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Research Article

Elevation of Complement C3/C4, Immunoglobulins, and hs-CRP in Women with Recurrent Implantation Failure: Insights from a Cross-Sectional Analysis

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ABSTRACT

Objectives: Serum levels of complement proteins C3, C4, immunoglobulins (IgGs), and C-reactive protein (CRP) are crucial in understanding the pathophysiology of recurrent implantation failure (RIF). This study aims to quantify these biomarkers and explore their clinical significance.

Methods: We conducted a cross-sectional study at Arash Hospital from December 2021 to December 2023, involving 50 women with a history of RIF after in vitro fertilization (IVF) and a control group of 50 healthy, fertile women. Serum levels of C3, C4, IgG, IgM, IgA, CRP, and hs-CRP were measured using immunoturbidimetric assays and ELISA.

Results: Serum levels of complement components C3 and C4, IgG, IgA, CRP, and hs-CRP were significantly elevated in women with RIF compared to fertile controls. A positive correlation existed between C3 and C4 in the RIF group, but no significant correlations were found for IgG, IgA, or IgM. In contrast, significant associations between IgG, C3, C4, and CRP, with IgG levels also correlating with IgA were observed in fertile controls. ROC curve analysis indicated strong discriminatory power for IgG, IgA, C3, and C4. CRP AUC was 0.962, and hs-CRP AUC was 0.994, distinguishing RIF from fertile women, with CRP showing 94% sensitivity and 92% specificity at 5.3 mg/dL, and hs-CRP showing 98% sensitivity and specificity at 2.92 mg/L.

Conclusion: The findings suggest that elevated serum levels of C3, C4, IgG, and IgA in the RIF group may be associated with the underlying mechanisms of RIF.

Keywords: Recurrent Implantation Failure; Infertility, IVF; complement C3; complement C4; Immunoglobulins, CRP

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Introduction

Recurrent implantation failure (RIF), which affects 2% to 5% of cases, is a common issue in women's reproductive health, defined as more than four unsuccessful clinical pregnancies after in vitro fertilization (IVF). Approximately 50% of recurrent implantation failure (RIF) cases remain idiopathic, highlighting the need for further investigation into underlying mechanisms. Recent advancements in reproductive immunology indicate a potential link between RIF and disturbances in the mechanisms governing maternal-fetal immune tolerance. The complement system, integral to both innate and adaptive immunity, plays a pivotal role in pregnancy. Notably, complement proteins C3 and C4 are essential for facilitating placental development and enhancing embryo implantation, suggesting their involvement in supporting successful pregnancy outcomes (1).

Dysregulation or hyperactivation of the complement system is associated with negative pregnancy outcomes, including RIF, preeclampsia, and preterm birth. These adverse effects primarily arise from heightened inflammatory responses and enhanced pro-coagulant activity. Research exploring the specific roles of complement components C3 and C4 in RIF has been somewhat limited, given the system's complexity. Recent studies have revealed that women with RIF exhibit alterations in their immune profiles, highlighted by the overexpression of various complement components (1, 2). Notably, Kabut et al. found significant elevations in the levels of iC3b, C3, C4, and SC5b-9 in the serum of women diagnosed with endometriosis, with these biomarkers showing a gradual increase in relation to the severity of the condition (3).

Immunoglobulins are crucial for evaluating humoral immunity during pregnancy. Evidence indicates that a healthy pregnancy is marked by an increase in total IgG levels during the first trimester, which subsequently decreases in the second and third trimesters. The complement system, consisting of proteolytic enzymes and regulatory proteins, plays a vital role in various pregnancy phases, including implantation, fetal development, and the onset of labor. Disruptions in this system can lead to complications detrimental to both maternal and fetal health. Koshak et al. (4) reported that women diagnosed with RIF exhibit significantly elevated levels of complement factors C3 and C4, as well as IgG. Notably, this increase is more marked in individuals with secondary infertility compared to those with primary infertility.

