, 11). Thus, γGT elevation may represent an integrative biomarker linking inflammation and CV risk in RA.

Our aim was to identify the factors potentially associated with increased γGT 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 ACR/European League Against Rheumatism (EULAR) classification for RA (12, 13), who attended the one 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 have received Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval before initiation of the study ("Comité de Protection des Personnes" Paris Ile de France I, n° CPPIDF1-2016-Juin-DAP13).

Data collection from RA patients

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

CV risk factors (high blood pressure, tobacco, diabetes, fasting glycemia, body mass index (BMI), metabolic syndrome), hepatotoxic factors (medication like analgesics, Non-steroidal anti-inflammatory drugs, NSAIDs, 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 based on evaluation of 28 joints (DAS28) (14), using Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (15). Health status was measured by the self-administered Stanford Health Assessment Questionnaire (HAQ). Systematic hand and foot x-rays 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 hospital visit. They included complete blood cell count, Westergren erythrocyte sedimentation rate (ESR), CRP concentration, serum creatinine concentration, and liver function tests (serum-glutamyl-

oxaloacetate-transferase S.G.O.T, serum glutamate-pyruvate transaminase S.G.P.T, γGT and alkaline phosphatase, APL). γGT levels were measured in succession by a standardized enzymatic colorimetric assay (Cobas 8000, Roche) recommended by the International Federation of Clinical Chemistry (IFCC). Rheumatoid factor (RF) and second-generation anti-cyclic citrullinated peptide (anti-CCP2) antibodies were detected by enzyme-linked immunosorbent assay (ELISA).

Definitions

Metabolic syndrome was defined according to the NCEP-ATP III classification criteria. Metabolic syndrome was considered as present when patients had 3 of the 5 following criteria: fasting glycemia ≥ 6.1 mmol/L, triglycerides ≥ 1.7 mmol/L, high density lipoproteins (HDL) < 1.04 mmol/L in men / 1.29 mmol/L in women, high blood pressure with systolic arterial pressure, (SAP)/ diastolic arterial pressure (DAP) ≥ 135/85 mmHg, waist circumference ≥ 102 cm in men / 88 cm in women. If patients received anti-hypertensive agent, there were considered as suffering from high blood pressure. When waist circumference was not available, it was replaced by BMI ≥ 25 kg/m2 according to the AACE criteria (16). Ten-year risk prediction of CV disease was estimated by the algorithm developed by the Framingham Heart Study (17). Increased γGT levels were defined according to our laboratory standard by a level > 35 IU/L. ESR and CRP were considered as elevated above 28mm hour-1 and 10 mg/L, respectively.

Ultrasonography (US) assessment: The equipment was a 7-15 MHz linear array transducer (Toshiba Aplio). The presence of hypoechoic synovial hyperplasia (SH) and joint effusion (JE), 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 the patient status. The presence of synovitis (SH and PD, without JE) was scored for each joint according to the semiquantitative OMERACT-EULAR-US composite PDUS scale, giving a score of 0–3 for each joint (0=absence,

no synovial hyperemia, 1= mild, hyperemia in less than 1/3 of the synovial surface area; 2= moderate, hyperemia in less than 2/3 of the synovial surface area; 3= marked, in more than 2/3 of the synovial surface area). A global synovitis score, derived from the Global OMERACT-EULAR Synovitis Score (GOESS), was calculated for 16 paired joints both hands (MCPs 1-5 and PIPs 1-5), both wrists (radio-ulnar, medio-carpal and radio-carpal) and both forefeet (MTPs 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 ± standard deviation (SD) or median (range), unless stated otherwise. Statistical analysis was performed using using Medcalc (v18.9.1). Correlations between γGT levels and numeric variables were assessed using Spearman's rank correlation test.

