HMGB1 AND ANTI-HMGB1 ANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS AND OTHER RHEUMATIC DISEASES

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The high-mobility group protein B1 (HMGB1) belongs to alarmins — a group of molecules involved in inflammatory responses. HMGB1 is actively studied in the context of certain rheumatic diseases (RDs), including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA), but the accumulated knowledge remains insufficient. HMGB1 can also act as an antigen, yet the level of anti-HMGB1 antibodies is poorly understood in RDs. The aim of this study was to investigate the concentrations of HMGB1 and anti-HMGB1 antibodies in four RDs. Using enzyme-linked immunosorbent assay (ELISA), plasma samples from patients with RA (n = 60), AS (n = 60), SLE (n = 24), PsA (n = 30), and healthy donors (HD) (n = 60) were analyzed. After adjustment for age and disease duration, it was shown that the concentration of HMGB1 was significantly increased in SLE ($p < 0.01$), RA ($p < 0.01$), and AS ($p = 0.017$), while a statistically non-significant increase in HMGB1 was observed in PsA ($p = 0.07$) compared to HD. Among the four diseases, the highest level of HMGB1 was found in SLE ($p < 0.01$). The concentration of anti-HMGB1 antibodies was also elevated in SLE ($p < 0.01$), RA ($p = 0.026$), and AS ($p = 0.028$). Using correlation and regression analysis, a strong direct association was established between the level of HMGB1 and the DAS28 index in RA ($p < 0.01$ for both analyses). The results of the study describe characteristic changes in HMGB1 and anti-HMGB1 antibody levels in RDs and indicate the involvement of HMGB1 in the pathogenesis of these diseases.

Keywords: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, systemic lupus erythematosus, HMGB1, anti-HMGB1 antibodies

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Compliance with ethical standards: The study was approved by the Ethics Committee of the Institute of Chemical Biology and Fundamental Medicine, Siberian Branch of the Russian Academy of Sciences (Protocol No. 3 dated June 19, 2023) and was conducted in accordance with the principles of the Declaration of Helsinki. All study participants provided written informed consent.

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HMGB1 И АНТИ-HMGB1 АНТИТЕЛА ПРИ СИСТЕМНОЙ КРАСНОЙ ВОЛЧАНКЕ И ДРУГИХ РЕВМАТИЧЕСКИХ ЗАБОЛЕВАНИЯХ

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Белок B1 группы высокой подвижности (англ. high-mobility group protein B1, HMGB1) относится к аларминам — группе молекул, участвующих в воспалительных реакциях. HMGB1 активно изучают в контексте некоторых ревматических заболеваний (РЗ), включая системную красную волчанку (СКВ), ревматоидный артрит (РА), анкилозирующий спондилит (АС) и псориатический артрит (ПсА), однако накопленных знаний недостаточно. HMGB1 может также выступать антигеном, но уровень анти-HMGB1 антител плохо изучен при РЗ. Целью работы было изучить концентрации HMGB1 и анти-HMGB1 антител при четырех РЗ. Методом иммуноферментного анализа проанализированы образцы плазмы пациентов с РА (n = 60), АС (n = 60), СКВ (n = 24), ПсА (n = 30) и здоровых доноров (ЗД) (n = 60). После поправки на возраст и длительность заболевания показано, что концентрация HMGB1 достоверно повышалась при СКВ ($p < 0,01$), РА ($p < 0,01$) и АС ($p = 0,017$), а при ПсА выявлено статистически незначимое повышение HMGB1 ($p = 0,07$) по сравнению с ЗД. Среди четырех заболеваний наибольший уровень HMGB1 выявлен при СКВ ($p < 0,01$). Концентрация анти-HMGB1 антител оказалась также выше при СКВ ($p < 0,01$), РА ($p = 0,026$) и АС ($p = 0,028$). Методами корреляционного и регрессионного анализа установлена выраженная прямая ассоциация между уровнем HMGB1 и индексом DAS28 при РА ($p < 0,01$ для обоих анализов). Результаты работы описывают характерные изменения уровня HMGB1 и анти-HMGB1 антител при РЗ и указывают на вовлеченность HMGB1 в патогенез этих заболеваний.

