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ORIGINAL RESEARCH

Correlation Analysis of Coagulation and Platelet Parameters with Clinical Outcomes in Rheumatoid Arthritis Patients and the Interventional Effect of Jianpi Huashi Tongluo Formula - Xinfeng Capsule: A Post Hoc Analysis Based on an Randomized Controlled Trial

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Background: Rheumatoid arthritis (RA) patients frequently present coagulation and platelet abnormalities. Jianpi Huashi Tongluo Prescription - Xinfeng Capsule (XFC), a traditional Chinese medicine compound preparation, has demonstrated efficacy in improving RA disease activity and inflammation in clinical trials (Clinical Trial.gov: NCT01774877), but its effects on coagulation and platelet parameters remain unclear.

Objective: To explore the relationship between coagulation/platelet parameters and RA disease activity, quality of life, and inflammatory indicators, and to assess the improvement effect of XFC treatment over 12 weeks.

Methods: A post-hoc analysis of 304 RA patients assessed disease activity (DAS28), quality of life (SAS/SDS), and coagulation/platelet parameters. Spearman correlation, logistic regression, restricted cubic spline (RCS), and ROC analyses explored relationships between parameters. Mediation analysis was performed to explore the mediating effects of inflammatory indicators. XFC and leflunomide (LEF) were compared for coagulation and platelet parameters improvements after 12 weeks.

Results: Coagulation and platelet parameters were significantly correlated with immune-inflammatory indicators, as well as with DAS28, SAS, and SDS scores. Logistic regression identified ESR/CRP as DAS28 risk factors, FBG/DD/PLT/PCT/CRP as SAS risks, and FBG/CRP as SDS risks. Specific combinations of parameter levels significantly increased the risks of DAS28, SAS, and SDS. RCS revealed non-linear relationships. Mediation analysis indicated that CRP/ESR mediated the relationship between coagulation parameters and disease activity, as well as quality of life. ROC indicated CRP best predicted DAS28, PLT for SAS, and ESR for SDS. The XFC group exhibited significant improvements in APTT, TT, PLT, PCT, and PDW, while the LEF group showed improvements in APTT, TT, FBG, and MPV. XFC outperformed LEF in improving FBG, PLT, PCT, PDW, and MPV.

Conclusion: Coagulation/platelet parameters in RA patients are closely associated with increased disease activity and decreased quality of life. Furthermore, XFC exhibits significant advantages over LEF in improving FBG, PLT, PCT, PDW, and MPV.

Keywords: rheumatoid arthritis, Xinfeng Capsule, post hoc analysis, DAS28, SAS, SDS

Introduction

Rheumatoid Arthritis (RA) is a chronic, progressive autoimmune disease primarily characterized by multi-articular inflammation. Its pathological foundation mainly includes synovitis and pannus, which lead to the destruction of articular cartilage and bone, subsequently causing joint deformity and functional loss.[1,2] Globally, the incidence of RA is approximately 0.5%-

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1%, while in China, this proportion is about 0.42%.[3] Notably, the ratio of male to female patients is approximately 1:4.[4] The pathogenesis of RA is complex, involving environmental, genetic, epigenetic modifications, infections, and other factors.[5,6] Currently, RA cannot be completely cured, but clinical treatment aims to achieve clinical remission or low disease activity. Commonly used therapeutic drugs include disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and biologics. However, long-term use of these drugs may lead to adverse reactions such as liver and kidney dysfunction, bone marrow suppression, and gastrointestinal reactions.[7,8]

The immune-inflammatory response occupies a central role in the pathogenesis of RA, with persistent inflammatory stimulation causing joint swelling, pain, and deformity, severely impacting patients' quality of life.[9] Recent studies have shown that the immune system and coagulation system are functionally interconnected.[10,11] Proinflammatory cytokines can activate coagulation factors and downregulate physiological anticoagulant pathways.[12–14] For instance, IL-6 can promote platelet hyperplasia, reactivity, and accelerate the formation of extraintestinal thrombosis, particularly in experimental colitis.[15] Based on this, multiple studies have indicated that coagulation-related indicators play a crucial role in assessing the activity of autoimmune diseases.[16] Preliminary research has found a close correlation between inflammatory indicators and coagulation indicators in RA patients.[17]

Previous studies have provided compelling evidence that interventions using Chinese herbal medicine preparations exhibit clinical efficacy in treating RA, aiming to promote spleen-strengthening, dampness-resolving, blood-activating, and collateral-unblocking, as well as wind-dispelling and dampness-eliminating and heat-clearing and detoxifying.[18] According to traditional Chinese medicine (TCM) theory, RA falls into the category of "bi syndrome", with "spleen deficiency and excessive dampness" being a significant mechanism in the pathogenesis of RA.[19,20] The relationship between "spleen deficiency" in TCM and the onset of RA is mainly manifested as: spleen deficiency leading to qi and blood insufficiency causing bi syndrome, spleen deficiency causing endogenous damp-turbidity leading to bi syndrome, and spleen deficiency causing the intermingling of phlegm and blood stasis leading to bi syndrome. Following the theoretical principle of "Jianpi Huashi Tongluo", it is advocated to adopt methods that strengthen the spleen and stomach, nourish the acquired constitution, support vital qi, tonify qi and nourish blood, and prioritize treating symptoms in acute cases by eliminating phlegm and resolving dampness. Guided by this theory, we explored the efficacy of Jianpi Huashi Tongluo Prescription in the treatment of RA and confirmed the clinical efficacy of Xinfeng Capsule (XFC), a traditional Chinese medicine compound.[21]

Jianpi Huashi Tongluo Prescription-Xinfeng Capsule (XFC), composed of four Chinese medicinal herbs: Astragalus membranaceus, Coicis Semen, Scolopendra, and Tripterygium wilfordii Hook. F., has the efficacy of "invigorating qi and strengthening the spleen, resolving dampness, and unblocking the collaterals" (Anhui Pharmaceutical Preparation Approval Number: Z20050062, Invention Patent Number: ZL201310011369.8). Jianpi Huashi Tongluo Prescription-Xinfeng Capsule has been incorporated into the guidelines of the Chinese Association of Chinese Medicine Rheumatology (Standard No.: T/CACM 1042–2017).[22] Previous systematic research on the preparation process, fingerprint chromatography, clinical efficacy, pharmacology, and toxicology of XFC has shown that its drug quality is stable and controllable, with no significant toxicological effects.[23] XFC contains various active ingredients such as Calycosin-7-glucoside, calycosin, Formononetinaldehyde, β-sitosterol, stigmasterol, and others,[24] which exhibit anti-inflammatory, antioxidant, immunoregulatory, pro-apoptotic, and hypercoagulable state-improving effects.[25,26] Notably, previous studies have also observed abnormal changes in coagulation indicators and platelets in patients with RA. XFC can effectively attenuate inflammatory responses and improve hypercoagulability by regulating the lncDSCR9/RPLP2/PI3K/AKT axis, thereby improving platelet and coagulation-related parameters in RA patients.[17,24] Furthermore, a cohort study involving ten thousand individuals revealed a significant correlation between the use of XFC and improvements in platelet and immune-inflammatory indicators.[27] Therefore, exploring the specific effects of XFC on coagulation and platelet parameters in RA patients will facilitate a more comprehensive assessment of its therapeutic efficacy.

Based on the aforementioned TCM theory and drug research, we previously conducted a randomized controlled trial involving 304 patients to verify the efficacy of XFC in the treatment of RA.[21] The trial adopted a multicenter, parallel-group, double-blind, randomized controlled design, dividing patients into two groups: the XFC + Leflunomide (LEF) placebo group and the LEF + XFC placebo group, with a treatment duration of 12 weeks. By comparing clinical and laboratory parameters at baseline, week 4, week 8, and week 12, we found that both groups demonstrated a certain trend of efficacy according to the 20%, 50%, and 70% improvement criteria recommended by the American College of Rheumatology (ACR), but the differences were not significant. Similarly, there were no significant differences in the improvement of the modified

Disease Activity Score 28 (DAS28) and laboratory indicators such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF). Scores on the Rheumatoid Arthritis Quality of Life (RAQOL), Health Assessment Questionnaire (HAQ), Self-rating Anxiety Scale (SAS), and Self-rating Depression Scale (SDS) decreased in both groups, but the changes were not statistically significant. Notably, the SDS score in the XFC group decreased more than in the other group. A total of 147 adverse event cases were reported, with no significant difference between the two groups. The most common adverse reactions included liver damage, anemia, leukopenia, upper abdominal discomfort, and hepatic necrosis. However, this study only analyzed the impact of XFC on RA disease activity and inflammatory indicators, without further exploring other factors that may affect RA disease activity, such as coagulation and platelet-related parameters.

To delve deeper into the interaction between coagulation and platelet-related parameters and inflammatory indicators, and to analyze their impact on RA disease activity (DAS28) and quality of life (SAS and SDS), this study conducted a comprehensive and in-depth post-hoc analysis of clinical trial data based on previous research findings. This study aims to provide an in-depth analysis of the efficacy of XFC in the treatment of RA and present new research evidence to support the clinical application of XFC in reducing RA disease activity and improving quality of life while also improving coagulation and platelet parameters.