Despite the acknowledgment of the immune system's importance for successful conception by many international reproductive and obstetric societies, routine immunological testing for female infertility is typically not endorsed. Some organizations advocate for the evaluation of autoantibodies in cases of recurrent pregnancy loss. Recently, a limited number of societies have started to recommend immunological assessments for recurrent implantation failure; however, these guidelines are largely based on insufficient evidence and are primarily directed toward research contexts (5). Presently, most reproductive societies do not provide directives for measuring total immunoglobulin and complement levels in these scenarios.

High-sensitivity C-reactive protein (hs-CRP) serves as a biomarker for systemic inflammation, exhibiting significant elevations in response to acute infections and tissue damage, while displaying moderate increases in chronic low-grade inflammatory states. Elevated serum levels of hs-CRP have been associated with decreased fecundability and adverse outcomes in assisted reproductive technology (ART) (6). A recent study highlighted that women undergoing in vitro fertilization (IVF) with elevated hs-CRP levels experienced markedly diminished rates of clinical pregnancy and live births when compared to their counterparts with lower hs-CRP concentrations (6).

This study aims to explore the clinical significance and contribution of complement components C3 and C4, immunoglobulins, C-reactive protein (CRP), and high-sensitivity CRP (hs-CRP) in the disruption of maternal-fetal immune tolerance in patients experiencing RIF. We will conduct a comprehensive analysis of serum concentrations of C3 and C4 in conjunction with other biomarker levels to elucidate their roles in the observed immunological dysregulation associated with RIF. This investigation seeks to enhance our understanding of the underlying mechanisms contributing to RIF and its relationship with immune tolerance.

Materials and Methods

Population study

This study was conducted between June 2021 and December 2023, receiving ethical approval from the Ethics Committee of Iran University of Medical Sciences (accession number: IR.IUMS.FMD.REC.1402.365). All participants provided informed consent. Current literature indicates that 2-5% of women experience RIF following more than four transfers of high-quality embryos (7, 8). The sample size was calculated using the Chi-square test, assuming a statistical power of 80% and a significance level of 0.05. Our research involved a sample size of 100 subjects, equally divided into two groups: 50 women with RIF and 50 controls **(7)**.

Inclusion and exclusion criteria

The study centered on a case-control study of 50 female patients under the age of 42 who were referred to RIF Medical Center of Referral Arash Hospital. These individuals had undergone IVF/ICSI treatment and had encountered a minimum of three unsuccessful fetal transmissions, despite receiving four or more

Table 1. Anthropometric and biochemical characteristics of studied subjects

	RIF patients mean±SD (Median, Min-Max)	Fertile women mean±SD (Median, Min-Max)	P-Value
Age	37.32±3.68 (39; 28 – 42)	36.68± 3.96 (36; 25 – 42)	0.405[1]
BMI (kg/m^2)	27.39±2.97 (26.95; 22.31 – 33.45)	26.54±2.40 (25.56; 21.93 – 32.49)	0.116[2]
P4 (ng/mL)	9.33±7.36 (10.1; 0.4 – 24.1)	14.81± 22.28 (11.4; 0.7 – 99.9)	0.102[2]
E2 (pg/ml)	94.34±41.93 (88; 37 – 201)	90.86±40.31 (95; 33.1 – 201)	0.637[2]

high-grade morphological embryos. A control group consisting of 50 women, all without prior history of IVF was included. These participants exhibited secondary infertility attributed to factors such as male infertility, tubal dysfunction, or idiopathic causes. Importantly, each woman in this group had previously achieved a successful spontaneous term pregnancy resulting in a live birth.

