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RESEARCH

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Role of serum survivin as a predictor of response to biological treatment in rheumatoid arthritis patients

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Abstract

Background Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disorder characterised by synovial hypertrophy, proliferation, and pannus formation encroaching on articular structures resulting in uncontrolled spread of joint destruction. Survivin is an anti-apoptotic protein that plays an important role in tissue growth and tumour development. The objective of this research is to study the role of Survivin as a predictor of treatment response to anti-tumor necrosis factor (anti-TNF) in RA patients who had failure of conventional disease modifying anti rheumatic drugs (DMARDs) treatment.

Results All patients had active RA evaluated with DAS 28 activity score: 73.3% of them had high disease activity, while 22.7% were in moderate activity. Serum survivin level ranged from 725 pg/ml to 2750 pg/ml. Its level was significantly higher in patients than in controls with a p value of < 0.001. After receiving anti-TNF treatment for 3 months, serum survivin level was reassessed, and it ranged from 525 pg/ml to 2100 pg/ml. There was a significant decreased in the biomarker serum level after receiving the treatment when compared to its level before starting treatment.

Conclusion Our results showed that the assessment of serum survivin may be a useful diagnostic tool for detection of RA patients also it has a valuable predictive value in assessment of responce to biologic treatments given to the patients. This conclusion was reached after detection of high survivin levels in the sera of RA with high disease activity and reduced functional outcomes. Moreover, the biomarker has a good prognostic value in detection of response to biologic treatment indicated by the reduction of serum level after receiving the treatment and improvement of clinical disease activity.

Keywords Rheumatoid arthritis, Survivin, Apoptosis, Disease activity

Background

Rheumatoid arthritis (RA) is an immune-mediated inflammatory disorder that affects about 1% of the population [1] with a pronounced female predilection [2].

The immune pathogenesis of the autoimmune disturbance and the exact nature of the causative agent are not fully revealed. Environmental, genetic, and immunologic factors all play a role in the evolvement of the disease. Pathologically, the synovium shows proliferation and pannus formation with infiltration of activated immune cells as T and B lymphocyte, macrophages with abundant inflammatory mediators, leading to tissue destruction and joint damage. The lymphocytes showing auto-reactive activity perform a significant and essential key role in the development and progression of the disease. Amplified cell proliferation and infiltration together with impairment of cell death all help in the development and progression of RA [3].

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The inhibitors of apoptosis proteins superfamily (IAPs) are a group of proteins that are involved in the formation, growth, and progress of malignant tissues. It may also have a role in RA disease's pathogenesis by contributing to the unusual survival auto-reactive cells [4]. The IAPs are proteins known to inhibit and suppress cell death, specifically in different types of malignancies [5]. Survivin, is expressed in almost all kinds of malignant cells in high amounts, while it has a little expression in the normal cells, where it has a role in many cellular processes for example in regulation of cell division and in apoptosis [6].

Survivin is identified to have many cellular functions, including inhibition of apoptosis in both the cytoplasm and the mitochondria of the cell by inhibiting activation of caspases, and regulation of the cell cycle progression in the nucleus by helping to form a structure called chromosomal passenger complex [7]. Thymocytes, bone marrow hematopoietic progenitors and stem cells, vascular endothelial cells, and colonic epithelial cells all consistently express survivin, which is essential for cellular renewal and differentiation in healthy tissues [8]. Survivin also contributes to different immune responses. In the innate immunity, it moderates the apoptotic threshold of neutrophils where its expression propagates during inflammatory reactions in these cells [9]. On the other hand during the adaptive immune response, survivin helps intensely in the T cell progression, maturation, activation, and homeostasis which is achieved by its proliferation–apoptosis coupling property. Throughout T-cell maturation stages in the thymus, survivin also has an essential role in transition from double negative (CD4–CD8–) to double positive (CD4 + CD8 +) thymocytes [10]. As a consequence of naive T cells activation in lymphoid organs, the expression of survivin is selectively amplified which shows how important its presence in the immune responses initiation [11].