Materials and Methods

Study Design and Post Hoc Analysis

The comprehensive details of the XFC trial (Clinical Trial.gov Identifier: NCT 01774877, Ethical Approval No.: 2012AH-038-01) have been previously reported.[21] Adhering to the ethical guidelines outlined in the Declaration of Helsinki, this study protocol received approval from the Medical Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine. Informed consent was obtained from all study participants (Ethical Approval No.: 2012AH-038-01). Notably, our hospital's ethics committee has been certified by the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) of the World Health Organization since 2012, reflecting our commitment to ethical standards in research. Briefly, the XFC trial was a large-sample, multicenter, centrally randomized, double-blind, double-dummy RCT conducted among adults aged 18–65 with RA. It aimed to evaluate the clinical effectiveness and safety of XFC versus LEF in treating patients with RA. The study was conducted from September 2012 to November 2014 at four reputable hospitals in China. Comprehensive follow-up assessments were conducted for all participants at baseline, Week 4, Week 8, and Week 12. In previous statistical analyses, the primary focus was on assessing improvements in the 20%, 50%, and 70% response criteria recommended by the American College of Rheumatology (ACR), the DAS28, and laboratory indicators such as ESR, CRP, RF, immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), anti-cyclic Citrullinated Peptides Antibodies (CCP), HAQ, SAS, SDS, and RAQOL questionnaire, all of which were continuous variables. Additionally, a total of 304 patients were randomly enrolled in this study, all meeting the RA diagnostic criteria jointly proposed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010.[28] Specifically, the XFC group included 17 males (12.2%) and 122 females (87.8%), while the LEF group included 27 males (18.9%) and 116 females (81.1%). The chi-square test (χ^2test) was used to compare differences in gender distribution between groups, yielding a P-value of 0.1239. The mean age was (48.9±10.5) years in the LEF group and (47.8±10.4) years in the XFC group, with disease durations of (61.8±65.6) months and (59.4±67.1) months, respectively. There were no statistically significant differences in baseline characteristics between the two groups (P>0.05). The complete baseline data distribution has been stratified and presented in Supplementary Table 1 of the previously published primary results paper for the trial.[21]

In the post hoc analysis presented in this paper, our primary focus is on assessing the relationship between coagulation indicators and inflammatory indicators, as well as their impact on clinical outcomes. The post hoc clinical outcomes are the baseline scores of DAS28, SAS, and SDS. Furthermore, improvements in coagulation indicators between Week 12 and baseline were analyzed, as well as differences in the proportion of abnormal coagulation indicators between the two groups. The average differences in indicator improvements between the XFC and LEF groups were also analyzed. The aforementioned post hoc analysis was conducted using the complete dataset of 304 participants. The research flowchart is shown in Figure 1.

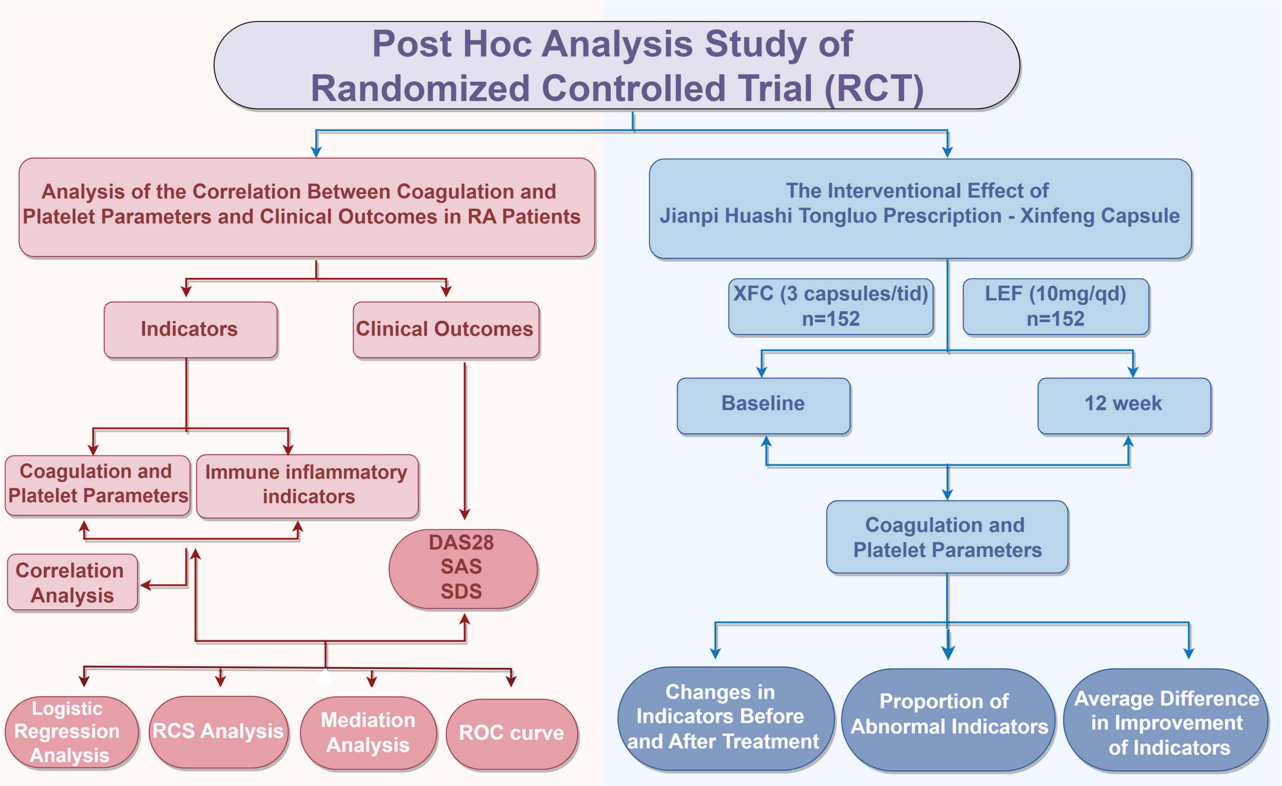

Figure 1 Flowchart of the Study. Created by By Figdraw (ID: YPOIA88b8b).

Study Indicators

A dataset of clinical indicators was collected and analyzed from RA patients participating in the XFC trial. The dataset included the following indicators: Primary Clinical Outcome Indicators: DAS28, SAS, SDS; Coagulation-related and Platelet-related Parameters: Activated Partial Thromboplastin Time (APTT), Thrombin Time (TT), Fibrinogen (FBG), D-dimer (DD), Platelet Count (PLT), Platelet Crit (PCT), Platelet Distribution Width (PDW), Mean Platelet Volume (MPV); Immunoinflammatory Indicators: ESR, CRP, RF, IgA, IgG, IgM, and CCP.

Correlation Analysis

A non-parametric measure of rank correlation, the Spearman correlation, was employed to study the statistical dependence between the rankings of two variables. The Spearman correlation coefficient between two variables is equivalent to the Pearson correlation coefficient between the rank values of those variables, assessing monotonic relationships (whether linear or not). In this study, Spearman correlation analysis was used to investigate the correlations between coagulation-related parameters, platelet-related parameters, immunoinflammatory indicators, and clinical outcome indicators (SAS, SDS, DAS28). The rank correlation coefficient (rho) and its 95% confidence interval for each pair of variables are calculated.

Logistic Regression Analysis

Logistic regression models were utilized for two purposes: to study the impact of immunoinflammatory indicators on coagulation and platelet-related parameters; and to examine the influence of immunoinflammatory and coagulation-related parameters, as well as platelet-related parameters, on clinical outcomes, including the combined effect of inflammation with coagulation and platelet-related parameters. In binary logistic regression analysis, a p-value less than 0.05 indicated a statistically significant relationship. An odds ratio (OR) greater than 1 suggested a risk factor, while an OR less than 1 indicated a protective factor. For DAS28, a value greater than 3.2 is defined as "High Disease Activity", and a value of 3.2 or less is considered "Low/Remission". For SAS/SDS, a score of 50 or above is defined as "Clinically Significant Anxiety/Depression", and a score below 50 is

considered "No Significant Symptoms". Additionally, based on the laboratory standards of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine, clinical thresholds (APTT > 25 sec, TT > 14 sec, FBG > 4 g/L, DD > 0.55 mg/L, PLT > 350 × 10^9/L, PCT > 0.28%, PDW > 0.28 fL, MPV > 13 fL, ESR > 38 mm/h, CRP > 10 mg/L, RF > 14 KIU/L, IgA > 4.2 g/L, IgG > 17.4 g/L, IgM > 2.8 g/L, CCP > 4 U/mL) are defined as "High", and values below these thresholds are defined as "Low".

Restricted Cubic Spline (RCS) Analysis

To elucidate the nonlinear dose-response relationships between indicators such as ESR, FBG, and PLT, and outcomes including SAS, SDS, and DAS28, we selected three knots for our analysis. We conducted restricted cubic spline analysis at the 10th, 50th, and 90th percentiles of the distribution for ESR, FBG, and PLT, setting the lowest point on the Y-axis as the inflection point for U-shaped curves. Initially, we examined the overall association (P-overall) between indicators like ESR, FBG, PLT, and outcomes such as SAS, SDS, DAS28. A P-overall value of less than 0.05 suggests a significant dose-effect relationship between them. Additionally, we tested for the presence of nonlinearity (P-nonlinear). A P-nonlinear value of less than 0.05 indicates a significant nonlinear relationship.

Mediation Analysis

To test whether inflammatory markers mediate the association between coagulation and platelet-related parameters and clinical outcomes, causal mediation analysis was conducted according to the method proposed by VanderWeele. The hypothetical causal model among variables is illustrated in Figure 2, where coagulation and platelet-related parameters are the predictor variables (X), CRP and ESR are the mediators (M), and clinical outcomes (DAS28, SAS, and SDS) are the outcomes (Y). Mediation analysis was used to examine whether the effect of the predictor variable X on the outcome variable Y (ie, X→Y) is at least partially mediated by the effect of X on the intermediate mediator M and the effect of M on Y (ie, X→M→Y). The indirect effect of X on Y through the mediator M, also known as the average causal mediation effect (ACME), quantifies the estimated difference in Y caused by a one-unit change in X through a series of causal steps involving M. If the specified confidence interval does not include zero, it is considered significant. The total effect of X on Y is the sum of the indirect and direct effects and is sometimes referred to as the overall effect. The mediator variables included in the study were continuous and were therefore analyzed using linear regression.

