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# Could potentially calprotectin be a promising biomarker to oracle biologic therapy response in rheumatoid arthritis?

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## Abstract

**Background:** The advent of novel biologic agents for the treatment of rheumatoid arthritis (RA) has proven to be highly productive. Nonetheless, high cost, side effects, and unresponsiveness to these agents dictates the assignment of biomarkers that can foretell treatment response. Currently, calprotectin (a member of the S100 protein family) is amongst the enormously studied candidates in this perspective. Yet, conflicting results have been published. The main purpose of this study was to explore the role of serum concentration of calprotectin to predict the response to biological therapy in RA patients, so as to customize RA treatment.

**Results:** Baseline serum calprotectin levels were significantly higher in RA patients compared to the control subjects ( $P$  value  $< 0.001$ ). After receiving biologic therapy, a remarkable reduction ( $P < 0.001$ ) in serum calprotectin was noted in RA cohort. Moreover, no correlation was found between the 28 joint count disease activity score (DAS28) and serum calprotectin levels neither before or after biologics. Intriguingly, no statistically significant association was detected between circulating calprotectin level and response to biological therapy.

**Conclusion:** Serum calprotectin concentrations could not be used as a biomarker to forecast clinical response to biological therapy in RA patients. However, further studies involving larger cohort of RA patients should be carried out to deliver more insight in this regard.

**Keywords:** Rheumatoid arthritis, Calprotectin, Biomarker, Predict, Biologic therapy, Disease activity, Prospective

## Background

Rheumatoid arthritis (RA) is a common, long-term, auto-immune, inflammatory disease that may cause progressive joint destruction and malformation, thus provoking a functional debility and poor quality of life [1]. Though the exact etiology of RA is yet undetermined, an interplay between genetic predisposition, environmental and hormonal mediators seems to trigger the disease development [2]. Aberrations in the cellular and humoral arms of the immune system result into the formation of

autoantibodies, especially rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies [3].

At present, immunomodulatory agents known as disease-modifying anti-rheumatic drugs (DMARDs) are generally available for the treatment of RA [4]. Conventional synthetic DMARDs include hydroxychloroquine, methotrexate, leflunomide, and sulfasalazine [5]. On top of that, targeted synthetic DMARDs (tsDMARDs), e.g., Janus kinase (JAK) inhibitors are considered another treatment option for RA [6]. On the other hand, the most commonly used biologic DMARDs (bDMARDs) include etanercept, infliximab, and adalimumab (inhibitors of tumor necrosis factor- $\alpha$ ; anti-TNF- $\alpha$ ) [7], tocilizumab (a humanized monoclonal antibody against the interleukin-6 receptor; IL-6R) [8], rituximab (a chimeric

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anti-CD20 monoclonal antibody) [9], abatacept (costimulation blocker) [10], and anakinra (a recombinant inhibitor of interleukin-1; IL-1) [11]. Importantly, bDMARDs are usually proposed for treatment of RA patients who fail to respond to conventional DMARDs with clinical or radiologic evidence of disease progression [12].

In clinical occasions, bDMARDs are often administered on a 'trial-and-error' manner and each patient does not respond likewise to the same medications [13]. Stratifying patients to amplify the likelihood of a strong treatment outcome will subsequently minimize the risk of unsuccessful treatment adverse effects and escalate cost-effectiveness which is of particular concern for the healthcare system. Accordingly, plenty of researches have been brought off to identify biomarkers that can predict the response to bDMARDs [14].

Calprotectin, a member of the S100 protein family, is among the widely investigated biomarkers in this context [15]. It is a heterodimeric complex of 2 non-covalently associated calcium-binding proteins, S100A8 (myeloid-related protein; MRP 8) and S100A9 (MRP 14). Calprotectin is located in the cytoplasm of neutrophils and monocytes. When released, it functions as a damage-associated molecular pattern (DAMP) or alarmin, via toll-like receptor 4 (TLR4) activation [16].

Calprotectin was specified this name owing to its protective role in epithelial defense as well as its bactericidal and fungicidal properties [17]. Normally, it is present in the serum at a concentration that varies from 0.1 to 1.6 µg/ml and is increased in many disorders such as infection, inflammation or cancer. The low molecular weight (36.5 kDa) of this protein allows its circulation from the site of inflammation to the blood. It is proposed that serum concentrations of calprotectin appear to mirror synovial levels with a ratio of 1:2–3 [18].