Ключевые слова: ревматоидный артрит, анкилозирующий спондилит, псориатический артрит, системная красная волчанка, HMGB1, анти-HMGB1 антитела

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Rheumatic diseases (RD) are an important medical and social problem due to their prevalence, impact on quality of life, and high economic costs of treatment. Systemic lupus erythematosus (SLE) is one of the most common autoimmune diseases, predominantly affecting young women aged 15–45 years, thereby indirectly worsening the demographic situation in addition to its direct effect on patients' lives. The global prevalence of SLE varies from 3 to 517 cases per 100,000 people; in recent decades, the incidence has been growing [1]. Another common RD is rheumatoid arthritis (RA): approximately 200 cases per 100,000 persons, and the incidence is steadily increasing and is projected to almost double by 2050 [2]. Ankylosing spondylitis (AS) occurs in 9–30 people per 100,000 persons [3]. Unlike most RDs, AS affects men more often than women (the approximate ratio is 2–3 to 1), typically — men of working age; 92% of patients experience the first symptoms of the disease before the age of 45 [4]. Compared to other diseases, psoriatic arthritis (PsA) has been studied much less, even though it is fairly common (more than 100 cases per 100,000 population) and significantly affects patients' quality of life [5]. Treatment of RDs increases the financial burden on the healthcare system each year [6]. The high prevalence and social significance of RDs necessitate the search for new biomarkers that would enable early diagnosis and timely therapy. In addition, a comparison of biomarkers among RDs can reveal the characteristic pathophysiological mechanisms of each RD and potential markers for differential diagnosis.

The pathogenesis of RDs is associated with the activation of inflammatory pathways of both innate and acquired immunity. Damage-associated molecular patterns (DAMPs), also known as alarmins, greatly contribute to the development of inflammatory responses [7]. Alarmins of nuclear origin play an important role in the pathogenesis of RDs [8–10]. One of them is high-mobility group protein B1 (HMGB1), which consists of box A, considered anti-inflammatory, box B, exhibiting pro-inflammatory functions, and an acid tail limiting the activity of this protein within the nucleus [11]. HMGB1 acts as a chemoattractant, bringing immune cells to the lesion site. The protein acts synergistically with DNA, triggering a powerful proinflammatory response that enables autoimmunity, including in cases of RDs [12]. The changes in HMGB1 concentrations associated with SLE and RA have been well studied [12, 13], but there is relatively little information in the literature regarding such changes in AS and PsA. Moreover, both the relationship between HMGB1 level and disease manifestations and the comparison of these parameters across various RDs remain largely uninvestigated.

The pathogenesis of RDs involves not only innate, but also adaptive immunity. Autoantibodies, especially antinuclear antibodies, are considered biomarkers of SLE. Antibodies to cyclic citrullinated polypeptide (ACCP) and rheumatoid factor (RF) are often found in RA patients. Some of these autoantibodies are included in the criteria for diagnosis [14, 15]. HMGB1 is known to also induce production of antibodies that can participate in the pathogenetic processes of RDs [16, 17]. However, very few studies have focused on anti-HMGB1 antibodies in RD cases, even though this protein plays an active role in the inflammatory response and the development of autoimmune reactions.

This study aimed to analyze blood concentrations of HMGB1 and anti-HMGB1 antibodies in patients with SLE, RA, PsA, and AS, as well as in healthy donors (controls), and to assess the relationship between these markers and the clinical characteristics of the diseases.

METHODS

Patients and healthy donors

The study was conducted from July 2023 to July 2025 in two establishments: Institute of Chemical Biology and Fundamental Medicine, Siberian Branch of the Russian Academy of Sciences, Novosibirsk; Research Institute of Fundamental and Clinical Immunology, Siberian Branch of the Russian Academy of Sciences, Novosibirsk.

The study included 60 patients with rheumatoid arthritis (RA) diagnosed according to the 2010 ACR/EULAR criteria; 60 patients with ankylosing spondylitis (AS) or axial spondyloarthritis diagnosed according to the modified New York and ASAS criteria; 30 patients with psoriatic arthritis (PsA) diagnosed according to the CASPAR criteria; 24 patients with systemic lupus erythematosus (SLE) diagnosed according to the 2019 ACR/EULAR criteria; and 60 healthy controls without active somatic pathology. The diagnoses and medical histories were established and collected by qualified rheumatologists at the Research Institute of Fundamental and Clinical Immunology, where the participating patients donated blood samples. Healthy controls gave their blood for the study at the Institute of Chemical Biology and Fundamental Medicine. The indices used to evaluate the clinical condition of the patients were as follows: for RA — the DAS28 index; for AS — the ASDAS-CRP/ASDAS-ESR and BASDAI indices; for PsA — the DAPSA index; and for SLE — the SELENA-SLEDAI index.