Statistical Analysis

Receiver Operating Characteristic (ROC) curves were employed to assess the predictive performance of coagulation and platelet-related parameters, as well as immune-inflammatory indicators, for clinical outcome indicators. The Area Under the Curve (AUC) and 95% Confidence Interval (CI) were calculated accordingly.

Dedicated Statistical Strategy for Post-Hoc Analysis

Longitudinal Parameter Comparison (Corresponding to Results 3.7): Intra-group Comparison Before and After Treatment: For continuous variables, the paired *t*-test was used when the data followed a normal distribution; otherwise, the Wilcoxon signed-rank test was applied (eg, for coagulation and platelet-related parameters).

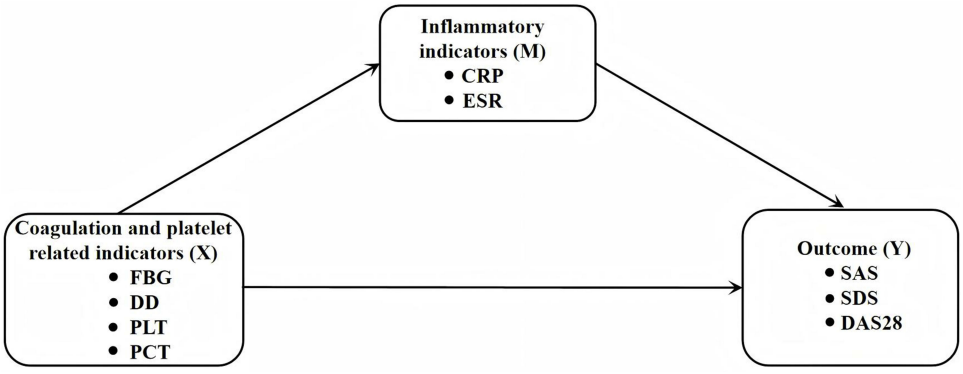

Figure 2 Schematic representation of mediation analysis.

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Inter-group Comparison of Abnormal Proportions (Corresponding to Results 3.8): Definition of Abnormal Values: Continuous variables were dichotomized based on clinical thresholds (APTT < 25 seconds, TT < 14 seconds, FBG > 4 g/L, DD > 0.55 mg/L, PLT > 350 × 10^9/L, PCT > 0.28%, PDW > 0.28 fL, MPV > 13 fL, ESR > 38 mm/h, CRP > 10 mg/L, RF > 14 KIU/L, IgA > 4.2 g/L, IgG > 17.4 g/L, IgM > 2.8 g/L, CCP > 4 U/mL, SAS > 50 points, SDS > 50 points, DAS28 > 3.2 points). Statistical Comparison of Proportions Between Groups: The χ^2test or Fisher's exact test (when expected counts < 5) was used to compare proportions between groups.

Quantification of Clinical Improvement Differences (Corresponding to Results 3.9): The Mann–Whitney *U*-test was utilized to calculate the Mean Difference (MD) in improvement between the two groups. A p-value of < 0.05 was considered statistically significant for the tested differences.

Results

Correlation Analysis Between Coagulation and Platelet-Related Parameters, Immune-Inflammatory Indicators, and Clinical Outcomes

Figure 3 presents the results of the correlation analysis. There is a negative correlation between TT and FBG. FBG positively correlates with SDS, PCT, SAS, DD, ESR, CRP, and DAS28. DD positively correlates with ESR, CRP, PCT, PLT, SAS, SDS, and DAS28. PLT positively correlates with PCT, CRP, SAS, and DAS28, but negatively correlates with PDW and MPV. PCT positively correlates with CRP, SAS, and DAS28, but negatively correlates with PDW and MPV. PDW positively correlates with MPV, but negatively correlates with SAS, DAS28, and CRP. MPV negatively correlates with CRP, SAS, and DAS28. ESR positively correlates with CRP, RF, IgA, IgG, SAS, SDS, and DAS28. CRP positively correlates with IgA, IgG, SAS,

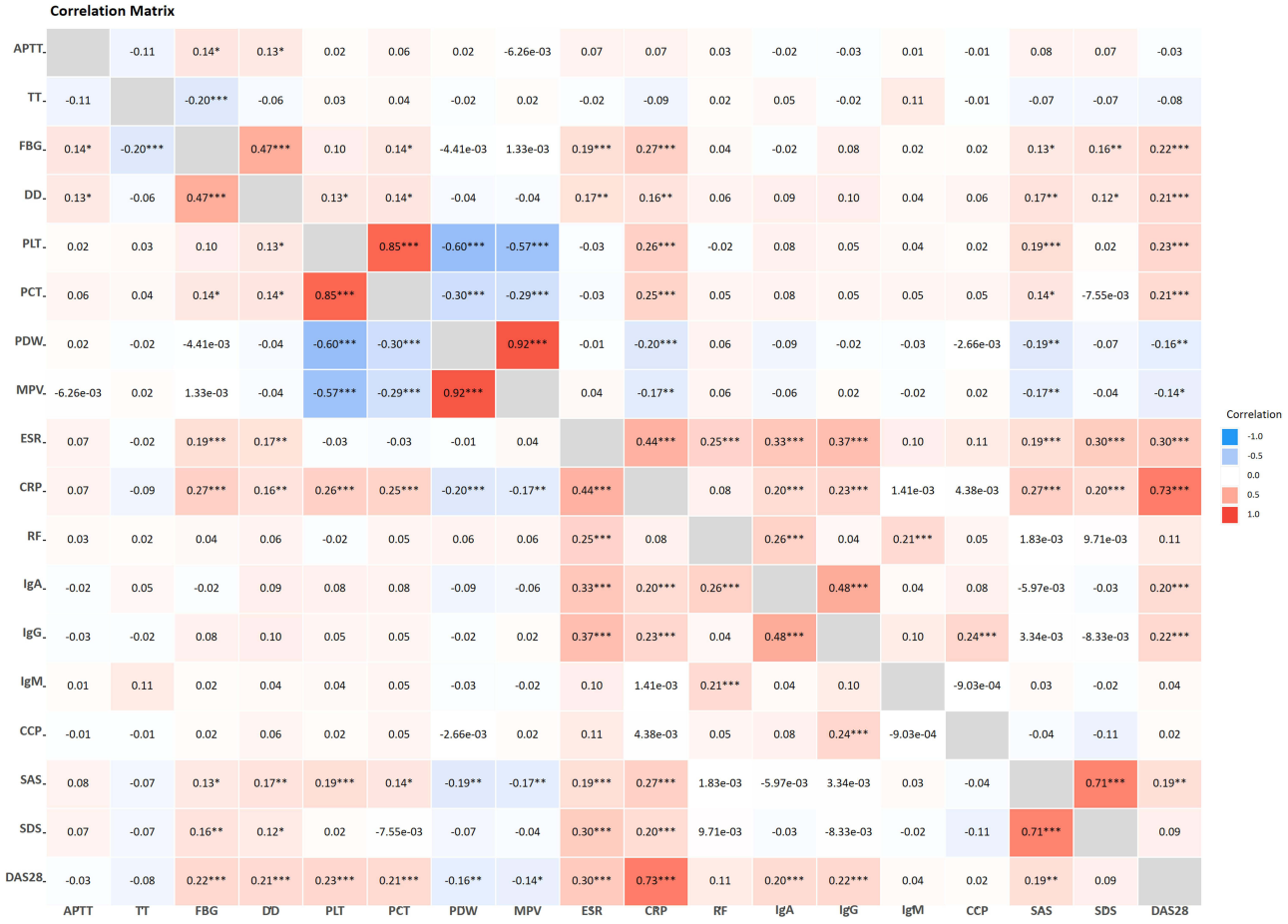

Figure 3 Heatmap of Correlation Analysis Between Coagulation and Platelet-Related Parameters, Immune-Inflammatory Indicators, and Clinical Outcomes. *P<0.05, **P<0.01, ***P<0.001.

SDS, and DAS28. RF positively correlates with IgA and IgM. IgA positively correlates with IgG and DAS28. IgG positively correlates with CCP and DAS28. SAS positively correlates with SDS and DAS28. All these correlations have p-values less than 0.01. The specific rho values are provided in Supplementary Table 2. These results reveal the complex associations between coagulation parameters, platelet parameters, immune-inflammatory indicators, and clinical outcomes.

Individual Relative Risk of Coagulation and Platelet-Related Parameters, Immune-Inflammatory Indicators on Clinical Outcomes

Using logistic regression models, significant associations were identified between coagulation and platelet-related parameters, immune-inflammatory indicators, and the risks of DAS28, SAS, and SDS (Figure 4 and Supplementary Tables 3–5 In the analysis of the results between coagulation and platelet-related parameters, immune-inflammatory indicators, and DAS28, a significant difference was observed between the high and low ESR level groups (OR = 7.55, 95% CI = 2.56–22.30, p <0.001). For CRP levels, a significant difference was noted between the high and low level groups (OR = 8.43, 95% CI = 2.32–30.59, p = 0.001). The analysis of the results between coagulation and platelet-related parameters, immune-inflammatory indicators, and SAS revealed that the high FBG level group showed a significant difference compared to the low FBG level group (OR = 3.02, 95% CI = 1.75–5.20, p < 0.001). For DD levels, a significant difference was observed between the high and low level groups (OR = 2.09, 95% CI = 1.16–3.77, p = 0.015). A significant difference was also found when comparing the high PLT and low PLT level groups (OR = 56, 95% CI = 12.88–243.44, p < 0.001). At the PCT level, a significant difference was observed between the high and low level groups (OR = 5.08, 95% CI = 2.92–8.85, p <0.001). For CRP levels, a significant difference was noted between the high