Serum survivin was proposed as a marker of disease activity in RA. It was shown to be over-expressed during the preclinical stage of RA, and along with antibodies to citrullinated peptides, and hence may act as a predictor for the development of RA several years ahead of the onset of clinical symptoms [12]. Also, there is an association between survivin and the pattern of regulatory cytokines (interleukin (IL) 1, 2, 9, and 12, also the granulocyte–macrophage colony-stimulating factor) controlling the development of pathological T helper (Th) 1 and Th17 lymphocytes during this preclinical stage [13].

Obvious individual heterogeneity concerning specific load of genetic and environmental factors, together with the tendency for the production of autoantibody, also the cellular and cytokine pool, all added up to genetic expression profiles of the inflamed synovia strongly suggests that a more tailored choice of anti-rheumatic treatment would produce significantly enhance the results. The demand for biomarkers and algorithms that are capable of predicting treatment response allowing the reduction of excessive expenses on the costs of inefficient medication has been recently given a high priority [13]. The aim of this study was to detect the role of serum survivin as a clinical predictor of anti-TNF treatment response in RA patients who failed conventional DMARDs treatment.

Patients and methods

This study was conducted on 30 patients with active rheumatoid arthritis who were recruited from the hospitals' department. Patients fulfilled the American College of Rheumatology/European league against rheumatism (ACR/EULAR) for rheumatoid arthritis classification criteria [14]. Inclusion criteria : Adult patients not responding to initial treatment with conventional DMARDS, and are going to shift to biological treatment with anti-TNF. Exclusion criteria were conditions that would interfere with level of Survivin as uncontrolled diabetes, patients with cancer or those who received chemotherapy, patients with active infections or sepsis, previous untreated tuberculosis and chronic viral infections as HIV, hepatitis B and C. The study also included 20 healthy subjects matched for age and sex who served as control group. Research ethics committee of the university approved the study. All participants signed an informed consent before participating in the study.

Clinical and laboratory assessment

Full medical history taking followed by thorough clinical examination were done for all patients. The disease activity score (DAS28) was calculated and was graded as remission (DAS28 < 2.6), low (DAS28 > 2.6–3.2), moderate (DAS28 > 3.2–5.1) and high (DAS28 > 5.1) activity [15]. Calculation of patients' DAS 28 at baseline before anti-TNF treatment and at 3 months after anti-TNF treatment was performed together with assessment of functional impairment using health assessment questionnaire (HAQ) [16]. Serum C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) were assessed at baseline before anti-TNF treatment and repeated after 3 months of treatment.

Determination of serum survivin levels

A venous blood samples of 3 cm was collected from antecubital vein of all participants, sera were separated and preserved frozen at the temperature of – 70 °C until it was analyzed. Measurement was performed by using the enzyme-linked immunosorbent assay (ELISA) human kit from (SinoGeneClon Biotech co., Ltd. Hang

Zhou, China) and was based on the biotin double antibody sandwich technology. The kit was for the assessment of the quantitative level of Human Survivin in the sample. It adopted purified Survivin antibody to coat microtiter plate, making solid-phase antibody, with added Survivin to wells, Combine Survivin antibody with labeled HRP (horseradish peroxidase) to form antibody-antigen-enzyme-antibody complex, after washing completely, TMB (Tetramethylbenzidine) substrate solution had been added, TMB substrate became blue color at HRP enzyme-catalyzed, reaction was terminated by the addition of a stop solution and the color change had been measured at a wavelength of 450 nm. The concentration of Survivin in the samples was then determined by comparing the O.D. of the samples to the standard curve.

Statistical analyses

Data were collected and revised for completeness and consistency. The collected data were coded, tabulated, introduced to a personal computer, and then analyzed using the SPSS program (Statistical Package for Social Sciences) for Windows Version 25.

- Descriptive statistics:

  Qualitative data were presented using the frequency and its related percentage.
  Quantitative data were presented using mean ± SD and range.
- Inferential statistics:
  An independent sample *t* test was used to compare between two groups with quantitative data and parametric distribution.
  Paired sample *t* test was used to compare differences between normally distributed paired measurements.
  A two-sided level of significance was set at a *p* value of ≤ 0.05.