To participate in the study, patients had to sign a voluntary informed consent form, be 18 years or older, have an established diagnosis of RA, PsA, SLE or AS. The exclusion criteria included the presence of other autoimmune diseases, a history of cancer, severe liver or kidney damage, acute inflammatory diseases within two weeks before blood sampling, surgical operations within the last two months, HIV infection, and pregnancy. Healthy donors had to sign an informed consent form, be over the age of 18, and not meet any of the exclusion criteria.

The blood samples were collected in vacuum tubes with K3EDTA (VACUETTE, Greiner Bio-One GmbH, Austria). Blood plasma was separated by centrifugation at 2000 × g for 30 minutes at 4 °C, then aliquoted and stored at –20 °C until analysis.

Determination of the concentration of HMGB1 and anti-HMGB1 antibodies

The concentration of HMGB1 was determined by enzyme immunoassay (ELISA) using the Human HMGB1 ELISA Kit (Cat. No.: E-EL-H1554, Elabscience, USA). The sensitivity of this kit was 18.75 pg/ml, the measuring range — 31.25–2000 pg/ml. The blood plasma was preliminarily diluted 10 times for analysis. The concentration of anti-HMGB1 antibodies was determined using the ELISA Kit for anti-HMGB1 antibody (Cat. No.: AEA399Hu, Cloud-Clone Corp., China). The sensitivity of this kit was 1.17 ng/ml, the measuring range — 3.12–200 ng/ml. Participants with concentrations below the sensitivity threshold were considered to have no anti-HMGB1 antibodies. The blood plasma used for anti-HMGB1 antibody analysis was diluted 1 : 100. Optical density was measured on a Multiskan™ FC Microplate Photometer (Thermo Fisher Scientific Inc., USA) at a wavelength of 450 nm according to the instructions of the manufacturer.

Table 1. Clinical and medical history data of the participants (patients with RDs and healthy individuals)

Parameter*	RA (*n* = 60) (1)	AS (*n* = 60) (2)	PsA (*n* = 30) (3)	SLE (*n* = 24) (4)	Healthy (*n* = 60) (5)	*p***
Sex (m/w), %	22/78	69/31	30/70	0/100	30/70	< 0.01
Age, years	52 (38; 61)	46 (38; 52)	44 (34; 56)	44 (31; 54)	45 (29; 51)	H.3.
Duration of the disease, years	9 (5; 17.5)	12 (7.8; 22.3)	12.5 (3; 21.3)	6 (3; 14)	–	2 vs. 4: < 0.01
BMI	26 (23; 29)	25.8 (21.5; 28.1)	25.9 (21.2; 30)	25.2 (21; 28)	23.5 (20.2; 26.3)	IS
ESR, mm/h	2.6 (0.8; 11.5)	2.8 (1.1; 6.2)	4.3 (2.4; 9.8)	2.2 (0.8; 8.9)	–	IS
CRP, mg/l	14.5 (6.8; 28)	10 (4; 18)	16 (10; 26)	15 (8.5; 38)	–	IS
Clinical index	DAS28: 3.4 (2.6; 4.6)	ASDAS-CRP: 1.7 (1.3; 2.5); ASDAS-ESR: 1.8 (1.31; 2.6); BASDAI: 1.9 (1.0; 3.2)	DAS28: 3.5 (1; 9.4); DAPSA: 14 (6; 22)	SELENA-SLEDAI: 4 (2; 8)	–	–

Note: * — the data are given as Me (Q_1; Q_3). ** — Yates-corrected chi-square test, or the Kruskal–Wallis test with Dunn's post-hoc test. BMI — body mass index, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, IS — insignificant

Statistical analysis

Statistical analysis and data visualization were performed using OriginPro 2021 and the Google Colab environment with Python 3.13.0, employing the NumPy (v2.3.3), SciPy (v1.16.2), and Matplotlib (v3.10.6) libraries. The type of distribution of data in individual samples was determined with the Shapiro–Wilk test. Since the data mostly did not distribute normally, the results are presented as a median (Q_1–Q_3). The values between the samples were compared using a rank ANCOVA followed by a post-hoc Dunn's test, with the covariates (age and duration of the disease) factored in. Categorical variables (frequency of occurrence of the trait) were evaluated using the chi-square test. The difference in the frequency of occurrence of the trait was estimated by calculating the odds ratio (OR). Spearman's rank correlation coefficient enabled the assessment of correlation. Multiple linear regression was used to evaluate the relationship between the dependent variable (DAS28) and the predictors. Before performing multiple regression, all data were normalized by logarithmization (log10).