Given the non-parametric distribution of serum γGT (Kolmogorov-Smirnov distance of 0.226, $p<0.001$), γGT levels according to binary variables, including markers of disease activity or CV risk factors were tested using Kruskal-Wallis test with Dunn correction. Comparisons of mean values were assessed by the unpaired t-test, and the chi-square test was used to seek for differences in frequency. Multivariate analyses by logistic regression were also performed to determine the factors independently associated with increased γGT levels and moderate/high CV risk. These analysis included γGT 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 one single step in each model. Odds ratio (OR) and 95% confidence intervals (CI) were then calculated. In this model, a *P* value <0.05 was considered statistically significant.

DAS28-γGT calculation

Given the potential association between inflammation and γGT levels and the growing interest of γGT levels for CV evaluation, our aim was to construct a simple screening tool providing to the

rheumatologist rapid informations related to both joint disease activity and CV risk. Thus, we constructed a composite index called DAS28-γGT, obtained by replacing ESR by γGT levels in the following formula: $0.56*\sqrt{TJ-28}+0.28*\sqrt{SJ-28}+2*ln(\gamma GT)+0.14*GH$. The weight of γGT in this formula was determined by applying different weight coefficient, 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 (**Table S1**). We retained the formula providing the optimal combination between the evaluation of disease activity and cardiovascular risk (weight coefficient of 2).

The diagnostic value of the DAS28-γGT was assessed by ROC curve analysis. We also constructed risk matrix to compare the diagnostic values of DAS28 and DAS28-γGT 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 factors 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.** γGT levels ranged from 7 to 219 U/L with a mean value of 32±32 IU/L and a frequency distribution illustrated in **Figure S1**; 32 (25%) patients had γGT values above 35 IU/L.

γGT and RA disease activity and severity

γGT levels correlated with CRP levels (rS=0.30, p=0.002) (**Figure 1A**). γGT levels were significantly higher in patients with CRP levels above 10 mg/L (median (range): 31.5 IU/L (9-219) vs. 20 IU/L (7-126), p<0.001) (**Figure 1B**). There was no correlation between γGT levels and ESR, as well as composite index evaluating RA disease activity (DAS28 and DAS 28-CRP). No

relationship was observed between γGT levels and tender/swollen joint counts, OMERACT-EULAR Synovitis Score on PDUS, presence of bone erosions or HAQ (**Table S1**).

γGT and cardiovascular risk factors

γGT 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). γGT levels were significantly increased in males (median (range) 32 (13-144) IU/L vs. 21 (7-219) IU/L, p=0.021), in patients with type 2 diabetes mellitus (median (range) 35 (8-215) IU/L vs. 21 (7-219) IU/L, p=0.024), high blood pressure (median (range) 31 (10-219) IU/L vs. 21 (7-88) IU/L, p<0.001), dyslipidemia (median (range) 28 (7-219) IU/L vs. 19 (8-215) IU/L, p=0.004) and metabolic syndrome (median (range) 48 (14-219) IU/L vs. 21 (7-144) IU/L, p=0.003). No link was observed with smoking status. γGT levels were also associated with the number of CV risk factors, with a dose-ranging effect (**Figure 2**). In addition, γGT levels correlated with the Framingham risk score (rS=0.44, p<0.001), evaluating the 10-year CV risk.

γGT, hepatic diseases, and hepatotoxic factors

γGT levels were higher in patients with alcohol consumption (median (range) 35 (20-144) IU/L vs. 22 (7-219) IU/L, p=0.012). Three RA patients had associated-primary biliary cirrhosis with positive anti-mitochondrial antibodies; all treated with ursodeoxycholic acid, and all with normal γGT levels. Fourteen patients had occult hepatitis B infection (undetectable HBV DNA, HBsAg-negative, anti-HBc and anti-HBs positive antibodies) requiring no specific treatment, and 3 with isolated γGT elevation. In addition, 3 patients had non-alcoholic fatty liver disease detected by liver ultrasound, associated with metabolic syndrome, and one had γGT levels > 35 IU/L. Increased γGT were 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 γGT levels and the use of NSAIDs, analgesics, corticosteroids (≤10 mg/day), conventional synthetic disease modifying anti-rheumatic

drugs (DMARDs) or targeted biologic DMARDs. A trend was observed for higher γGT in patients treated with >10 mg/day of corticosteroids (median (range): 29.5 IU/L (17-61) vs. 20 IU/L (7-219), p=0.058).