In the past few years, a plethora of studies highlighted the role of calprotectin as a biomarker for response to bDMARDs among RA patients. Undesirably, contradictory results have been disclosed. Thereby, this study was designed in an attempt to assess the worth of serum concentration of calprotectin as an oracle to the response to bDMARDs, so as to personalize RA treatment.

## Methods

### Study design, subjects, and setting

This prospective cohort study enrolled a total of 25 consecutive adult patients (16 females and 9 males, mean age  $\pm$  SD;  $41.32 \pm 10.04$  years) who fulfilled the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 classification criteria for RA [19]. The study cohort was recruited in the period from January 2019 to December 2019 from the Out-patient Clinics of Rheumatology and Rehabilitation in

Mansoura University Hospital (MUH), Egypt. Additional 30 age- and gender-matched healthy individuals were included as a control group.

Our sample size was calculated using G \*power program [20]. A previous study concluded that the mean calprotectin level  $\pm$  SD was  $190.2 \pm 80.4$  µg/dl in the study group and  $63.1 \pm 20.3$  µg/dl in the control group [21] with an alpha error = 0.05 and a study power = 0.95, accordingly the required sample size was at least 7 per group.

### Exclusion criteria

Patients < 18 years, pregnant or nursing females, and RA patients with any other concomitant autoimmune disease or current or past history of malignancy were excluded from the study. Furthermore, patients with any form of current acute or chronic infection and organ transplant recipients were not eligible to our study.

### Patients' assessment

Thorough history taking and clinical evaluation was done for each patient. Disease activity was assessed by the 28 joint count disease activity score (DAS28) and C-reactive protein (CRP) at baseline and 12 weeks after receiving bDMARDs. DAS28 was measured using swollen joint count (SJC) and tender joint count (TJC) as well as the patient rating for general health on a 100-mm visual analog scale (VAS). A DAS28 < 2.6 indicates remission, 2.6–3.2 low disease activity, 3.2–5.1 intermediate disease activity, and > 5.1 high disease activity [22].

Complete blood count (CBC), liver function tests, kidney function tests, serum C-reactive protein (CRP), rheumatoid factor IgM (RF), erythrocyte sedimentation rate (ESR), and anti-cyclic citrullinated peptide (anti-CCP) were assessed using the currently available hospital laboratory protocols.

### Determination of serum calprotectin concentrations in the study subjects

Serum calprotectin levels were measured in the enrolled 25 RA patients at baseline and 12 weeks after receipt of bDMARDs, as well as in the 30 healthy controls. About 3 ml fasting, peripheral venous blood specimens were collected from each participant. Blood samples were centrifuged immediately after being collected to prevent the release of calprotectin from activated leucocytes and sera were subsequently stored at  $-80$  °C until the analysis. The assessment was done using the commercially available enzyme-linked immune-sorbent assay (ELISA) kit according to manufacturer's guidelines (Shanghai Korain Biotech CO., Ltd., China). All values were expressed in ng/ml.

### Biologic DMARDs' protocols for RA cohort

Approximately 80% of the included RA patients in this study were receiving bDMARDs for the first time and 20% received previous courses of bDMARDs, but they were starting a new course at the time of their enrollment. The prescribed drugs included infliximab (remicade); 1–3 mg/kg intravenous infusion 0, 2, 6 weeks, maintenance every 8 weeks (36% of RA patients), etanercept (enbrel); 50 mg subcutaneous every week (28%), adalimumab (humera); 40 mg subcutaneous every other week (20%), tocilizumab (actemra); 4–8 mg/kg intravenous infusion every month (12%) and golimumab (simponi); 50 mg subcutaneous every month (4%).

The response to bDMARDs was recorded after 3 months according to the commonly applied EULAR response criteria [23] as follows: good responders; having a DAS28  $\leq 3.2$  + a decrease in DAS28  $> 1.2$ , moderate responders; having either DAS28  $\leq 3.2$  + a decrease in DAS28  $> 0.6$  and  $\leq 1.2$  or DAS28  $\leq 5.1$   $> 3.2$  + a decrease in DAS28  $> 0.6$  or DAS28  $> 5.1$  + a decrease in DAS28  $> 1.2$ , and non-responders; having either a decrease in DAS28  $< 0.6$  or a DAS28  $> 5.1$  + a decrease in DAS28  $\leq 1.2$ .