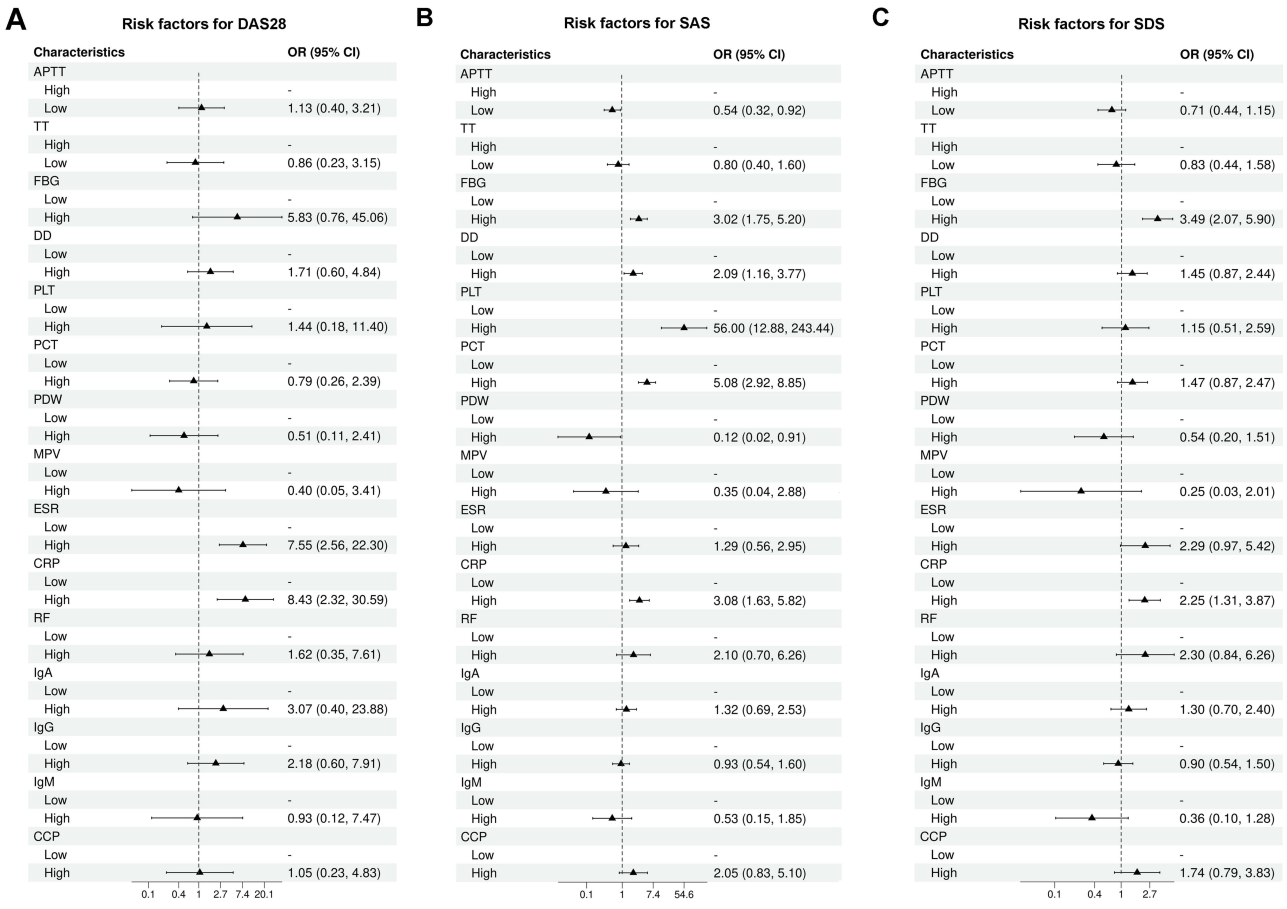

Figure 4 Individual Relative Risk of Coagulation and Platelet-Related Parameters, Immune-Inflammatory Indicators on Clinical Outcomes. (**A**) Impact of Coagulation and Platelet-Related Parameters, Immune-Inflammatory Indicators on DAS28; (**B**) Impact of Coagulation and Platelet-Related Parameters, Immune-Inflammatory Indicators on SAS; (**C**) Impact of Coagulation and Platelet-Related Parameters, Immune-Inflammatory Indicators on SDS.

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and low level groups (OR = 3.08, 95% CI = 1.63–5.82, p <0.001). In the analysis of the results between coagulation and platelet-related parameters, immune-inflammatory indicators, and SDS, higher FBG levels were significantly associated with a higher risk of SDS (OR: 3.49, 95% CI: 2.07–5.90, p < 0.001). Higher CRP levels were also significantly associated with a higher risk of SDS (OR: 2.25, 95% CI: 1.31–3.87, p = 0.003). In summary, these results indicate that ESR and CRP levels are closely related to the risk of DAS28; FBG, DD, PLT, PCT, and CRP levels are closely related to the risk of SAS; and FBG and CRP levels are closely related to the risk of SDS.

Relative Risk of Combined Coagulation and Platelet-Related Parameters with Inflammatory Indicators on Clinical Outcomes

We further analyzed the combined associations of FBG, DD, PLT, PCT, CRP, and ESR with DAS28, SAS, and SDS (Figure 5 and Supplementary Table S6). Patients with simultaneously elevated levels of ESR and CRP or those with "high levels of ESR and low levels of CRP" both demonstrated a significantly increased risk of DAS28 compared to those with low levels of both indicators. Moreover, compared to patients with low levels of both indicators, those with simultaneously elevated levels of FBG and CRP exhibited a significantly increased risk of SAS, with an adjusted odds ratio (OR) of 6.42 (95% CI: 2.92–14.12, p < 0.001). Additionally, the group with "low levels of FBG and high levels of CRP" was also associated with a higher risk of SAS, with an adjusted OR of 2.19 (95% CI: 1.04–4.64, p = 0.040). Similar results were found for the combination of PLT and CRP. Furthermore, compared to patients with low levels of both indicators, those with simultaneously elevated levels of DD and CRP had a significantly increased risk of SAS, with an adjusted OR of 5.00 (95% CI: 1.67–14.99, p = 0.004). Comparable findings were observed for the combination of PCT and CRP. Simultaneously, patients with simultaneously elevated levels of FBG and CRP also showed a significantly increased risk of SDS compared to those with low levels of both indicators, with an adjusted OR of 5.69 (95% CI: 2.81–11.54), p < 0.001.

RCS Analysis of the Relationship Between Coagulation and Platelet-Related Parameters, Inflammatory Indicators, and Clinical Outcomes

In Figure 6, we employed the Restricted Cubic Spline (RCS) method to visually model the relationships between FBG, PLT, and ESR, and SAS, SDS, and DAS28. A nonlinear correlation was observed between FBG and SAS (P-overall < 0.001, P-nonlinear = 0.007). When FBG exceeded 3.1, the curve began to rise significantly, indicating a gradual increase in SAS risk with further increases in FBG levels (Figures 6A and B). Similarly, a nonlinear correlation was found

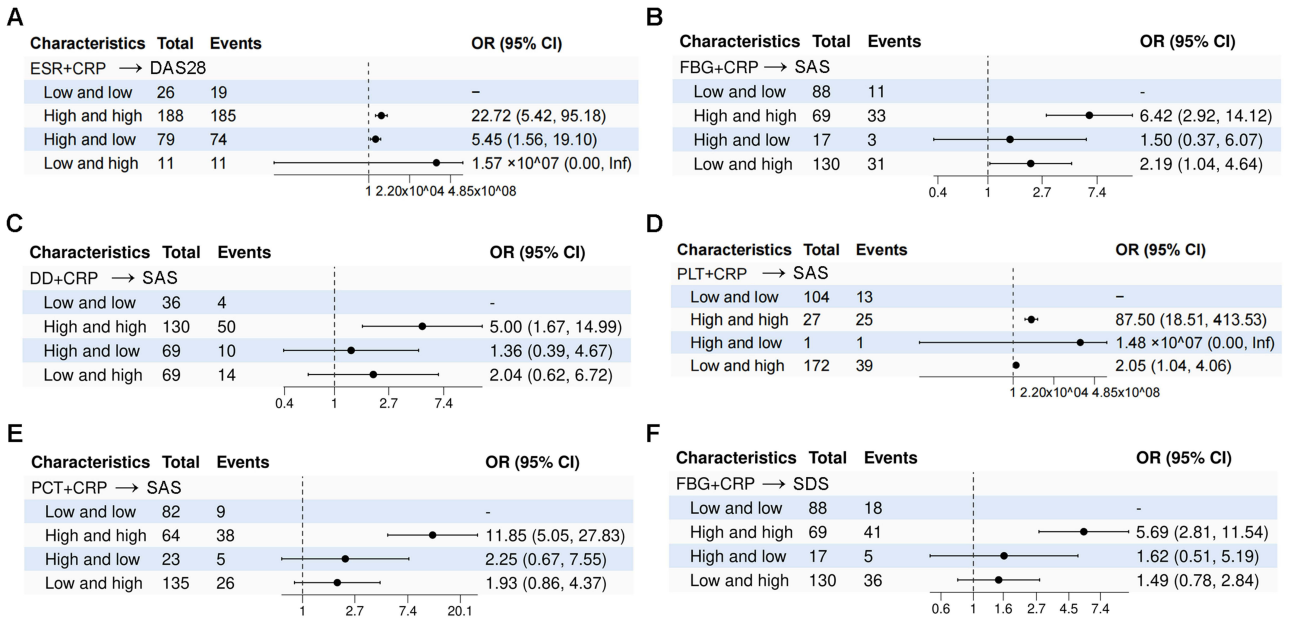

Figure 5 Relative Risk of Combined Coagulation and Platelet-Related Parameters with Inflammatory Indicators on Clinical Outcomes. (**A**) Relative Risk for DAS28; (**B**–**E**) Relative Risk for SAS; (**F**) Relative Risk for SDS.