Multivariate analyses

A first logistic regression analysis confirmed the independent association between increased γGT 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 γGT levels and the presence of a metabolic syndrome were independent 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. (**Table S2**).

Value of the DAS28-γGT for RA disease activity and the presence of CV risk factors

Since γGT levels reflected both systemic inflammation and the number of CV risk factors, we hypothesized that γGT 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-γGT and tested its merit for the assessment of RA disease activity and the presence of CV risk factors.

DAS28-γGT 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 Global OMERACT-EULAR Synovitis Score on PDUS (rS=0.39, p=0.004), and HAQ (rS=0.35, p<0.001). Correlation coefficients were similar between DAS28-γGT, DAS28 and DAS28-CRP for HAQ (0.35 vs. 0.39 and 0.31, respectively) and close for the Global OMERACT-EULAR Synovitis Score on PDUS (0.39 vs. 0.53 and 0.54). The discriminating capacities of DAS28-γGT and DAS28 to identify patients with active disease (DAS28-CRP>3.2 or DAS28-CRP>5.1) were similar (**Figure S2**). For the classification variable DAS28-CRP >3.2, the AUC were 0.88 and 0.90 for the DAS28-γGT and DAS28, respectively. For the classification variable DAS28-CRP >5.2, the AUC were 0.95 and 0.96 for the DAS28-γGT and DAS28, respectively.

DAS28-γGT 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 (range) 8.6 (6.98-10.26) vs. 7.34 (4.80-12.14) p=0.047), high blood pressure (median (range) 8.16 (5.41-12.14) vs. 7.26 (4.80-11.47) p=0.012) dyslipidemia (median (range) 8.24 (4.80-12.14) vs. 7.08 (5.04-11.81), p=0.011) and metabolic syndrome (median (range) 8.47 (6.23-12.03) vs. 6.40 (4.80-12.14), p=0.045).

DAS28-γGT 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) conversely to the DAS28 and DAS28-CRP, which were not significantly modified by these factors. DAS28-γGT 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-γGT 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-γGT to identify patients with high RA disease activity and CV risk compared to the DAS28, which was only relevant to identify patients high RA disease activity, but did not bring additional value for the detection of increased CV risk factors (**Figure 4A-B**).

In our cohort, patients with a DAS28-γGT <5.5 were all in remission and at low cardiovascular risk (2). A large majority (93%) of patients with a DAS28-γGT between 5.5 and 7.5 were in remission or LDA, but 41% were at medium or high CV risk according to the Framingham risk score (**Table S3**), supporting the evaluation of CV risk factors (**Figure S3**). Patients with a DAS28-γGT >7.5 were at risk of active disease and/or CV risk, supporting the priority evaluation of both joint involvement and CV risk (**Table S3 and Figure S3**).

DISCUSSION

γGT 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 G-SH homeostasis and defense against oxidative stress (19). Beyond its physiological functions, isolated elevation of serum γGT levels could reflect hepatic lesions as well as systemic conditions, including hyperthyroidism, metabolic syndrome, body mass index and others.

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

Increased γGT 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 γGT levels and BMI, 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 recently suggested that increased γGT levels may predict the occurrence of CV diseases in the general population (23, 24). Moreover, increased serum γGT 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 γGT and increased CV diseases remain unknown. Increased γGT levels could be a marker of the presence of concomitant CV risk factors. However, some studies suggested a direct involvement of γGT in the pathophysiology of atherosclerosis especially in the plaque progression and instability (26, 27).