Results

Demographic data

This study included 30 RA patients who joined the study after failure of conventional DMARDs treatment and they were starting to receive anti-TNF treatment. The mean age of the patients was 37.7 ± 9.4 years and they were 25 females and 5 males (F: M 5:1) with a mean disease duration of 6.6 ± 4.5 years and range 1–16 years. The 20 healthy controls were matched for age (35.4 ± 8.2 years) and sex (16 females and 4 males; F: M 4:1). Descriptive data of the studied cases at the beginning of the study is shown in Table 1.

Table 1 Descriptive and clinical data of the studied cases before receiving biologic treatment

Variable	Mean ± SD	Range
Duration of morning stiffness	49.5 ± 17.2 min	30–90
HAQ score	1.6 ± 0.46	0.8–2.3
Number of tender joints	8.4 ± 3.3	4–17
Number of swollen joints	7.1 ± 2.4	3–12
ESR	36.4 ± 12.9	20–70
CRP	9.9 ± 6.2	3.6–23.1
DAS 28	5.6 ± 0.59	4.4–6.9

CRP C-reactive protein, *DAS* Disease activity score, *ESR* Erythrocyte sedimentation rate, *HAQ* Health assessment questionnaire

Table 2 Comparison between cases and controls regarding survivin test results

	Cases (no. = 30) Mean ± SD	Controls (no. = 20)	*P* value
Survivin	1860.7 ± 501.2	843.5 ± 381.1	≤ 0.001* S

An independent sample *t* test was used. Significant at $P \leq 0.05$

We found that 66.7% of our patients (20) were rheumatoid factor positive and also 86.7% of them (26) were anti-CCP positive.

Before receiving treatment, 73.3% of the patients (22) were in high disease activity while 22.7% of them were in moderate activity (8 patients) according to DAS28 activity score.

Serum survivin level was measured at the beginning of the study for all patients before they started receiving their biologic treatment in form of anti-TNF treatments. We found that the survivin serum level ranged from 725 pg/ml to 2750 pg/ml with a mean 1860.7 and standard deviation of ± 501.2. Also the serum level of survivin was measured in the 20 apparently healthy controls, were it ranged from 540 pg/ml to 1650 pg/ml, with a mean 843.5 and standard deviation of ± 381.1. The survivin level was significantly higher in patients than in controls with a *P* value of < 0.001 (Table 2, Fig. 1).

A cut-off value for Survivin at 1125 pg/ml was found to differentiate RA cases from controls significantly (AUC 0.94; $p < 0.001$) with a sensitivity of 93.3%, specificity of 85% and accuracy of 94%. This is shown in Fig. 2.

Ten of our patients (33.3%) received Enbrel (Etanercept) 50 mg solution for subcutaneous injection in pre-filled syringe once every week (5 of them were on combined therapy with Methotrexate (MTX) 12.5 mg subcutaneous injection weekly, 4 of them were on combined therapy with Leflunomide 20 mg once daily, and one patient was only on biologic treatment). 10 of our patients (33.3%)