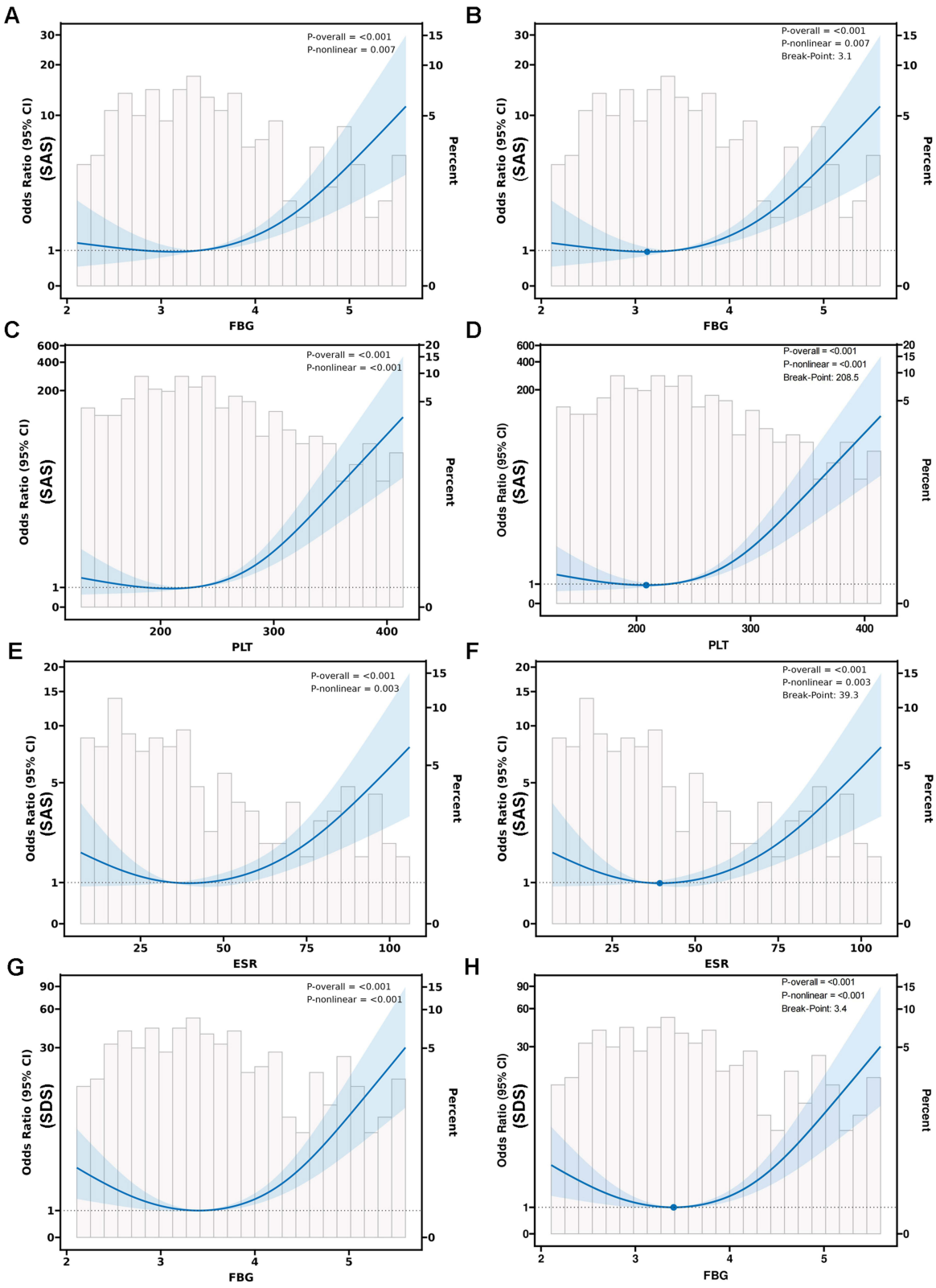

Figure 6 RCS Curves Illustrating the Relationships Between Coagulation and Platelet-Related Parameters, Inflammatory Indicators, and Clinical Outcomes. (**A**) and (**B**): Nonlinear correlation between FBG and SAS (**B**: Break-Point=3.1). (**C**) and (**D**): Nonlinear correlation between PLT and SAS (**D**: Break-Point=208.5). (**E**) and (**F**): Nonlinear correlation between ESR and SAS (**F**: Break-Point=39.3). (**G**) and (**H**): Nonlinear correlation between FBG and SDS (**H**: Break-Point=3.4).

Notes: For continuous variables, standardization is crucial. Without standardization, OR/RR/HR/Coefficient represents the change in the effect size for every unit increase in the independent variable. After standardization, it indicates the change in the effect size for every one standard deviation (SD) increase in the independent variable.

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between PLT and SAS (P-overall < 0.001, P-nonlinear < 0.001). When PLT exceeded 208.5, the curve started to rise markedly, suggesting an escalating SAS risk with increasing PLT levels (Figures 6C and D). A nonlinear correlation also existed between ESR and SAS (P-overall < 0.001, P-nonlinear = 0.003). When ESR surpassed 39.3, the curve began to climb notably, indicating a gradual rise in SAS risk with further elevations in ESR levels (Figures 6E and F). Additionally, a nonlinear correlation was identified between FBG and SDS (P-overall < 0.001, P-nonlinear < 0.001). When FBG exceeded 3.4, the curve started to ascend significantly, suggesting an increasing SDS risk with further increases in FBG levels (Figures 6G and H). Notably, no nonlinear associations were found between the remaining coagulation and platelet-related parameters, inflammatory indicators, and clinical outcomes, and therefore, the relevant results are not presented here.

Mediation Analysis Between Coagulation and Platelet-Related Parameters and Clinical Outcomes

The mediation analysis results presented in Table 1 reveal that the relationship between CRP and DAS28 is partially mediated by ESR. The relationship between FBG and SAS is partially mediated by CRP, with a significant model (Direct: P-value = 0.000, and the confidence interval (0.094, 0.910) not containing 0). Similarly, the relationships between DD and SAS, PLT and SAS, PCT and SAS are all partially mediated by CRP. Additionally, the relationship between FBG and SDS is also partially mediated by CRP.

Table 1 Mediation Analysis Between Coagulation and Platelet-Related Parameters and Clinical Outcomes

Path	Coef	Se	Pval	CI[2.5%]	CI[97.5%]	Sig
CRP (X)→ESR (M)→DAS28 (Y)						
ESR ~ X	0.416	0.054	0.000	0.311	0.522	Yes
Y ~ ESR	0.006	0.001	0.000	0.004	0.008	Yes
Total	0.011	0.001	0.000	0.009	0.013	Yes
Direct	0.010	0.001	0.000	0.008	0.012	Yes
Indirect	0.001	0.000	0.060	−0.000	0.001	No
FBG (X)→CRP (M)→SAS (Y)						
CRP ~ X	2.769	0.656	0.000	1.477	4.060	Yes
Y ~ CRP	0.137	0.020	0.000	0.097	0.177	Yes
Total	1.314	0.241	0.000	0.840	1.789	Yes
Direct	0.991	0.236	0.000	0.527	1.455	Yes
Indirect	0.323	0.211	0.000	0.094	0.910	Yes
DD (X)→CRP (M)→SAS (Y)						
CRP ~ X	1.970	0.846	0.021	0.305	3.635	Yes
Y ~ CRP	0.150	0.020	0.000	0.111	0.190	Yes
Total	1.615	0.304	0.000	1.018	2.213	Yes
Direct	1.344	0.284	0.000	0.786	1.902	Yes
Indirect	0.271	0.123	0.016	0.069	0.579	Yes
PLT (X)→CRP (M)→SAS (Y)						
CRP ~ X	0.156	0.020	0.000	0.117	0.195	Yes
Y ~ CRP	0.141	0.020	0.000	0.102	0.181	Yes
Total	0.049	0.008	0.000	0.034	0.064	Yes
Direct	0.032	0.008	0.000	0.016	0.048	Yes
Indirect	0.017	0.004	0.000	0.009	0.026	Yes

(*Continued*)

Table 1 (Continued).

Path	Coef	Se	Pval	CI[2.5%]	CI[97.5%]	Sig
PCT (X)→CRP (M)→SAS (Y)						
CRP ~ X	0.051	0.399	0.899	−0.735	0.836	No
Y ~ CRP	0.137	0.020	0.000	0.097	0.178	Yes
Total	−0.306	0.148	0.040	−0.598	−0.014	Yes
Direct	−0.313	0.138	0.024	−0.584	−0.041	Yes
Indirect	0.007	0.040	0.812	−0.081	0.086	No
FBG (X)→CRP (M)→SDS (Y)						
CRP ~ X	2.769	0.656	0.000	1.477	4.060	Yes
Y ~ CRP	0.094	0.022	0.000	0.051	0.136	Yes
Total	1.391	0.245	0.000	0.909	1.873	Yes
Direct	1.200	0.248	0.000	0.711	1.689	Yes
Indirect	0.191	0.133	0.008	0.027	0.488	Yes

Notes: The Average Total Effects model was established using linear regression, with the formula: Y ~ X.The Average Direct Effects model was also established using linear regression, with the formula: Y ~ X + M. Path: Mediation pathways (X: independent variable; M: mediator; Y: dependent variable). Coef: Regression coefficient. Se: Standard error. Pval: P-value for significance testing. CI[2.5%] and CI[97.5%]: 95% confidence interval bounds. Sig: "Yes" indicates statistical significance (P < 0.05); "No" indicates non-significance.

Predictive Value of Coagulation and Platelet-Related Parameters and Inflammatory Indicators for Clinical Outcomes

We further evaluated the predictive value of coagulation and platelet-related parameters and inflammatory indicators for DAS28, SAS, and SDS using ROC curves (Figure 7 and Supplementary Table 7). Among them, CRP demonstrated the best predictive value for DAS28, with an AUC value of 0.980. PLT showed the best predictive value for SAS, with an AUC value of 0.735. ESR exhibited the best predictive value for SDS, with an AUC value of 0.644.