RESULTS

Sample characteristics

A total of 234 people participated in the study: 60 patients with RA, 60 with AS, 30 with PsA, 24 with SLE, and 60 healthy individuals. Table 1 gives the clinical and medical history data of the participants. According to DAS28, most RA patients exhibited moderate disease activity. Eighty percent of them had a positive RF value, and 82% were found to have ACCP. Patients with AS mostly had low disease activity according to the ASDAS-CRP and ASDAS-ESR indices, but moderate activity according to the BASDAI index. Seventy-six percent of them carried the HLA-B27 allele. The majority of PsA patients had moderate disease activity according to the DAS28 and DAPSA indices. Among patients with SLE, more than half had low disease activity. The sex distribution of participants varied across disease subgroups, and patients with RA tended to be older, reflecting the typical age and sex characteristics of each disease. In addition, AS patients had a longer duration of the disease than SLE patients (Table 1).

All patients were undergoing therapy. In particular, 56% of patients with RA, 90% with AS, and 50% with PsA were taking biologic disease-modifying antirheumatic drugs (bDMARDs). Patients with SLE did not take bDMARDs. As for other drugs, 43% of patients with RA, 32% with AS, 40% with PsA, and 8% with SLE were taking methotrexate. For SLE, the most common drug was hydroxychloroquine (71%).

Concentration of HMGB1 and anti-HMGB1 antibodies

Analyzing the concentrations of HMGB1 and anti-HMGB1 antibodies, we included age and disease duration as covariates to account for the respective trends observed in the sample, particularly within the RA and AS subgroups. The analysis was performed using the ANCOVA rank method followed by a post-hoc Dunn's test. For the control group, only the age covariate was factored in. The analysis showed that after adjusting for age and duration of the disease, the plasma concentration of HMGB1 in patients with SLE (Me [Q_1–Q_3]: 22.6 [12.8–33.5] ng/ml), RA (15 [9–23]), and AS (12.5 [7.6–18.9]) was significantly higher than in healthy controls (8.6 [5.7–12.2]) (Fig. 1A). The HMGB1 level in PsA cases (11.6 [5.9–20.1]) did not significantly differ from that in the controls. In SLE cases, the concentration of this protein was higher than in patients with AS and PsA. In the ANCOVA model, age and duration of the disease did not significantly affect the indicators. Thus, the highest level of HMGB1 was found in patients with SLE.

The levels of HMGB1 among subgroups did not differ significantly depending on the clinical features of the diseases. In particular, the difference in concentrations of the protein in RF-positive (17.5 [9–25.2]) and RF-negative (13.6 [6.1–23.4]) RA patients was insignificant (p = 0.33), same as in ACCP-positive (17.5 [9–25.4]) and ACCP-negative (9.7 [6.9–22.1]) RA patients (p = 0.26). In AS, there was a statistically insignificant trend towards an increase in HMGB1 levels in HLA-B27-positive patients (12.8 [9.6–18.9]) compared with HLA-B27-negative (9 [6.2–13.7]) patients (p = 0.07).

Analysis of the concentration of anti-HMGB1 antibodies adjusted for age and duration of the disease showed a significant increase in the level of these antibodies in SLE (Me [Q_1–Q_3]: 1121 [691–2859] ng/ml), RA (737 [104–1219]) and AS (543 [55–1546]) cases compared with healthy individuals (167 [0–602]) (Fig. 1B). In PsA patients, the concentration of anti-HMGB1 antibodies (550 [0–1158]) did not differ from that in the control group. The highest median level of anti-HMGB1 antibodies was observed in patients with SLE, but no significant differences were found for the four diseases considered. Age and duration of the disease were insignificant in the ANCOVA model.