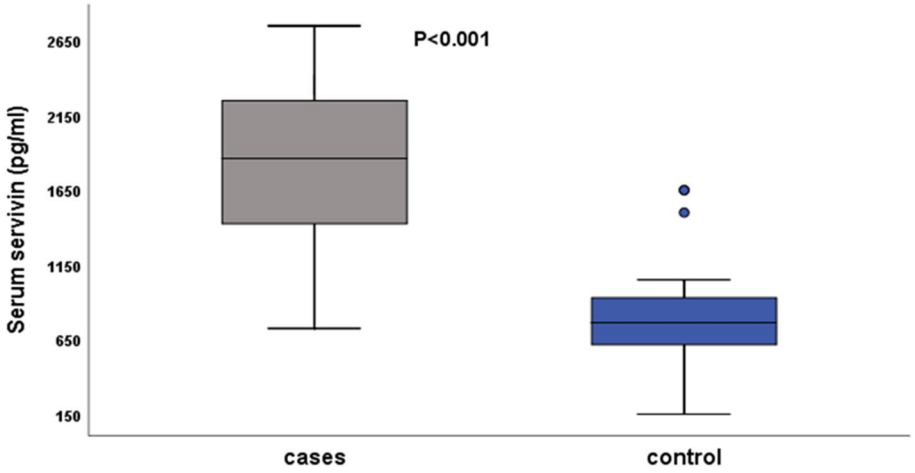

Fig. 1 Serum survivin level (pg/ml) in rheumatoid arthritis patients and control

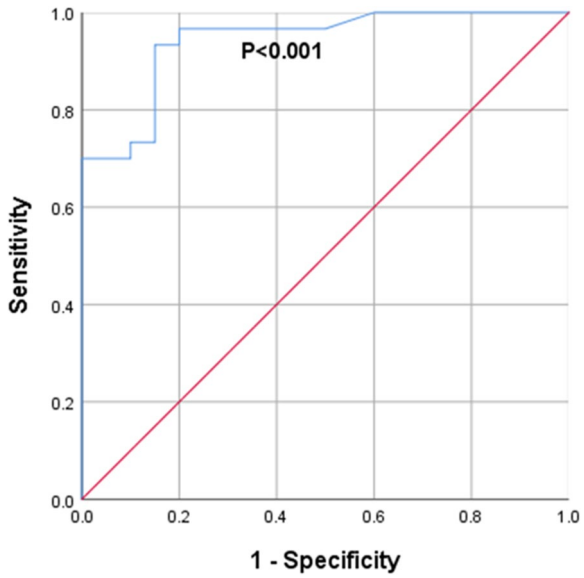

Fig. 2 Receiver operating characteristic (ROC) curve for serum survivin level to differentiate between cases and control

received Amgevita 40 mg solution for subcutaneous injection in pre-filled syringe where each single dose pre-filled syringe contains 40 mg of adalimumab given every 2 weeks (7 of them were on combined therapy with MTX 12.5 mg subcutaneous injection weekly and 3 of them were on combined therapy with Leflunomide 20 mg once daily). The last 10 patients (33.3%) received Simponi 50 mg given as subcutaneous injection once every month (5 of them were on combined therapy with MTX 12.5 mg subcutaneous injection weekly, 3 of them were on combined therapy with Leflunomide 20 mg once daily, and 2 patients were only on biologic treatment). Assessment of disease activity was done again using DAS28 activity score. Out of 30 patients, only 1 was still in high activity (3.3%), 19 in moderate activity (63.3%), 6 in low activity (20%), and 4 (13.3%) entered in a state of remission.

Table 3 Descriptive and clinical data of the studied cases after 3 months of anti-TNF treatment and its comparison to clinical data before receiving biologic treatment

Variable	Mean ± SD	Range	Sign. to pre-treatment data
HAQ score	1.1 ± 0.42	0.8–2.3	$P < 0.0001$
Number of tender joints	3 ± 1.8	0–7	$P < 0.0001$
Number of swollen joints	2.8 ± 1.3	1–5	$P < 0.0001$
ESR	19.3 ± 12.1	5–40	$P < 0.0001$
CRP	5.5 ± 3.5	3.6–23.1	$P = 0.0013$
DAS 28	3.7 ± 0.84	0.6–18	$P < 0.0001$

ESR Erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS* Disease activity score, *HAQ* Health assessment questionnaire

Significant at $P \leq 0.05$

Descriptive data of the studied cases after receiving anti-TNF for 3 months shown in Table 3. There was a highly significant difference in clinical data including HAQ score, number of tender and swollen joints, ESR, CRP, and DAS 28 score when compared to those collected before the start of treatment.

Serum survivin level was measured for all patients after receiving anti-TNF treatment, it ranged from 525 pg/ml to 2100 pg/ml with a mean 1441.3 and standard deviation of ± 422.1. Survivin level was significantly decreased in patients after receiving the treatment when compared to the serum level before starting the treatment course as shown in Table 4, Fig. 3.