Post Hoc Analysis of the Impact of XFC and LEF on Coagulation and Platelet-Related Parameters Before and After Treatment

Given that previous RCT has conducted detailed analyses on the changes in inflammatory indicators before and after treatment with XFC and LEF, this study focuses specifically on coagulation and platelet-related parameters to further investigate the impact of XFC and LEF. The results indicate that, compared to baseline (1 week), XFC significantly improved the levels of APTT, TT, PLT, PCT, and PDW at week 12. Meanwhile, LEF significantly improved the levels of APTT, TT, FBG, and MPV during the same period (Table 2). These findings collectively suggest that both XFC and LEF possess the ability to effectively regulate coagulation function and platelet-related parameters during treatment, which may subsequently contribute to positive health outcomes for patients.

Post Hoc Analysis of the Proportion of Abnormal Coagulation and Platelet-Related Parameters Between Two Groups

This study further compared the proportions of abnormal coagulation and platelet-related parameters between the XFC group and the LEF group (Figure 8). The results showed significant differences in the proportions of abnormal PLT and DD values between the two groups at baseline: the proportion of abnormal PLT (PLT > $350x10^9$/L) was significantly higher in the LEF group compared to the XFC group (p = 0.0266), and the proportion of abnormal DD (DD > 0.55 mg/L) was also significantly higher in the LEF group (p = 0.0084).

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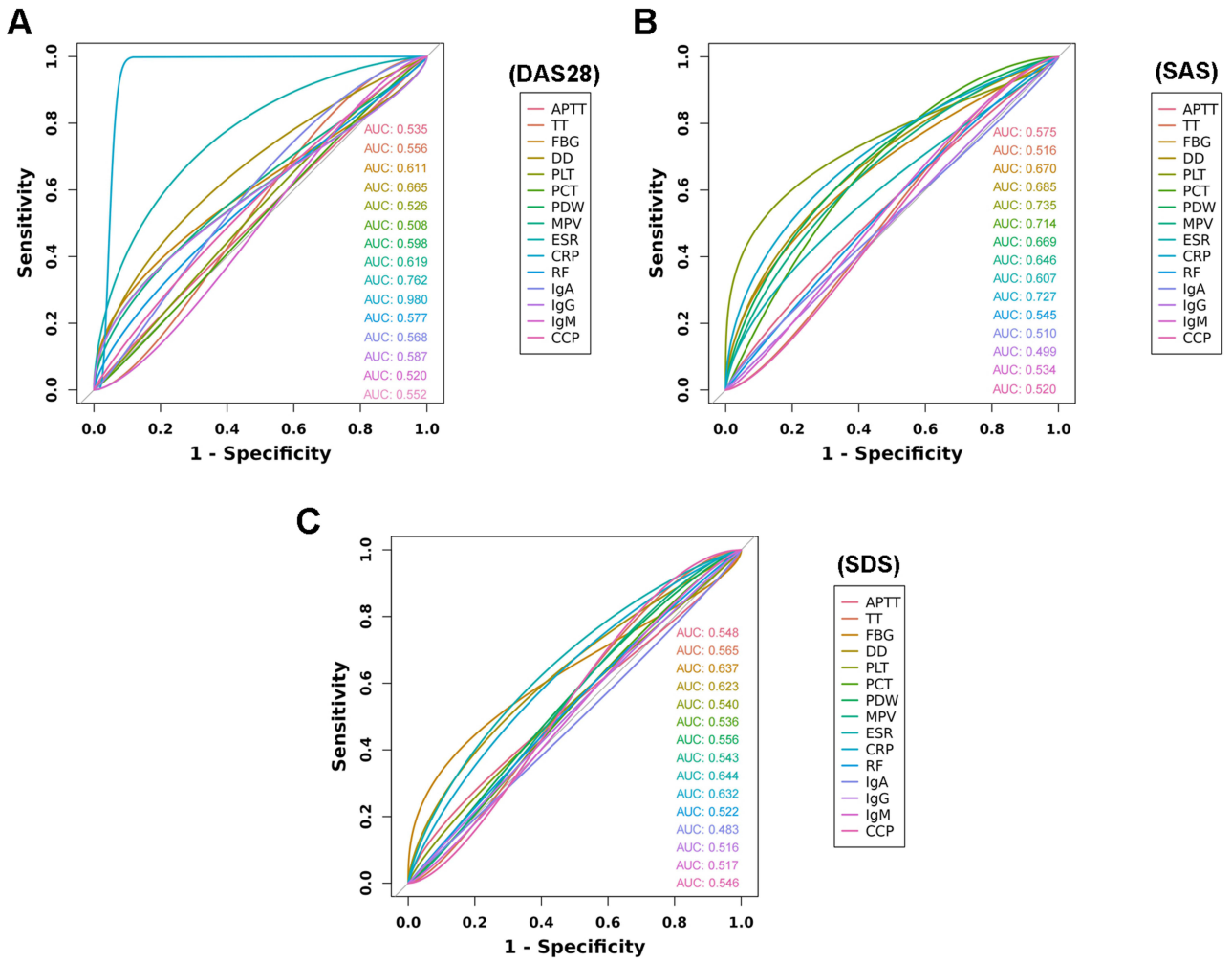

Figure 7 Predictive Value of Coagulation and Platelet-Related Parameters and Inflammatory Indicators for Clinical Outcomes: ROC Curves. (**A**) Predictive ROC curves for coagulation/platelet parameters and inflammatory indicators assessing DAS28. (**B**) Predictive ROC curves for coagulation/platelet parameters and inflammatory indicators assessing SAS. (**C**) Predictive ROC curves for coagulation/platelet parameters and inflammatory indicators assessing SDS.

Furthermore, by the 12th week, multiple abnormalities began to emerge in the LEF group. Specifically, the proportion of abnormal APTT (APTT < 25 sec) was significantly higher in the LEF group compared to the XFC group (p = 0.0228); the proportion of abnormal TT (TT < 14 sec) was also significantly higher in the LEF group

Table 2 Effects of XFC and LEF on Changes in Coagulation and Platelet-Related Parameters Before and After Treatment

Characteristic	XFC Group (n=152)			LEF Group (n=152)		
	1 week	12 week	p-Value	1 week	12 week	*p*-Value
APTT (sec)	25.1 (22.5, 27.8)	26.9 (24.9, 31.3)	<0.001	24 (21, 27)	27 (24, 31)	<0.001
TT (sec)	18.65 (17.20, 19.63)	17.60 (16.80, 18.80)	0.0052	18.8 (17.5, 19.9)	17.6 (16.6, 18.6)	<0.001
FBG (g/L)	3.50 (2.90, 4.27)	3.53 (2.86, 4.48)	0.9782	3.40 (2.70, 4.08)	3.98 (3.13, 4.77)	<0.001
PLT (×10^9/L)	229 (190, 274)	217 (168, 253)	0.0112	225 (181, 283)	232 (192, 305)	0.4172
PCT (%)	0.24 (0.21, 0.28)	0.23 (0.19, 0.25)	0.0012	0.24 (0.20, 0.32)	0.25 (0.21, 0.30)	0.4082
PDW (fL)	11.70 (10.70, 13.30)	12.50 (11.35, 14.50)	0.0052	12.00 (10.90, 14.05)	11.70 (10.50, 13.15)	0.1022
MPV (fL)	10.30 (9.60, 11.00)	10.40 (9.65, 11.30)	0.1452	10.30 (9.65, 11.15)	10.00 (9.40, 10.60)	0.0092
DD (mg/L)	0.81 (0.37, 1.61)	0.78 (0.32, 1.99)	0.8442	0.97 (0.44, 1.80)	0.90 (0.40, 2.22)	0.8362