The level of anti-HMGB1 antibodies varied among the participants. Based on the sensitivity of the ELISA kit (1.17 ng/ml),

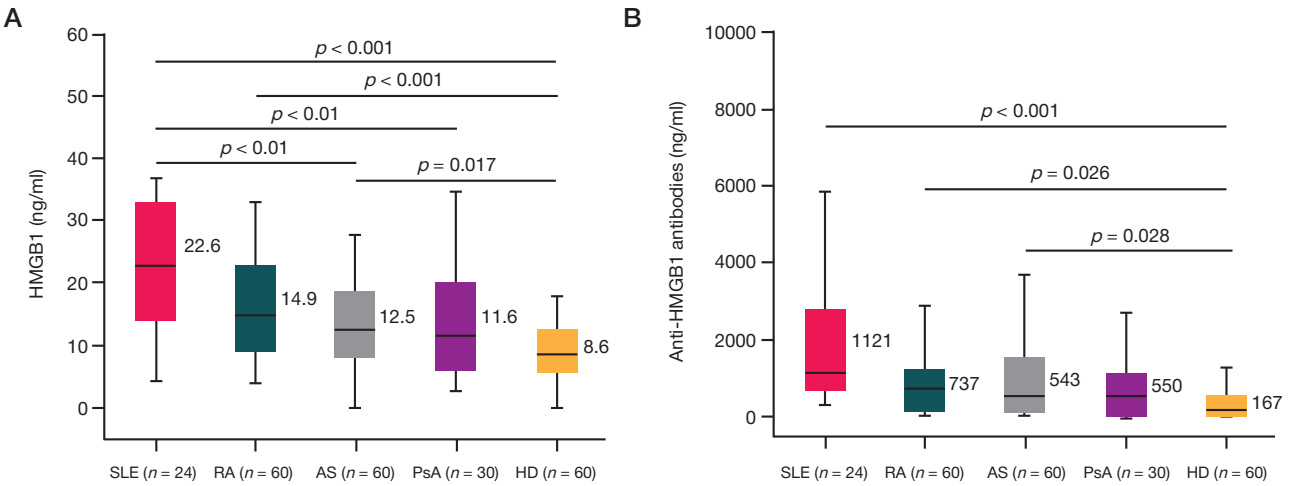

Fig. 1. The blood plasma concentration of HMGB1 (**A**) and anti-HMGB1 antibodies (**B**) in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and healthy donors (HD). The analysis was performed using the ANCOVA rank method followed by a post-hoc Dunn's test, adjusted for age and duration of the disease. The median values are shown to the right of the boxes

the participants were divided into anti-HMGB1-negative (below the threshold) and anti-HMGB1-positive (above the threshold) (Fig. 2). We identified the smallest number of anti-HMGB1–positive participants in the control group. Among patients with RDs, the frequency of this status decreased progressively from SLE to RA, AS, and PsA. Anti-HMGB1 antibodies were detected in SLE cases 40.2 times more often (95%CI: 2.3–692, p = 0.0003) than in healthy individuals. In RA and AS, such antibodies were also detected 2.7 (1.23–5.9, p = 0.02) and 2.45 (1.13–5.33, p = 0.04) times more often, respectively, than in the controls. Among the group of participants with RDs, anti-HMGB1 antibodies were detected in patients with SLE 15.3 (0.87–267, p = 0.04) times more often than in RA cases, 16.6 (0.96–291, p = 0.03) times more often than in AS patients, and 25.1 (1.38–455, p = 0.008) times more often than in participants with PsA. Thus, the incidence of anti-HMGB1 antibodies in SLE is higher than in other RDs.

No significant differences were found among the clinical subgroups. In particular, the levels of anti-HMGB1 antibodies in RF-positive RA patients (784 [23–1219]) and in RF-negative patients (717 [502–1051]) did not differ (p = 0.69), same as between ACCP-positive (679 [32–1117]) and ACCP-negative patients (1117 [542–1431]) (p = 0.12). In AS, the levels of anti-HMGB1 antibodies in HLA-B27-positive (584 [32–1388]) and HLA-B27-negative (369 [13–1383]) participants also did not differ significantly (p = 0.62).