Serum γGT levels are also a marker of systemic inflammation. γGT levels correlated with CRP levels and our logistic regression analysis revealed an independent association between increased γGT 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 γGT elevation, inflammation and atherosclerosis, but the pathogenic contribution of γGT in this association remains unknown. In addition, although we did not observe any link between γGT levels and the presence of bone erosions, γGT may also display osteoclastogenic activity mediated by Toll-like receptor 4 (TLR4) and directly intervene in RA pathology (29).

Taken together, our data suggest that serum γGT levels may reflect both systemic inflammation and metabolic condition. In order to provide to rheumatologists a simple tool, feasible in clinical practice, we constructed a new composite index called DAS28-γGT, replacing ESR by γGT levels. DAS28-γGT 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-GT has not been designed to be a substitute to 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 loosing validity compared to the DAS28, and may help the rheumatologists to decide whether they have to go more in depth regarding CV evaluation, as proposed in the algorithm presented in **Figure S3**. This CV evaluation is critical in daily practice because CV events are responsible of 10 to 30% of the deaths in patients with RA and are the leading cause of death in this population (30-32). 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. Recent guidelines from the European League Against Rheumatism (EULAR) recommend the identification and aggressive management of traditional risk factors in addition to RA disease activity control to decrease the CV risk (33). The consequence of our results is that, with a simple/usual 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 relative 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 possibility of confounders and lack of evidence for causal associations. Is it also important to note the low strength of the identified correlations between γGT 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 γGT levels on CV events, which had a low prevalence in our study sample. Prospective studies are requested to determine the validity of DAS28-γGT levels and its predictive value for the occurrence of CV events in RA populations.

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

Keywords: rheumatoid arthritis, γGT levels, inflammation, cardiovascular risk factors

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Figure legends:

Figure 1: **Association between γGT and systemic inflammation**
A, Rank correlation between γGT (UI/L) and C-Reactive Protein (CRP, mg/L); **B,** γGT levels (IU/L) according to CRP levels (mg/L). *** p<0.001 by Kruskall-Wallis test with Dunn correction

Figure 2: γGT levels (UI/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

Figure 3: DAS28-γGT levels and cardiovascular risk factors
A, DAS28-γGT 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-γGT

Figure 4: Risk matrix comparing the diagnostic values of the DAS28 (A) and the DAS28-γGT (B) according to C-Reactive Protein (CRP) levels, the importance of synovial vascularization by Power Doppler Ultrasounds (PDUS) and the number of cardiovascular (CV) risk factors.
A cut-off of 7 was chosen for the global synovitis score, corresponding to the 75th percentile value. This cut-off provided the best sensitivity (Se) and specificity (Sp) for active disease, defined by a DAS28 >5.1 (Se: 87.5%, Sp 88%, area under the ROC curve, AUC, 0.89).
The "low-risk" cut-off of 7.5 for DAS28-γGT 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" cut-off of 8.4 for DAS28-γGT 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%).

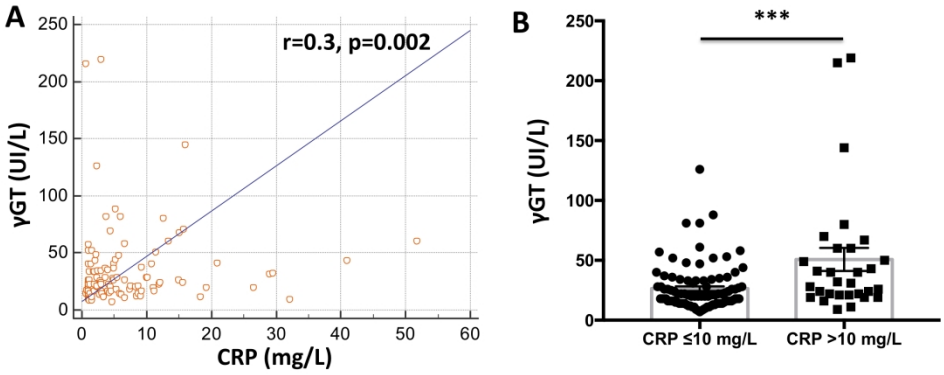

Figure 1

254x190mm (300 x 300 DPI)