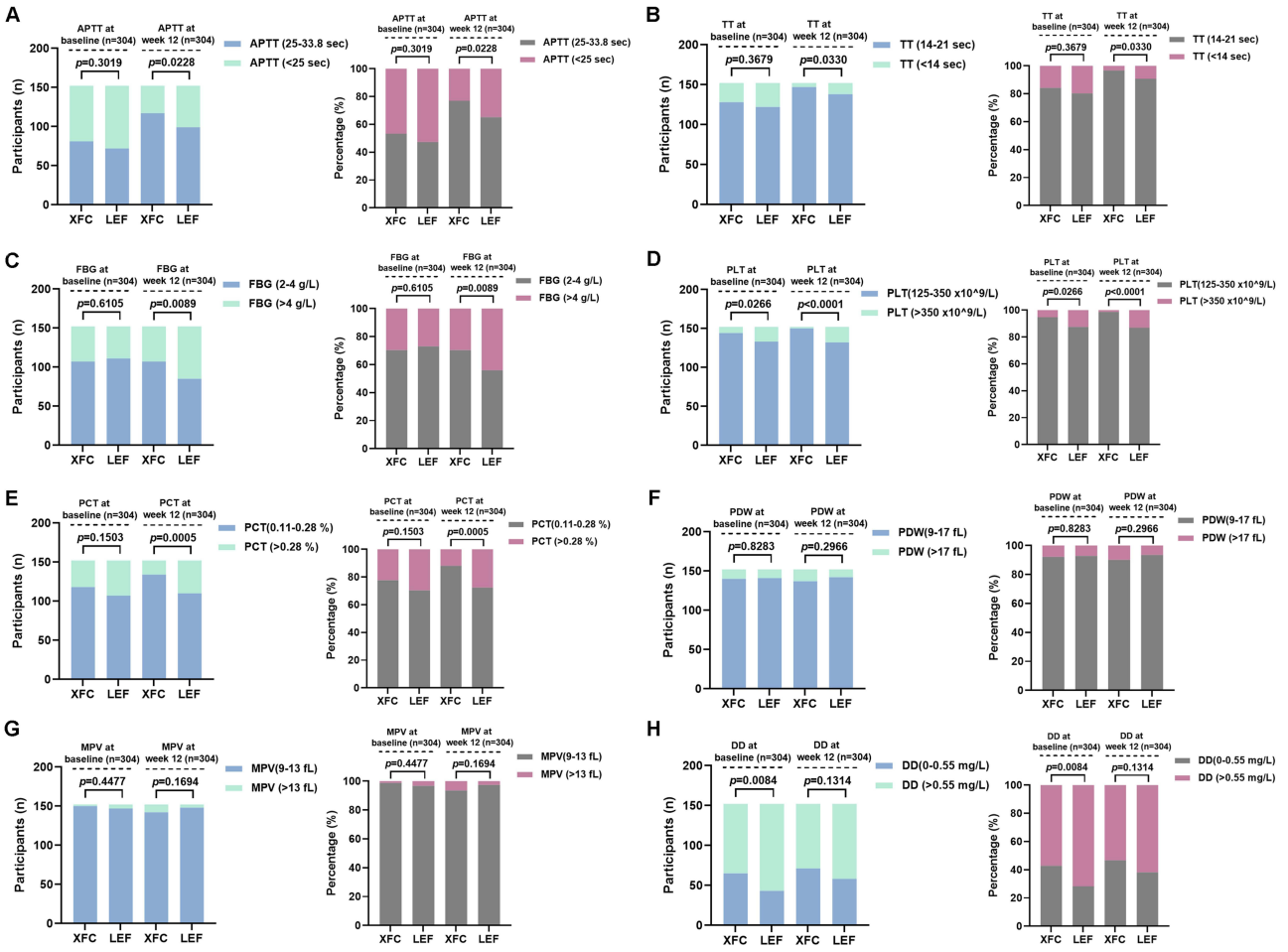

Figure 8 Post Hoc Analysis of the Proportion of Abnormal Coagulation and Platelet-Related Parameters Between Two Groups. (**A**) Proportion of patients with abnormal APTT. (**B**) Proportion of patients with abnormal TT. (**C**) Proportion of patients with abnormal FBG. (**D**) Proportion of patients with abnormal PLT. (**E**) Proportion of patients with abnormal PCT. (**F**) Proportion of patients with abnormal PDW. (**G**) Proportion of patients with abnormal MPV. (**H**) Proportion of patients with abnormal DD.

(p = 0.0330); the proportion of abnormal FBG (FBG > 4 g/L) was significantly higher in the LEF group (p = 0.0089); the proportion of abnormal PLT (PLT > $350x10^9$/L) was markedly higher in the LEF group (p < 0.0001); similarly, the proportion of abnormal PCT (PCT > 0.28%) was significantly higher in the LEF group compared to the XFC group (p = 0.0005). In contrast, there were no significant differences in the proportions of abnormal PDW, MPV, and DD between the LEF group and the XFC group at the 12th week. These findings reveal that the LEF group exhibited more significant abnormalities in coagulation and platelet-related parameters, especially by the 12th week.

Post Hoc Analysis of the Average Difference in Improvement of Coagulation and Platelet-Related Parameters Between Two Groups

Further analysis of the improvement in coagulation and platelet-related parameters between the XFC group and the LEF group revealed that the XFC group demonstrated more significant improvements in increasing FBG, PLT, PCT, PDW, and MPV compared to the LEF group (Figure 9). This indicates the superiority of XFC in improving these coagulation and platelet parameters.

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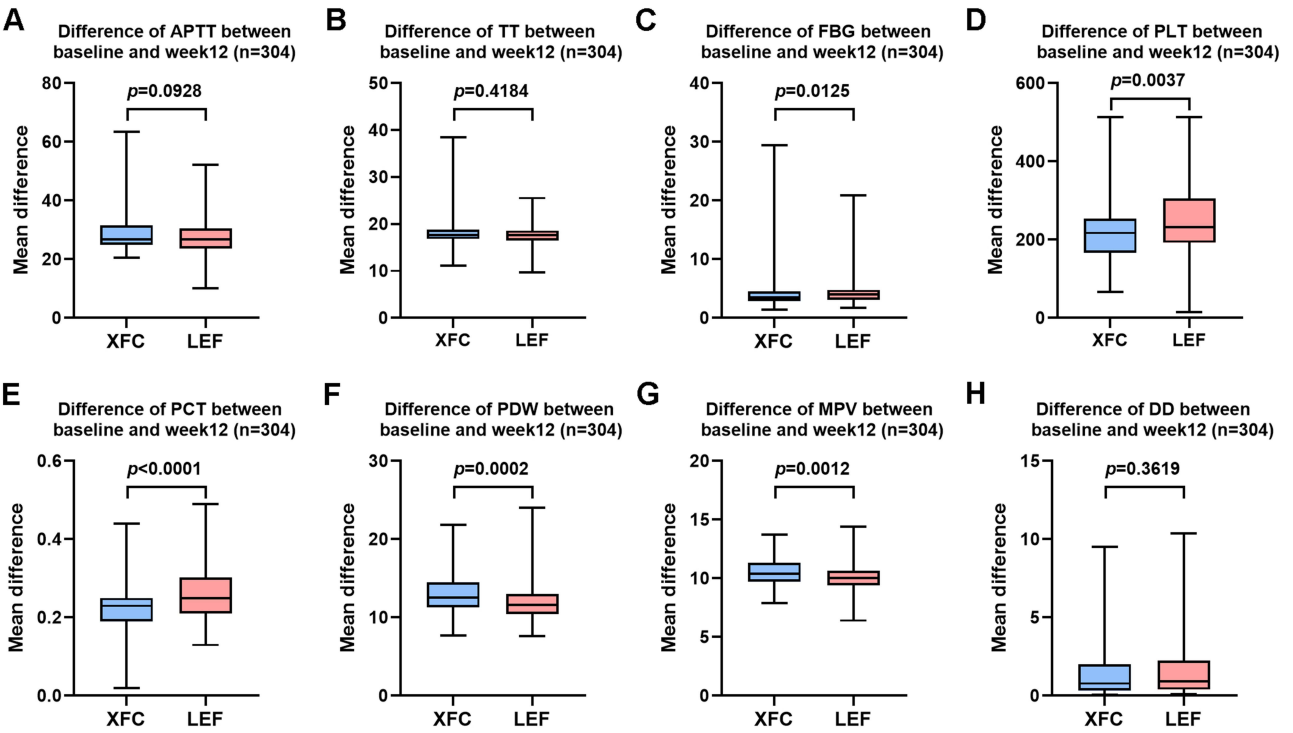

Figure 9 Post Hoc Analysis of the Average Difference in Improvement of Coagulation and Platelet-Related Parameters Between Two Groups. (**A**): Mean difference in improvement of APTT between the two groups. (**B**): Mean difference in improvement of TT between the two groups. (**C**): Mean difference in improvement of FBG between the two groups. (**D**): Mean difference in improvement of PLT between the two groups. (**E**): Mean difference in improvement of PCT between the two groups. (**F**): Mean difference in improvement of PDW between the two groups. (**G**): Mean difference in improvement of MPV between the two groups. (**H**): Mean difference in improvement of DD between the two groups.

Discussion

RA is a chronic autoimmune disease closely associated with progressive disability, systemic complications, early mortality, and substantial socioeconomic costs.[3,29] In China, the total number of RA patients has exceeded 4 million, with a peak incidence age concentrated between 30 and 50 years. More concerningly, the natural lifespan of RA patients is typically shortened by 5 to 10 years compared to that of healthy individuals.[30,31] Numerous domestic and international studies have found that RA patients often experience varying degrees of emotional and psychological changes, which severely diminish their quality of life.[32,33] For RA patients, disease activity often predicts adverse outcomes such as functional disability, radiological joint damage, and comorbidities. Traditionally, the assessment and monitoring of RA disease activity have primarily relied on parameters such as tender joint count, swollen joint count, patient global assessment score (on a 10-point scale), CRP, and ESR.[34] However, it is noteworthy that some patients with active RA may have normal CRP and ESR levels. Given the complexity and multifaceted nature of RA, there is an urgent need for more powerful biomarkers to identify active disease early and optimize long-term patient management strategies. Furthermore, despite extensive research into the underlying mechanisms causing RA, they remain incompletely understood. Currently, therapeutic approaches using drugs to block RA progression still have certain limitations.[35] In this context, traditional Chinese medicine (TCM), as an important component of complementary and alternative medicine, has gained widespread global recognition due to its excellent therapeutic effects and minimal side effects. TCM has a long history of treating RA and has demonstrated significant advantages and positive outcomes in both clinical and basic research.[36]

XFC is a hospital preparation of the First Affiliated Hospital of Anhui University of Chinese Medicine and has been included in the Guidelines of Chinese Association of Chinese Medicine Rheumatology (Standard No.: T/CACM 1042–2017).[22] Previous studies have characterized the fingerprint of XFC in detail using HPLC and established a simple, accurate, and sensitive identification and quality evaluation system for XFC through similarity analysis, hierarchical cluster analysis, and single-marker multi-component quantitative analysis.[37] These studies clearly identified

Calycosin-7-glucoside, calycosin, and Formononetinaldehyde as the main active components of XFC. Although XFC contains Tripterygium wilfordii Hook. f. components with hepatotoxicity, the toxicity may be mitigated when combined with drugs such as Astragalus membranaceus and Coicis Semen. Results from a six-month gavage experiment in SD rats showed that the general condition, body weight, and food intake of rats in all dose groups remained stable Although there were slight changes in hematological and biochemical indicators, they remained within the normal physiological range. Although statistically significant differences were observed in the organ coefficients of the lungs and spleen, histopathological examination revealed no abnormalities. Studies have confirmed that at clinically prescribed doses, XFC exhibits no significant long-term toxicity and demonstrates good medication safety.[38] In a previous study, we confirmed that XFC was comparable to leflunomide in reducing ACR20/50/70 scores, DAS28, ESR, CRP, RF, CCP, IgA, IgG, IgM, C3, C4, and other indicators; simultaneously, XFC significantly improved the quality of life of RA patients compared to the leflunomide group.[21] Building on this foundation, the present study conducted a post hoc analysis using data from a prospective, multicenter, randomized controlled trial. The aim was to assess the efficacy of XFC on coagulation and platelet-related parameters after 12 weeks of administration and to investigate the interplay between these parameters and clinical outcomes, including the SAS, SDS, and DAS28.