Correlations

Correlation analysis revealed a direct link between HMGB1 levels and CRP and ESR parameters in RA, AS, and PsA (Fig. 3). Antibodies to HMGB1 positively correlated only with CRP in patients with RA and with ESR in patients with AS. Unexpectedly, in patients with SLE, neither HMGB1 nor anti-HMGB1 antibodies correlated with ESR and CRP (Fig. 3A), which is probably due to the small sample size. These findings highlight the pro-inflammatory role of HMGB1 in RA, AS, and PsA.

An analysis of the correlation between HMGB1 levels and the DAS28 index in patients with RA showed a strong positive association (Rs = 0.56, p = 8.4e–6) (Fig. 3B). In patients with PsA, HMGB1 levels positively correlated with the DAPSA index (Rs = 0.38, p = 0.04), but not with the DAS28 index (Fig. 3C). In the same subgroup of participants, the level of antibodies to HMGB1 positively correlated with both the DAS28 index (Rs = 0.52, p = 0.005) and the DAPSA index (Rs = 0.52, p = 0.005). No statistically significant correlations with the studied markers and clinical indices were found in patients with AS and SLE (Fig. 3).

Regression analysis

In this study, multiple regression analysis was used to assess the relationship between the concentrations of HMGB1 and anti-HMGB1 antibodies (as independent predictors) and clinical indices (as dependent variables). For RA, the DAS28 score was used; for AS, the ASDAS-CRP, ASDAS-ESR, and BASDAI scores; for PsA, the DAS28 and DAPSA scores; and for SLE, the SELENA-SLEDAI score. Of the seven regression models built, only the model for RA turned out to be significant (Table 2). This model explains the 31.1% variation of the logarithmic DAS28 index. It has been shown that a 1% increase in HMGB1 concentration is associated with a 0.49% increase in DAS28 (p < 0.001). As for anti-HMGB1 antibodies, there were no significant associations established (p = 0.145) (Table 2).

Since ESR is one of the variables used to calculate the DAS28 index, a regression model was also built in which ESR and CRP served as predictors of DAS28. The model turned out to be significant (R2adj. = 0.351; F = 15.31; p < 0.001). As expected, ESR, unlike CRP, was a significant predictor

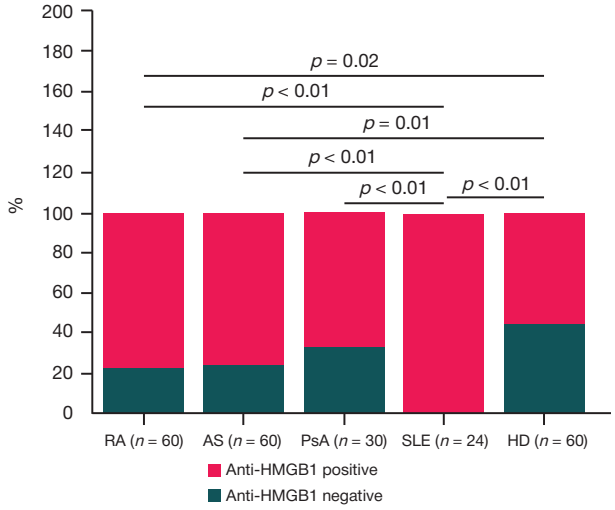

Fig. 2. The frequency of occurrence of anti-HMGB1 antibodies in patients with RA, AS, PsA, SLE, and healthy donors (HD). Statistical significance was assessed using the chi-square test