The correlation between the serum level of survivin level and the degree of activity using DAS 28 score was done before and after receiving treatment. There was a

Table 4 Comparison between cases before and after treatment regarding serum survivin level

	M ± SD	*P* value
Before TTT	1860.7 ± 501.2	< 0.001* S
After TTT	1441.3 ± 422.1	

Paired sample *t* test was used, significant at $P \leq 0.05$

Table 5 Correlation between serum survivin levels and DAS28 before and after TTT

Before treatment	Survivin level in RA patients ($n = 30$)		After treatment	Survivin level in RA patients ($n = 30$)	
	r	*P* value		*r*	*P* value
DAS28	0.05	0.79	DAS28	0.47	**0.007***

DAS Disease activity score, Pearson Correlation test was used. Bold values are significant at $P \leq 0.05$

significant correlation between the biomarkers level and the degree of activity after the treatment as shown in Table 5, Fig. 4.

Discussion

The pathogenesis of RA is a multifactorial algorism being a combination of genetic polymorphisms, immune dysfunction and apoptosis [17]. The inhibitors of apoptosis proteins family (IAPs) are group of proteins that are involved in the development, progression, and severity of malignant disorders and might also participate in abnormal survival of autoreactive lymphocytes involved in the pathogenesis of RA [4]. Survivin is a multifunctional protein that consists of 142 amino acids and present in cytoplasm, nucleus, and also in mitochondria and the smallest member of this family [18]. Survivin is considered one of the strongest parameter of apoptosis among the inhibitors of apoptosis proteins family [17].

In RA, the enhanced proliferation rate of inflammatory cells and fibroblast-like synoviocytes (FLS) and the ability of these cells to be resistant to apoptosis may be caused by the overproduction of survivin [19]. Apoptosis is an important mechanism for maintenance of tolerance and for the eliminating the self-reactive lymphocytes from the immune repertoire. Survivin is essential for prevention of apoptosis and functioning of autoreactive lymphocytes that are involved in multiple rheumatic illnesses diseases. Uncontrolled inflammation encourages the formation of autoantibodies, facilitates antigen presentation, and maintains autoreactive cells persistence [20]. Survivin dysfunction or aberrant expression derive autoreactive lymphocytes which enforces RA and other autoimmune conditions such as Lichen planus, systemic lupus erythematosus (SLE), myasthenia gravis, multiple sclerosis, systemic sclerosis (SSC), psoriasis, and inflammatory bowel disease [21]. Serum survivin is over-expressed in the preclinical phase of RA, and, together with antibodies to citrullinated peptides, may act as a predictive for development of RA several years ahead of clinical symptoms [22]. The deficient apoptosis that occurs in the inflamed synovial tissues results in cartilage and bone damage. Also the resistance to apoptosis is an important parameter that may affect the effectiveness of the patient's treatment [23]. Histological examination of synovial tissues of active RA patients had proved its expression