### Statistical analysis

Data were processed and analyzed using SPSS program version 24.0 for Windows (SPSS Inc., Chicago, IL, USA). Qualitative data were described as numbers and percentages with Pearson's chi-square ( $\chi^2$ ) test used for comparison, meanwhile Fisher's exact test was used as a correction for  $\chi^2$  test when  $> 25\%$  of cells have count  $< 5$  in  $2 \times 2$  tables. Quantitative data were described using median and range for non-parametric data and mean  $\pm$  standard deviation (SD) for parametric data after testing normality using Kolmogorov-Smirnov test. The Student  $t$  test was used to compare between 2 independent groups (parametric). The Mann-Whitney  $U$  test was used for comparison between groups (non-parametric) and the Wilcoxon signed rank test to compare between the 2 studied periods.

The Spearman's rank-order correlation coefficient ( $r_s$ ) was used to determine the strength and direction of a linear relationship between 2 non-normally distributed continuous variables. The Kruskal–Wallis (KW) test was done to detect the possible association between serum calprotectin level and response to biological therapy. Receiver operating characteristic (ROC) curves were plotted to assess the diagnostic accuracy of serum calprotectin for discrimination of patients with high and moderate disease activity and to compare the diagnostic accuracy of calprotectin, CRP and ESR in this regard.

Significance of the obtained results was judged at  $P$  values  $\leq 0.05$  [24].

### Results

The demographic, clinical, radiological, and laboratory parameters of RA patients are shown in Table 1. Overall, a total of 25 patients with RA (mean age  $41.32 \pm 10.04$  years, 64% females), and 30 healthy control subjects (mean age  $38.53 \pm 9.93$  years, 70% females) were enrolled in the current study. The mean disease duration was  $8.32 \pm 5.45$  years from preliminary clinical presentation.

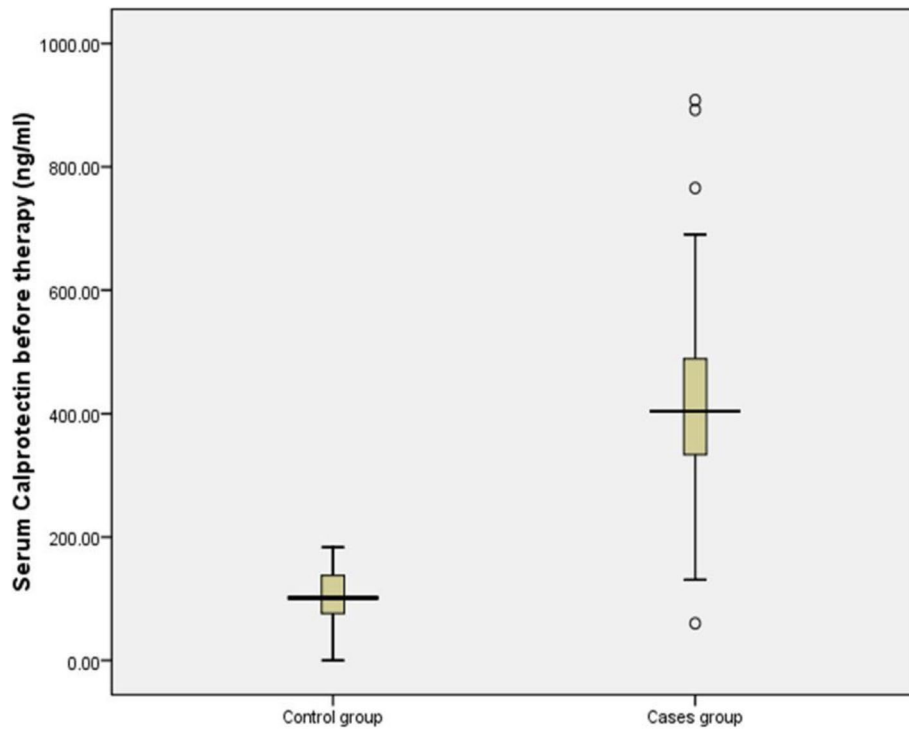
Baseline serum calprotectin levels were significantly higher in RA patients compared to the control subjects ( $P < 0.001$ ). After commencing biologic therapy, a substantial reduction in serum calprotectin was noted among the enrolled patients with a statistically significant difference ( $P < 0.001$ ). Values are illustrated in Figs. 1 and 2, respectively.

At baseline, 24% of the enrolled patients exhibited a moderate DAS28 and 76% had a high score. After initiating biologics, 68% and 32% of the patients showed moderate and high DAS28, respectively ( $P < 0.001$ ). Also, a significant decline in the DAS28 among the enrolled patients after receipt of bDMARDs was noted ( $P < 0.001$ ) as shown in Fig. 3.