Abnormal changes in coagulation indicators and platelet parameters are present in RA and are closely related to inflammatory responses.[17,39] FBG, as a core element in the coagulation cascade, its deposition within joints is not only a prominent feature of RA but may also contribute to the formation of pannus tissue.[40] DD, on the other hand, is a commonly used indicator for assessing the activation status of the coagulation system. As an important plasma glycoprotein, FBG not only participates in physiological processes such as wound healing and tissue regeneration but also plays a crucial role in the pathogenesis of inflammatory arthritis by regulating proinflammatory pathways like NF-κB signaling.[41] Studies have shown a significant correlation between plasma FBG levels and RA disease activity, which may be related to the increase in FBG concentration during exacerbations of synovitis and articular cartilage damage in RA patients.[42] Additionally, in cases of systemic inflammation and infection, levels of fibrinogen degradation products (FDPs) and d-dimer also rise.[43,44] This aligns with the findings of our study, where we observed a significant correlation between plasma FBG and d-dimer levels with the severity of RA in patients.

On the other hand, MPV has been studied as a potential indicator of disease activity in various inflammatory diseases.[45] In conditions such as cancer, atherosclerosis, and RA, platelet survival is associated with various receptors, including GPIb/IX/V, CD40, and selectins.[46] In inflamed synovium of RA, platelets are a significant source of prostaglandins, and platelet-derived vesicles containing IL-1 are widely distributed in synovial fluid, inducing synovial fibroblasts to produce inflammatory mediators. Furthermore, 5-hydroxytryptamine produced by platelets increases vascular permeability in inflamed synovium.[47] Studies have demonstrated a positive correlation between MPV and disease activity in RA patients.[48] Increasing evidence suggests that platelets not only participate in hemostasis and thrombosis but also play a significant role in inflammatory processes.[49,50] Systemic rheumatoid inflammatory stimuli stimulate platelet production in the bone marrow, a process mediated by various cytokines, growth factors, and autoantibodies. A large number of platelets can be detected in the synovium and synovial fluid of RA patients.[49] Previous research has shown that serum platelet parameters (such as PLT) are significantly elevated in RA patients and are associated with the risk of rehospitalization.[39] Platelet index (PI), as a marker of platelet activation, includes PLT, MPV, PDW, and PCT, which can be easily obtained through automated blood cell counting.[51] MPV reflects the average size of platelets in the blood, PCT measures the percentage of total platelet mass relative to blood volume, and PDW describes the size distribution of platelets produced by megakaryocytes.[52] In RA patients, PLT and PCT values correlate with the DAS28 and inflammatory markers.[53] PCT is a positive acute-phase reactant in patients with active RA.[54] Studies have also shown that, compared to controls, RA patients with high disease activity have decreased PDW,[52] indicating that PDW is a negative acute-phase reactant in patients with active RA.[54] In summary, coagulation and platelet-related parameters play important roles in the pathogenesis and disease activity of RA.

This study further unveils the intricate and diverse correlations between coagulation and platelet parameters, and immune-inflammatory indicators through correlation analysis. These parameters are closely associated with the DAS28, SAS, and SDS in patients with RA. Univariate and multivariate logistic regression models reveal significant associations between levels of FBG, DD, PLT, PCT, CRP, and ESR with the risks of DAS28, SAS, and SDS. Notably, concurrent

elevations in ESR and CRP, or high ESR combined with low CRP levels, significantly increase the risk of DAS28. Simultaneous increases in FBG and CRP markedly elevate the risks of SAS and SDS, while concurrent elevations in DD and CRP also significantly increase the risk of SAS. Additionally, combinations of PLT with CRP and PCT with CRP exhibit similar trends of increased risk. Further analysis using RCS demonstrates nonlinear associations between FBG and both SAS and SDS, with increasing FBG concentrations significantly elevating the risks of SAS and SDS. Additionally, a nonlinear relationship was observed between PLT and SAS, as well as between ESR and SAS. Mediation analysis shows that the relationship between CRP and DAS28 is partially mediated by ESR, and the relationships between FBG, DD, PLT, PCT, and SAS are partially mediated by CRP, as is the relationship between FBG and SDS. ROC curve analysis reveals that CRP has the best predictive value for DAS28, PLT for SAS, and ESR for SDS.

Given that previous RCT has thoroughly analyzed changes in inflammatory indicators before and after treatment with XFC and LEF, this study focused on coagulation and platelet-related parameters to further explore the effects of XFC and LEF. The results showed that compared to baseline, XFC significantly improved APTT, TT, PLT, PCT, and PDW levels at week 12; whereas LEF significantly improved APTT, TT, FBG, and MPV levels during the same period. This suggests that both XFC and LEF can effectively regulate coagulation function and platelet-related parameters during treatment, exerting a positive impact on patients' health status. Upon further comparing the proportions of abnormal coagulation and platelet-related parameters between the XFC group and the LEF group, we found that although there were differences in the proportions of abnormal PLT and DD values at baseline, by the 12th week, the LEF group exhibited significantly higher proportions of abnormal APTT, TT, FBG, PLT, and PCT compared to the XFC group. Notably, there were consistently no significant differences in the proportions of abnormal PDW, MPV, and DD values between the two groups. These findings reveal more pronounced abnormalities in coagulation and platelet-related parameters in the LEF group, especially at the 12th week. Further analysis showed that the XFC group demonstrated more significant improvements in FBG, PLT, PCT, PDW, and MPV compared to the LEF group, indicating the superiority of XFC in regulating these coagulation and platelet parameters.

The strengths of this study are primarily reflected in three aspects. Firstly, it conducts a post hoc extension analysis of our team's previous clinical registry studies, further enriching and deepening the research on coagulation and platelet parameters in RA. Secondly, by employing various algorithms, the study clearly analyzes the relationships between coagulation and platelet parameters, immune inflammation, disease activity, and quality of life. Thirdly, it objectively evaluates the multi-pathway, multi-dimensional, and multi-level regulatory effects of Jianpi Huashi Tongluo Formula-Xinfeng Capsule (XFC), a traditional Chinese medicine compound, on RA using the evidence-based medicine method of randomized controlled trials. However, this study has several limitations that may affect the comprehensiveness and generalizability of the results: (1). Sample Selection and Representativeness: The 304 RA patients included in this study may not fully represent the characteristics of all RA patients. Factors such as patients' geography, age, gender, disease duration, and comorbidities may affect coagulation and platelet parameters, and the sample in this study may not adequately cover the full range of these variables. (2). Limitations of Post Hoc Analysis: This study is a post hoc analysis based on a completed clinical trial, meaning that the study design and data collection may not have been specifically tailored to explore coagulation and platelet parameters. Therefore, some relevant data may be incomplete or not detailed enough, limiting the depth and breadth of the analysis. (3). Limitations of Observation Time Points: This study only observed the effects of XFC treatment after 12 weeks and did not follow up on changes in coagulation and platelet parameters over a longer period. This may result in inadequate assessment of the long-term efficacy and safety of XFC. In summary, although this study provides valuable evidence for the efficacy of XFC in improving coagulation and platelet parameters in RA patients, its limitations should be carefully considered, and improvements and validations should be made in future studies.

Conclusion

In summary, this study has not only confirmed the close relationship between coagulation and platelet parameters in RA patients and the reduction in disease activity and quality of life, but also unveiled the unique therapeutic efficacy of XFC in improving these critical parameters. These findings provide compelling scientific evidence for the application of XFC in the treatment of RA, and lay a solid foundation for its further clinical promotion and mechanistic research. However,

this study has certain limitations: The representativeness of the sample may be influenced by factors such as geography, age, and disease duration. Being based on post-hoc analysis of clinical trials, the study has limitations in the depth and breadth of some data. Furthermore, only short-term efficacy over 12 weeks was observed, lacking long-term follow-up results. Future studies need to further expand sample diversity and extend the observation period to comprehensively assess the clinical value of XFC.

Abbreviations

AIC, Akaike Information Criterion; APTT, Activated Partial Thromboplastin Time; AUC, area under the curve; CCP, anti-cyclic Citrullinated Peptides Antibodies; CRP, C-reactive protein; DAS28, Disease Activity Score 28; DD, D-dimer; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; FBG, Fibrinogen; HAQ, Health Assessment Questionnaire; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LEF, Leflunomide; MPV, Mean Platelet Volume; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PCT, Platelet Crit; PDW, Platelet Distribution Width; PLT, Platelet Count; RA, Rheumatoid arthritis; RAQOL, Rheumatoid Arthritis Quality of Life; RCS, restricted cubic spline; ROC, RCT, randomized controlled trial; receiver operating characteristic; RF, rheumatoid factor; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; TCM, traditional Chinese medicine; TT, Thrombin Time; XFC, Xinfeng Capsule.

Data Sharing Statement

Data underpinning this study's findings are accessible upon reasonable request to the corresponding author, Jian Liu, at liujianahzy@126.com.

Ethics Approval and Consent to Participate

Adhering to the ethical guidelines outlined in the Declaration of Helsinki, this study protocol received approval from the Medical Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine. Informed consent was obtained from all study participants (Ethical Approval No.: 2012AH-038-01).

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Disclosure

The authors declare no competing interests in this work.

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