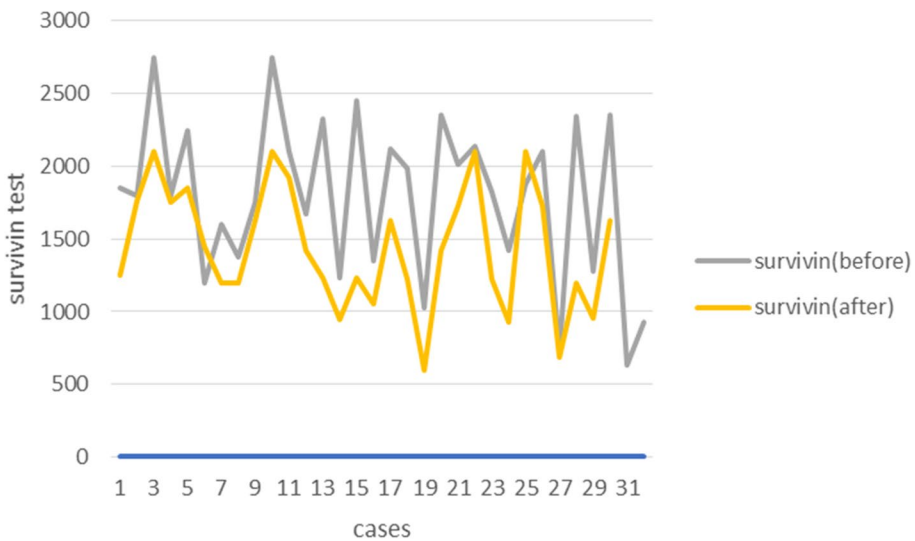

Fig. 3 Serum survivin level (pg/ml) before and after TTT in the studied cases

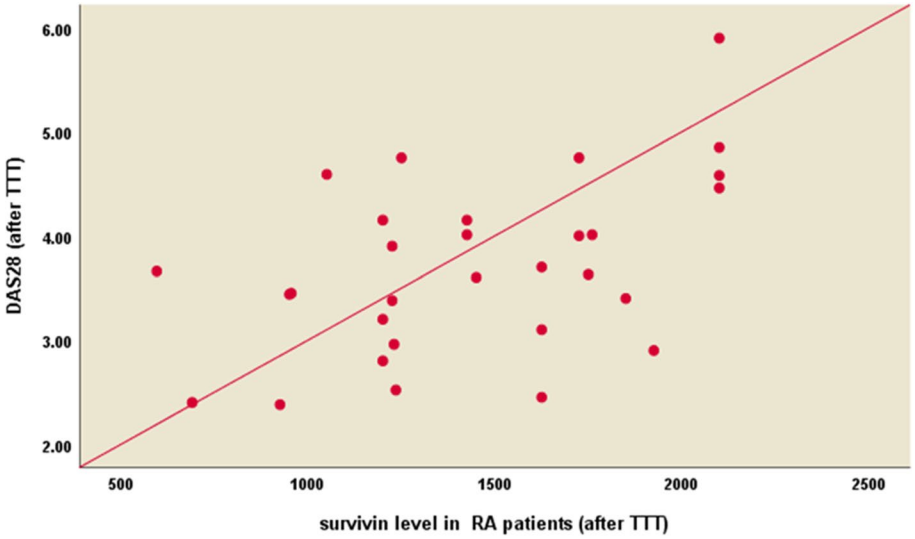

Fig. 4 Scatter plot between serum survivin level and DAS28 after TTT

[24] and improves the early diagnosis of RA among patients with undifferentiated arthralgia [25].

In our research we found that serum survivin level were significantly higher in RA patients than in apparently healthy controls. These results were obtained from patients before receiving biologic treatment and they were showing failure of conventional DMARDs treatment. Most of the patient (66.7%) were in high disease activity while 22.7% were in moderate activity according to DAS 28 score. This could explain the high survivin level found in all patients, and supports the fact that survivin helps in disease progression and worsens joint inflammation and cartilage destruction.

The cut-off value on ROC curve that differentiated active cases from controls was 1125 pg/ml with a sensitivity of 93.3%, specificity of 85% and accuracy of 94%, which allowed to consistently distinguish RA patients from controls. This could lead us to the observation that the biomarker could be an easy and reliable marker for diagnosis of RA and for the prediction of disease activity as well. Our results were consistent with Baraka et al., who concluded from his study the presence of an elevated serum and synovial fluid level of survivin in RA patients with a significant difference from controls.