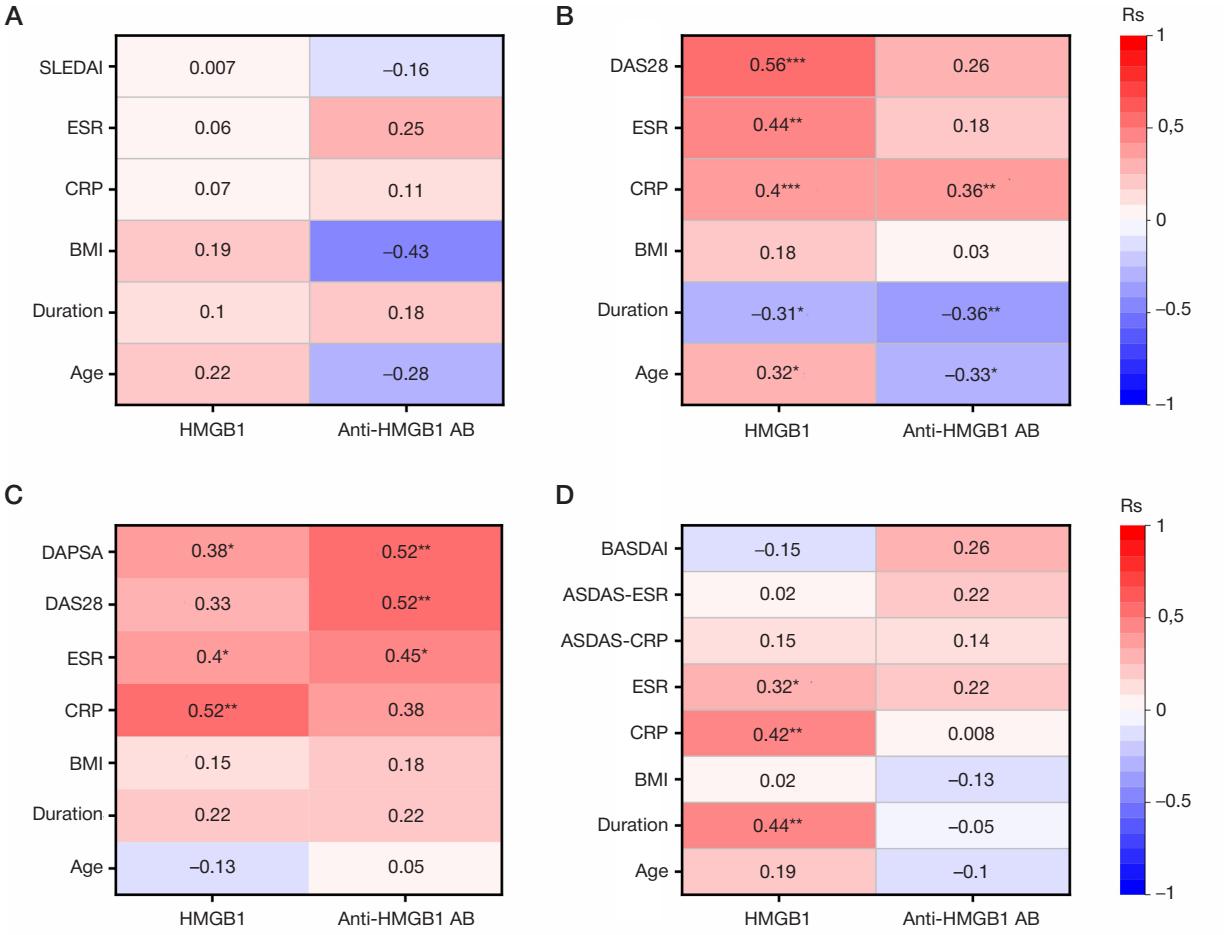

Fig. 3. Correlation of the concentration of HMGB1 and anti-HMGB1 antibodies with the clinical characteristics of SLE (**A**), RA (**B**), PsA (**C**) and AS (**D**). Spearman's rank correlation coefficients (Rs) are color-coded. * — $p < 0.05$, ** — $p < 0.01$, *** — $p < 0.001$

of DAS28. In the regression model, a 1% increase in ESR is associated with a 0.265% increase in DAS28. Thus, HMGB1, along with ESR, was a predictor of DAS28.

DISCUSSION

Previous studies have shown that blood HMGB1 concentrations are elevated in patients with RA [18], AS [19], PsA [20] and SLE [21, 22] compared with healthy individuals. In this work, the recorded increase in HMGB1 levels in SLE, RA, and AS (Fig. 1A) is consistent with the data reported in the literature [18–20]. However, we observed only an upward trend — a 1.39-fold increase in HMGB1 concentration — in PsA, which may be attributable to the small sample size and treatment effects. Therefore, it is necessary to continue investigation of HMGB1 levels and its role in PsA.

Previous studies have focused on the analysis of HMGB1 concentrations in certain RDs [18–21]. In this work, we compare four RDs. The highest level of HMGB1 was detected in SLE (Fig. 1A), which may indicate that the inflammation is most pronounced in SLE compared with other considered diseases, since HMGB1 is an inflammatory mediator [12]. Nevertheless, given the detected increase in HMGB1 levels and the association with DAS28 (Fig. 1A, Fig. 3B, Table 2), it can be assumed that HMGB1 is also involved in the pathogenesis of RA. Therefore, existing therapeutic strategies targeting HMGB1, including monoclonal antibodies [12], may be effective for treating patients with SLE and RA; however, further studies are needed to evaluate the effects of HMGB1 suppression in these diseases.