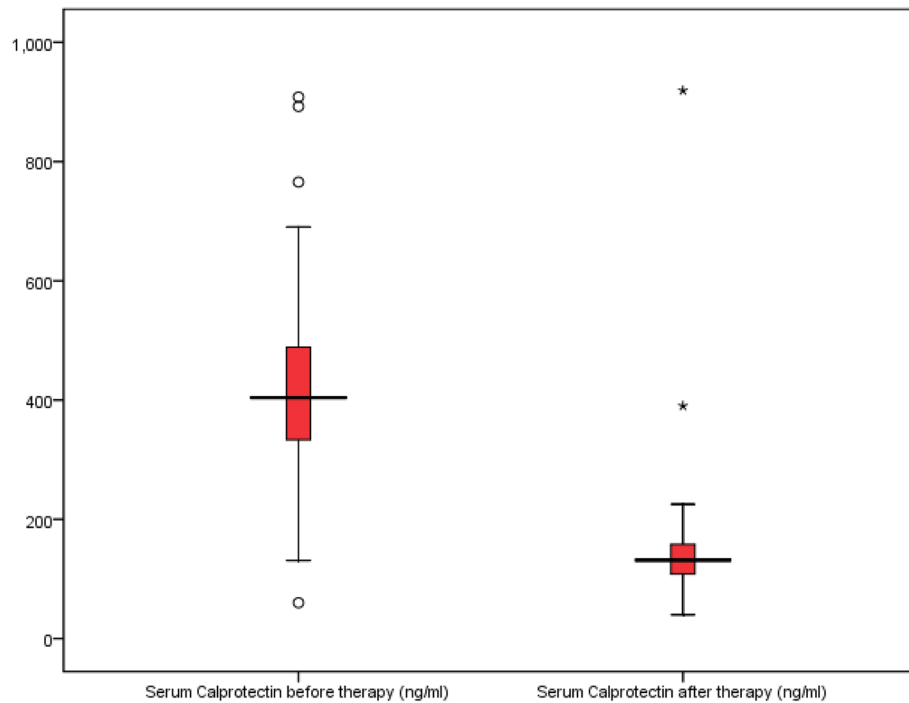
**Table 1** Baseline features of rheumatoid arthritis cohort

Parameters	RA patients (n = 25)
Age (years); mean $\pm$ SD	41.32 $\pm$ 10.04
Gender (number, percentage)	
-Females	16 (64%)
-Males	9 (36%)
Disease onset (years); mean $\pm$ SD	33 $\pm$ 11.29
Disease duration (years); mean $\pm$ SD	8.32 $\pm$ 5.45
Morning stiffness (min); mean $\pm$ SD	41 $\pm$ 25.81
Swollen joints	6.72 $\pm$ 3.38
ESR (mm/h); mean $\pm$ SD	65.76 $\pm$ 29.24
CRP (mg/l); mean $\pm$ SD	53.61 $\pm$ 24.91
DAS28; mean $\pm$ SD	5.91 $\pm$ 0.98
RF (IgM) positivity	21 (84.0%)
RF (IU/ml); mean $\pm$ SD	133.76 $\pm$ 88.21
Anti-CCP positivity	15 (60%)
Anti-CCP (RU/ml); mean $\pm$ SD	322.20 $\pm$ 112.60
bDMARDs at inclusion	
-Infliximab (remicade)	9 (36%)
-Etanercept (enbrel)	7 (28%)
-Adalimumab (humera)	5 (20%)
-Tocilizumab (actemra)	3 (12%)
-Golimumab (simponi)	1 (4%)

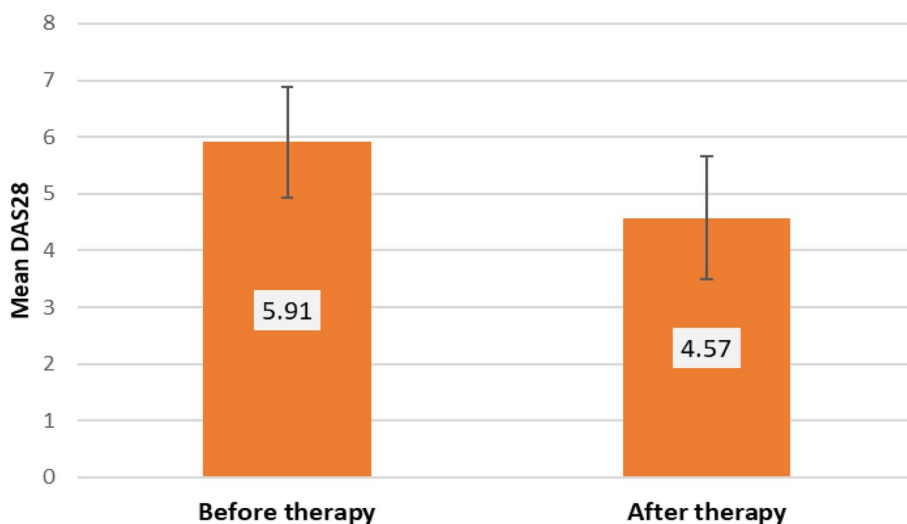
**Abbreviations:** CRP C-reactive protein, ESR erythrocyte sedimentation rate, CCP cyclic citrullinated peptide, RF rheumatoid factor, bDMARDs biologic disease-modifying anti-rheumatic drugs, n number, SD standard deviation