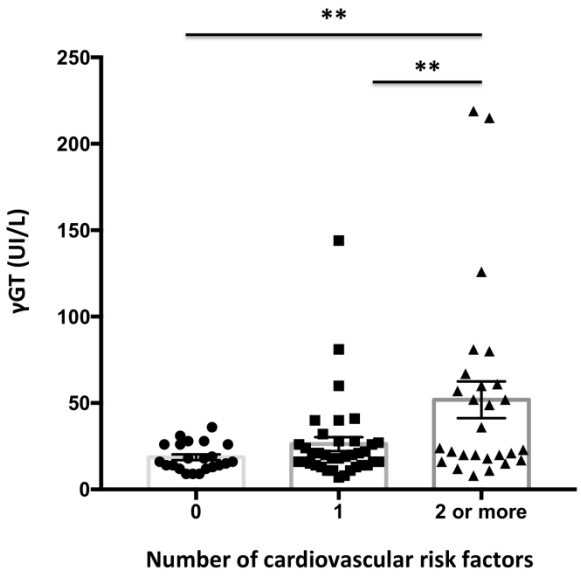

Figure 2

254x190mm (300 x 300 DPI)

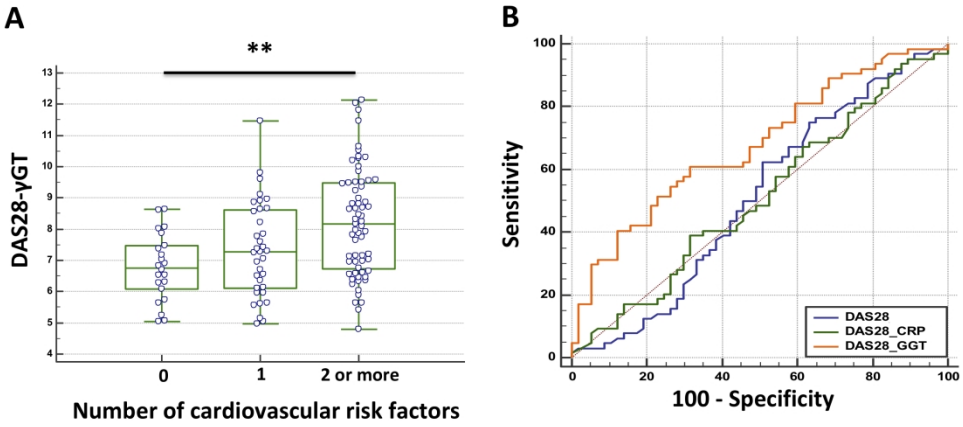

Figure 3

254x190mm (300 x 300 DPI)