The regression (Table 2) and correlation (Fig. 3B) analyses revealed association of HMGB1 level with DAS28 in RA, which seemed intriguing. We have shown that a 1% increase in HMGB1 concentration is associated with a 0.49% increase in DAS28 (Table 2). Moreover, in a regression model using ESR as a predictor of DAS28, we found that a 1% increase in ESR was associated with a 0.265% increase in DAS28. Thus, the level of HMGB1 turned out to be a comparable predictor of DAS28 in RA, same as ESR, which is used to calculate this index. Therefore, HMGB1 may serve as a potential biomarker for RA disease activity. However, HMGB1 is a non-specific marker of inflammation, which reduces its diagnostic and predictive value in the context of RA.

The positive correlation of HMGB1 with ESR and CRP in RA, AS, and PsA (Fig. 3) highlights the pro-inflammatory role of this protein in these diseases. This is consistent with

Table 2. Multiple regression analysis for DAS28 as a dependent variable, and HMGB1 and anti-HMGB1 antibodies as predictors

Variable	β	St. error	*t*	*p*	Model
Constant	–1.6808	0.468	–3.588	< 0.001	$R^2_{корр.} = 0.311$; F = 11.13; $p < 0.001$
HMGB1	0.4878	0.108	4.51	< 0.001	
Anti-HMGB1 antibodies	0.0646	0.043	1.495	0.145	

the data reported in the literature. For example, HMGB1 has been shown to correlate with ESR and CRP in AS [19]. In our work, no such association was found for SLE, although it was recorded earlier [22]. The possible reasons for this is the small sample size or the effects of anti-inflammatory therapy.

The appearance of HMGB1 in the bloodstream may be associated with both active secretion and cell death [11]. In various variants of the latter, the protein can be released with other nuclear components, including DNA [11]. Evidence suggests an increase in circulating extracellular DNA levels in SLE [9, 23], RA [24], and AS [25, 26]. These data are consistent with our findings showing elevated HMGB1 levels in SLE, RA, and AS (Fig. 1A), as circulating extracellular DNA can be isolated in complex with this protein. It is feasible to further investigate the mechanisms of HMGB1 release in RDs.

The elevated level of HMGB1 may be associated with the formation of antibodies to HMGB1 [16]. In this study, high concentration of anti-HMGB1 antibodies were detected in SLE, RA, and AS (Fig. 1B). Such antibodies were most often found in patients with SLE (Fig. 2), who also had the highest level of HMGB1 (Fig. 1A). Interestingly, in PsA, the antibody level did not differ from the control, which is consistent with the low concentration of HMGB1 in these cases. However, these patients unexpectedly showed a positive correlation of anti-HMGB1 antibodies with DAS28 and DAPSA (Fig. 3C), which requires further study. The elevated level of anti-HMGB1 antibodies in SLE we have registered is consistent with the literature data [16]. However, there is no previously reported findings about the antibodies in RA, AS, and PsA, so this study fills this knowledge gap.

The limitations of this work include a relatively small sample size, a trend towards a higher age of RA patients, differences in the duration of the disease, and an unbalanced sex ratio due to the characteristics of the analyzed RDs. We adjusted for age and duration of the disease, but further studies should find out the influence of sex on the considered indicators.

CONCLUSIONS

This study revealed an increase in the blood plasma concentration of HMGB1 in SLE, RA and AS, while in PsA there was only an increase trend compared with healthy donors. Among the four rheumatic diseases, the greatest increase in HMGB1 was found in patients with SLE. The level of anti-HMGB1 antibodies was also significantly increased in patients with SLE, and to a lesser extent in RA and AS. However, there were no pronounced associations with the clinical parameters of SLE. On the contrary, in RA, the level of these markers was associated with the clinical characteristics of patients, which was confirmed both by the correlation analysis and the regression model. These data indicate that HMGB1 may be involved in complex pathogenetic mechanisms primarily in RA, which confirms the relevance of this molecule as a therapeutic target. Anti-HMGB1 antibodies were associated with clinical indices in patients with PsA, which necessitates further investigation of the contribution of these antibodies to the pathogenesis of PsA.

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