**Fig. 1** Box and Whisker plot of baseline serum calprotectin concentrations among the study cohort. Rheumatoid arthritis patients showed remarkably higher levels [404.1 (60.0–908.2 ng/ml)] as compared to the healthy controls [101.45 (0.0–183.7 ng/ml)];  $P < 0.001$



**Fig. 2** Box and Whisker plot of serum calprotectin before and after therapy among rheumatoid arthritis patients. Three months after biologic therapy, a significant decline in serum calprotectin from 404.1 (60.0–908.2 ng/ml) to 131.70 (39.9–171.73 ng/ml) was observed ( $P < 0.001$ )



**Fig. 3** Disease activity score 28 (DAS28) among the enrolled rheumatoid arthritis patients. There was a statistically significant decline in the mean DAS28 amongst RA patients from  $5.91 \pm 0.98$  to  $4.57 \pm 1.08$  ng/ml three months after initiation of biologic therapy ( $P < 0.001$ )

**Table 2** Correlation between DAS28 and serum calprotectin levels

	DAS28 before bDMARDs	
Serum calprotectin (ng/ml) before bDMARDs	$r_s$	-0.091
	$p$	0.667
	DAS28 after bDMARDs	
Serum calprotectin (ng/ml) after bDMARDs	$r_s$	0.053
	$p$	0.801

DAS28 Disease Activity Score 28, bDMARDs biologic disease-modifying anti-rheumatic drugs,  $r_s$  Spearman's correlation coefficient,  $P \leq 0.05$ ; statistically significant

In this study, no correlation was found between DAS28 and serum calprotectin levels neither before or after bDMARDs (results are presented in Table 2). Furthermore, a ROC curve was plotted to demonstrate validity of serum calprotectin in discriminating high disease activity patients from those with moderate activity. Before starting bDMARDs, the area under the curve (AUC) was 0.654 (95% CI 0.437–0.872);  $P = 0.221$ , whereas after therapy, the AUC was 0.522 (95% CI 0.252–0.792);  $P = 0.861$  (data are shown in Fig. 4).