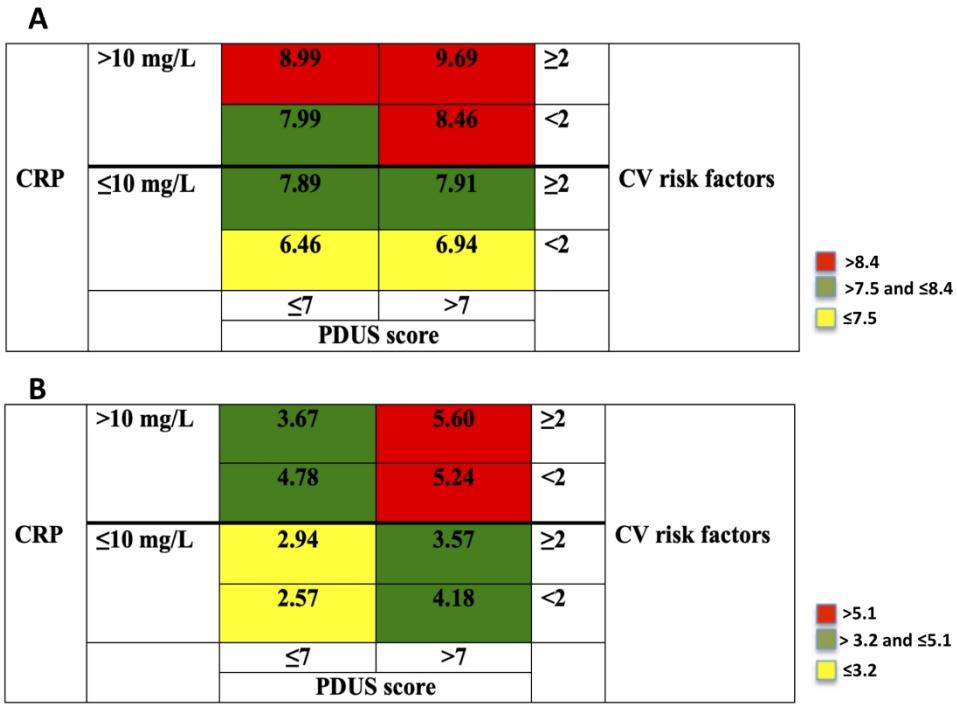

Figure 4

254x190mm (300 x 300 DPI)

Table 1: Study population

	Patients with rheumatoid arthritis and normal γGT (n=97)	Patients with rheumatoid arthritis and γGT >35 IU/L (n=32)	p-value
Demographics			
Age (years), mean ± SD	57±14	62±9	0.061
Females, n (%)	87 (90)	24 (75)	0.043
Disease characteristics			
Disease duration (years), mean ± SD	13±11	16±12	0.193
Positive rheumatoid factor, n (%)	78 (80)	24 (75)	0.550
Positive anti-CCP2 antibodies, n (%)	78 (80)	27 (84)	0.618
Erosions on hand/foot x-rays, n (%)	57 (59)	22 (69)	0.315
Disease activity:			
DAS28, mean ±SD	3.43±1.35	3.55±1.70	0.684
DAS28 >3.2, n (%)	38 (39)	10 (31)	0.418
DAS28-CRP, mean ±SD	2.72±1.15	3.12±1.36	0.106
DAS28-CRP >3.2, n (%)	29 (30)	12 (38)	0.402
ESR (mmH1), mean ±SD	20.0±18.5	21.7±19.5	0.657
ESR>28 mmH1, n (%)	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, n (%)	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, n (%)	64 (66)	22 (69)	0.756
Current corticosteroid use, >10 mg/day, n (%)	6 (6)	4 (13)	0.058
Current use of NSAIDs	19 (20)	7 (22)	0.808
Current conventional DMARD use, n (%)	90 (93)	28 (88)	0.374
Current anti-TNF-α use, n (%)	16 (16)	6 (19)	0.695
Current rituximab use, n (%)	24 (25)	8 (25)	1.000
Current tocilizumab use, n (%)	10 (10)	2 (6)	0.495
Current abatacept use, n (%)	7 (7)	2 (6)	0.846
Modifiable cardiovascular risk factors			
Smokers, n (%)	24 (25)	13 (41)	0.132
High blood pressure, n (%)	21 (22)	16 (50)	0.007
Diabetes mellitus, n (%)	8 (8)	7 (22)	0.098
Dyslipidemia, n (%)	30 (31)	19 (59)	0.020
BMI, kg/m2, mean ±SD	24 ± 5	28±6	0.003
BMI >30 kg/m2, n (%)	14 (14)	10 (31)	0.097
Patients with 2 or more 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

SD: Standard Deviation, DAS: Disease Activity Score, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive protein, HAQ: Health Assessment Questionnaire, DMARD: Disease Modifying Anti-Rheumatic Drug, TNF-α: Tumor Necrosis Factor-α, BMI: Body Mass Index CV: Cardiovascular

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

Variables	Univariate p-value	Odds ratio (95% CI)	p-value
Age (years)	0.061	1.02 (0.98-1.07)	0.337
Female gender	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

BMI: Body Mass Index, CRP: C-reactive protein, CI Confidence Interval