The elevated DAS28 score found in our patients together with affection of their quality of life where their HAQ score mean was 1.6 and SD ± 0.46, although all the patients were on combined therapy of conventional DMARDs, led to the decision of shifting their therapeutic plan to anti-TNF treatment. Serum survivin level was reassessed after completion of 3 months of treatment. Only 1 patient was still experiencing high disease activity although there was a decrease in her activity score. All the rest of 29 patients showed a decrease in their degree of disease activity when reassessed with DAS28 activity score showing fair response to treatment. Also there was an evident improvement in their functional assessment and HAQ score. The clinical and laboratory improvement was reflected on the survivin serum level. The significant reduction in the biomarker level when compared to that measured before the start of anti-TNF treatment (mean 1860.7, SD ± 501.2) to 3 months after treatment (mean 1441.3, SD ± 422.1) may be a good reflection of the control on the inflammatory process that occurred within the joints. The significant correlation between patients' DAS28 score and the serum level of survivin after receiving the medical treatment shows the importance of the biomarker in detecting the improvement that was observed clinically and serologically. The changes that happened in the biomarker level was linked to the control of the inflammatory process that occurred in sera and consequently in synovia of patients. Survivin is expressed in high amounts by the synovial tissue of RA patients especially the vascular endothelial cells and intimal lining layer synoviocytes. Its presence in this intimal lining layer approves the local production of survivin in the joints of RA patients [26]. Due to their uncontrolled proliferation, invasive behavior, synovial tissue proliferation, and pannus formation, FLS, as effector cells, contribute significantly to joint destruction in RA [27]. In 2010, Smith et al., studied synovial biopsy specimens obtained at arthroscopy from 16 RA patients before and after treatment with a DMARDs, were they detected and quantified apoptosis regulating proteins including Survivin FLIP protein, Bcl-2 and X-linked inhibitor of apoptosis protein (XIAP) and also the presence of activated caspases,

all using immunohistochemistry. They concluded that apoptotic pathways are defective in RA synovial tissue from patients with active disease, with abundant expression of inhibitors of the apoptosis in RA synovial tissue. Also, they concluded that DMARD treatment can modulate apoptosis in the RA synovial membrane, successfully reducing the expression of these inhibitors in synovial tissue and reduce the chronic inflammatory synovial infiltrate through activation of apoptotic pathways [28]. Survivin was proved to be a reliable marker of diagnosis of RA with good prognostic features as a detector for the response to treatment. It can take a vital role as a diagnostic and prognostic biomarker in RA and many other rheumatological diseases.

Limitations of the study

Conduction of further studies on survivin antagonist to evaluate their effect on ameliorating RA disease progression is recommended, also further assessment of its role in longer follow-up durations of patients, also its relation to RF, anti-CCP, and extra articular manifestations is recommended.

Conclusion

Our results indicated that measurement of serum survivin may be useful diagnostic tool for RA patients. This conclusion was reached after detection of high levels of survivin in the sera of patients with RA and its association with high disease activity and poor functional outcomes. Also it may be a good prognostic factor as indicated by the reduction of serum level after receiving medical treatment and the improvement of clinical disease activity. Conduction of studies on survivin antagonist to evaluate their effect on ameliorating RA disease progression is recommended.

Abbreviations

ACR	The American College of Rheumatology
Anti-TNF	Anti-tumor necrosis factors
Anti-CCP	Anti-cyclic citrullinated peptide
BCL-2	B cell lymphoma-2
IAPs	Inhibitors of apoptosis proteins
CRP	C-reactive protein
DAS28	Disease activity score
DMARD	Disease modifying anti-rheumatic drugs
ESR	Erythrocyte sedimentation rate
ELISA	Enzyme-linked immunosorbent assay
EULAR	European league against rheumatism
FLIP	FLICE-inhibitory protein
FLS	Fibroblast-like synoviocytes
HAQ	Health Assessment Questionnaire
HIV	Human immunodeficiency virus
HRP	Horseradish peroxidase
IL	Interleukin
MTX	Methotrexate
NSJ	Number of swollen joints
NTJ	Number of tender joints
RA	Rheumatoid arthritis
RF	Rheumatoid factor
ROC	Receiver operating characteristic
SD	Standard deviation
SLE	Systemic lupus erythematosus
SSC	Systemic sclerosis
Th	T helper
TMB	Tetramethylbenzidine
TTT	Treatment
XIAP	X-linked inhibitor of apoptosis protein

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Authors' contributions

All authors have contributed to designing the study, recruitment of patients, collecting and analyzing, interpretation of data, and preparing and revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generalized and/or analyzed during the current study are available from the authors upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethical Approval for the study was obtained from Ain Shams University, Faculty of Medicine Research Ethics Committee (REC) FWA 000017585. FMASU R 212/2022. A written informed consent was obtained from all participants to contribute in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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