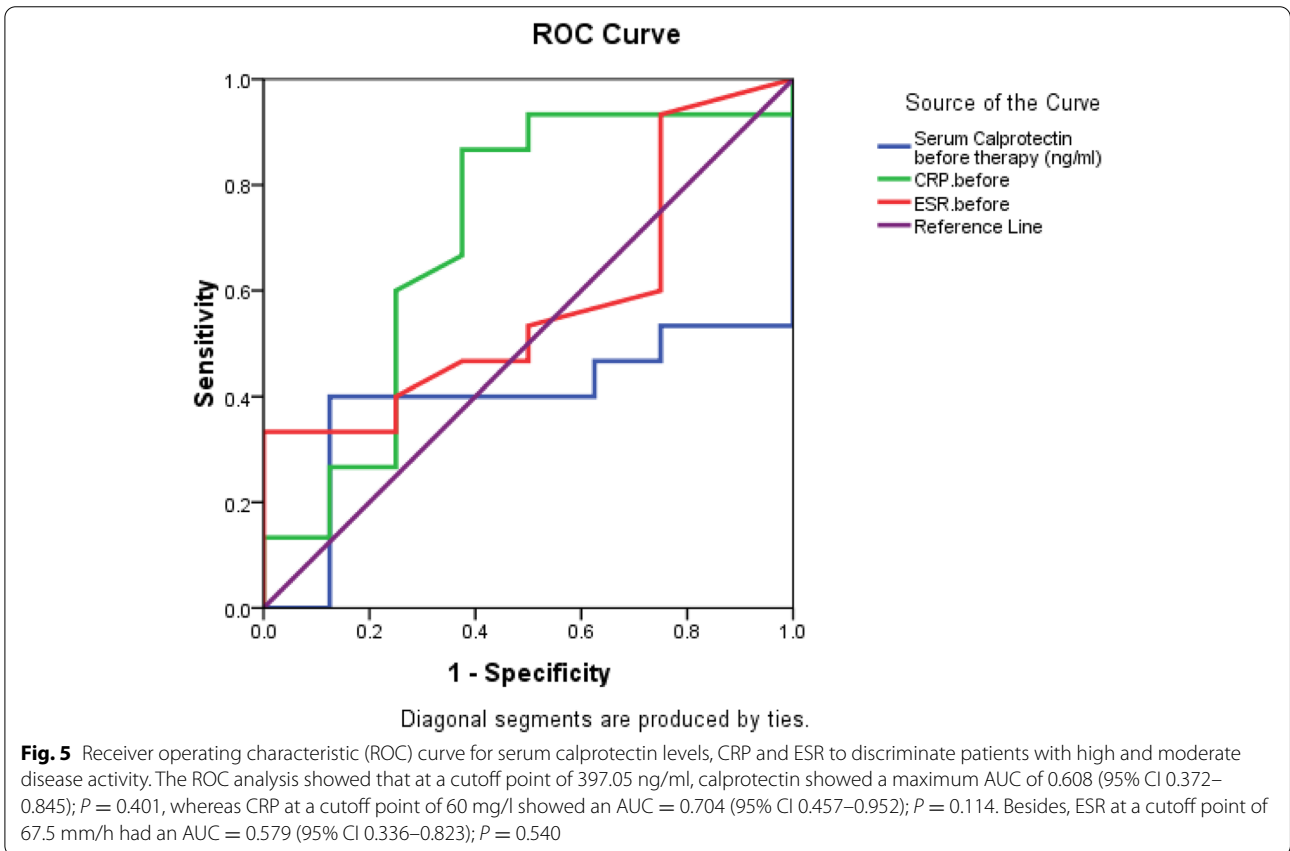
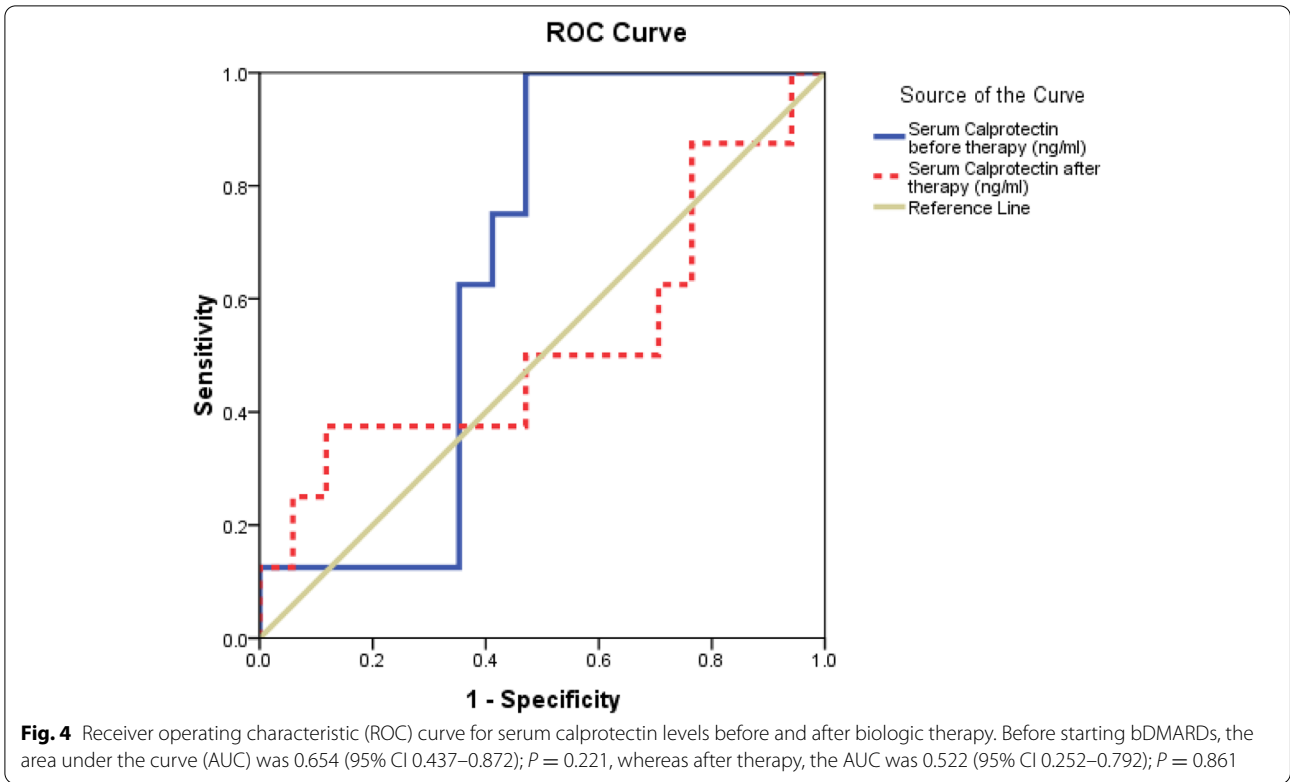
Additional ROC curve was designed to compare the diagnostic accuracy of serum calprotectin, CRP and ESR for discrimination of patients with high and moderate disease activity (Fig. 5). The ROC analysis showed that at a cutoff point of 397.05 ng/ml, calprotectin showed a maximum AUC of 0.608 (95% CI 0.372–0.845);  $P = 0.401$ , whereas CRP at a cutoff point of 60 mg/l showed an AUC = 0.704 (95% CI 0.457–0.952);  $P = 0.114$ . Besides, ESR at a cutoff point of 67.5 mm/h had an AUC = 0.579 (95% CI 0.336–0.823);  $P = 0.540$ .

Three months after receiving bDMARDs, 3 EULAR response phenotypes were obtained in the included RA patients; 1 was good responder (4%), 18 were moderate responders (72%) and 6 were non-responders (24%). The median serum calprotectin level in the good responder was 140.55 ng/ml, in the moderate responders 136.80 ng/ml and in the non-responders 96.18 ng/ml. No statistically significant association was found between serum calprotectin level and response to biological therapy. Of note, patients that developed a moderate response to biologic therapy were the only group to show a significant reduction in their serum calprotectin levels after receipt of biologics. Results are presented in Table 3.

### Discussion

The birth of new era of therapeutics in RA is one of the foremost historic alterations in the future of patients with established RA. Though the list of bDMARDs is continually escalating, no scientifically based approach is currently available for selecting which drug a patient should receive [25]. Therefore, several studies have been undertaken to identify consistent biomarkers, that can be used to foretell treatment outcome [26]. Nowadays, serum calprotectin has acquired endorsement in this aspect. However, there is no consensus in the literature in terms of the correlation between circulating calprotectin levels and response to bDMARDs. For that reason, we carried out this study to investigate the prognostic value of serum calprotectin for clinical response to bDMARDs in patients with RA.

In this 1-year, prospective, cohort study of 25 RA patients, the baseline serum calprotectin levels were



**Table 3** Association between serum calprotectin and response to biologic therapy

	Non-responders (n = 6)	Moderate responders (n = 18)	Good responder (n = 1)	Test of significance
Serum calprotectin before treatment (ng/ml)				
Median (range)	388.35 (60.0–486.0)	415.65 (130.8–908.2)	488.7 (488.7–488.7)	$P = 0.526^*$
Serum calprotectin after treatment (ng/ml)				
Median (range)	96.18 (39.9–919.05)	136.80 (45.45–390.20)	140.55 (140.55–140.55)	$P = 0.746^*$
	$z = 0.734$ $P = 0.463$	$z = 3.72$ $P < 0.001^{**}$	NA (Only one case)	
% of reduction	37.5%	68.7%	71.2%	

Abbreviations: NA not applicable, n number

\*\*  $P \leq 0.05$ ; statistically significant

\* Calculated using Kruskal–Wallis test

significantly higher in RA patients [404.1 (60.0–908.2 ng/ml)] as compared to the healthy subjects [101.45 (0.0–183.7 ng/ml)];  $P < 0.001$ . This result is analogous to the findings of an earlier study [27]. It is proposed that during inflammatory response, calprotectin which is a key leucocyte-related cytosolic protein, is secreted by the primed leucocytes at the site of the inflamed joint, so it is a definite biomarker of joint inflammation [28].

Interestingly, a noteworthy reduction in serum calprotectin level ( $P < 0.001$ ) was perceived among the engaged RA cohort 3 months after commencement of biologic therapy. In line with our finding, Choi et al. 2014 [29] and Yunchun et al. 2018 [30] described that during effective treatment with biologic drugs of different categories, serum levels of calprotectin were diminished. Additionally, they noticed that responders to biologics had a major reduction in calprotectin levels 4 weeks after receipt of treatment, while non-responders did not express this effect.

Another crucial objective of the present study was to investigate a likely correlation between serum calprotectin levels and DAS28 both at baseline and 3 months after initiating bDMARDs. Definitely, no relationship was detected between both parameters (Table 2). Concomitant with our result, Smith et al. [31] found no statistically significant association between serum calprotectin levels and DAS28 at baseline or during follow-up. In contrast, Aghdashi et al. [32] from a cross-sectional study and Wang et al. [33] from a retrospective study found a significant correlation between serum calprotectin levels and DAS28 among their study cohort ( $P = 0.02$  and  $P < 0.01$ , respectively). Discrepancy of results could be attributed to different study designs from the existing one.

In an attempt to compare the diagnostic accuracy of serum calprotectin, CRP and ESR for discriminating patients with high and moderate disease activity, we plotted another ROC curve (Fig. 5). Unfortunately,

calprotectin and ESR showed poor discrimination (AUC = 0.608 and 0.579, respectively), whereas CRP showed an AUC = 0.704, indicating acceptable performance.

In the entire RA cohort, different response patterns to biologic therapy were observed where 4% demonstrated good response, 72% moderate response and 24% did not respond to biologic therapy. In our study, we targeted to specify whether serum calprotectin can predict response to bDMARDs or not. In an attempt to establish such a likely association, Kruskal–Wallis test was done. Unexpectedly, no significant correlation was detected neither before ( $P = 0.526$ ) nor after receipt of bDMARDs ( $P = 0.746$ ) in our 3 identified EULAR response phenotypes. A similar conclusion was also drawn by Smith and his co-investigators [31], where no clue of association between calprotectin concentration and EULAR response to etanercept was detected (non-responders *versus* moderate responders,  $P = 0.957$ ; and non-responders *versus* good responders,  $P = 0.316$ ). Moreover, Tweehuysen et al. concluded that no supplementary prognostic value of serum calprotectin was proposed for treatment response to adalimumab or etanercept in their group of RA patients [34].

In contrast to the present data, an earlier study by Choi et al. confirmed that serum calprotectin levels can powerfully foresee the response to biological therapy in RA patients [35]. Likewise, Nair and his co-workers emphasized that by means of circulating calprotectin levels coupled with clinical predictors, it is possible to tailor treatment regimens for RA patients initiating biologic therapy which can subsequently amplify the cost-benefit [36].

Indeed, our study has some limitations that worth-mentioning. First, given the high cost of biological therapy, our study included a relatively small sample size. Second, no follow-up samples were collected from our cohort, so we were unable to detect changes of serum calprotectin levels over time. Finally, the results of this

study reflect a single-center experience, which may interfere with the globalization of the current findings.

## Conclusions

Overall, our study disclosed that serum calprotectin level was not valid in differentiating RA cases with moderate disease activity from cases with high disease activity as there was no significant correlation between serum calprotectin level and DAS28 score. More importantly, baseline serum calprotectin level had no significant association with response to biological therapy. Therefore, serum calprotectin could not be used as a predictor for clinical response to biological therapy in patients with RA. Hereafter, further studies including larger cohort of RA patients should be considered to validate the findings of the present work.

## Abbreviations

RA: Rheumatoid arthritis; bDMARDs: Biologic disease-modifying anti-rheumatic drugs; DAS28: 28 Joint Count Disease Activity Score; EULAR: European League Against Rheumatism; ROC curve: Receiver operating characteristic curve.

## Acknowledgements

To all the patients and control subjects who participated in the current study.

## Authors' contributions

RA (the corresponding author) proposed the point of research and was involved in writing the manuscript. AF extracted the relevant data from the patients and control subjects and performed the laboratory investigations mainly serum calprotectin evaluation. EH was involved in assessing the patients and participated in analyzing the data. TO participated in data extraction and analysis. All authors have read and approved the manuscript.

## Funding

The study had no funding from any resource.

## Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

## Declarations

### Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study design was approved by the local institutional review board (IRB) of the Faculty of Medicine, Mansoura University, Egypt (Approval No. MS. 18.07.207). A written informed consent was obtained from all participants prior to their enrollment. Confidentiality and personal privacy were respected in all levels of the study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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Received: 19 August 2021 Accepted: 25 October 2021  
Published online: 07 December 2021

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