Exclusion criteria including: poor embryo quality and ovarian response, known disorders of the uterus or endometrial pathologies, hereditary or acquired thrombophilias, diabetes and thyroid diseases, polycystic ovary syndrome (PCOS), intrauterine pathologies, adenomyosis, endometriosis, and women/men with positive anti-lupus anticoagulant, abnormal chromosomal karyotypes or miscarriage, endocrine disorders, infectious diseases and users of contraceptives. Additionally, individuals with chronic conditions such as heart failure, hepatic dysfunction, renal insufficiency, and chronic inflammatory disorders are of particular concern. Inclusion Patient and control groups were required to meet inclusion criteria of regular ovulation periods (28-32 days) and normal endocrine profiles.

Peripheral blood samples

During the implantation period, all patients and control subjects were required to provide a 5 mL sample of peripheral blood. The blood samples were collected through venipuncture and left to stand for 15 minutes at room temperature, and then centrifuged at 1000 rpm for 15 minutes. Serum was aliquots and stored at -70°C until analysis.

Hormone assay

Hormone levels such as E2 (Cat No: 2834-96), P4 (Cat No: 2534-96), and hs-CRP (Cat No: 0234-96) were measured, using the ELISA method (MonoKit, Tehran, Iran).

Assessment of serum Levels of C3, C4 and Immunoglobulins

Serum concentrations of complement components and immunoglobulins including CRP (Ref No: DDPO1170-S), complement C3 (Ref No: 917-390), and C4 (Ref No: 917-400), as well as IgG (Ref No: 917-430), IgM (Ref No: 917-440), and IgA (Ref No: 917-420)—were measured using immunoturbidimetric analysis. All assays were conducted strictly according to the manufacturer's protocols provided by Delta Darman Teb. Biomarker levels were reported in milligrams per deciliter (mg/dL), and all measurements were performed using the Olympus AU400 analyzer (Olympus Corp., Tokyo, Japan) at a certified laboratory in Tehran, Iran.

Statistical Analysis

Data analysis was conducted using SPSS version 16.0 (IBM Corp., Armonk, NY, USA). Normality of the data distribution was evaluated via the Shapiro–Wilk test, revealing that only age conformed to a normal distribution, allowing it to be treated as a continuous parametric variable. All other variables were deemed nonparametric. Parametric data were summarized as mean ± standard deviation (SD) and subjected to independent sample t-tests for inter-group comparisons. For nonparametric data, results were expressed as median (minimum–maximum), with the Mann–Whitney U test employed for pairwise comparisons and the Kruskal–Wallis test applied for comparisons involving three or more groups. Correlation analyses utilized Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation coefficient for nonparametric variables. A threshold of $p < 0.05$ was adopted to determine statistical significance across all analyses. Graphical representations were crafted using GraphPad Prism version 8.0.0 for Windows.

Results

Demographic characteristics

Table 1 outlines the clinical profiles of patients with RIF compared to fertile controls without RIF. The analysis revealed no statistically significant differences in age, body mass index (BMI), or Serum levels of progesterone and estrogen between the two cohorts. Additionally, the etiology of infertility was comparable across both groups. Both the RIF patients and the fertile women exhibited similar mean values for retrieved oocytes and embryos.

Serum levels of Complement, Igs, CRP and hs-CRP

Serum levels of C3, C4, IgG and IgA significantly increased in women with RIF than fertile controls. The median (Min – Max) of serum levels of C3 and C4 in RIF women were significantly higher than fertile women (Fig. 1a-b). The serum concentration of IgG and IgA were significantly enhanced in RIF women compared to control (1249; 1059 - 1591 mg/dL vs. 1194; 551 – 1297 mg/dL and 261; 182 – 315 mg/dL vs. 167; 87 - 321 mg/dL respectively) (Fig. 1c-d). Furthermore, in women with RIF, the levels of CRP and hs-CRP were significantly higher than fertile women (6.4; 2.5 – 14.1 mg/dL vs. 3.98; 1.2 – 7.3 mg/dL) and (3.9; 0.5 – 8.9 mg/L vs. 1.1; 0.4 – 3.24 mg/L) (Fig. 1e-f). However, the serum IgM was similar in both groups.

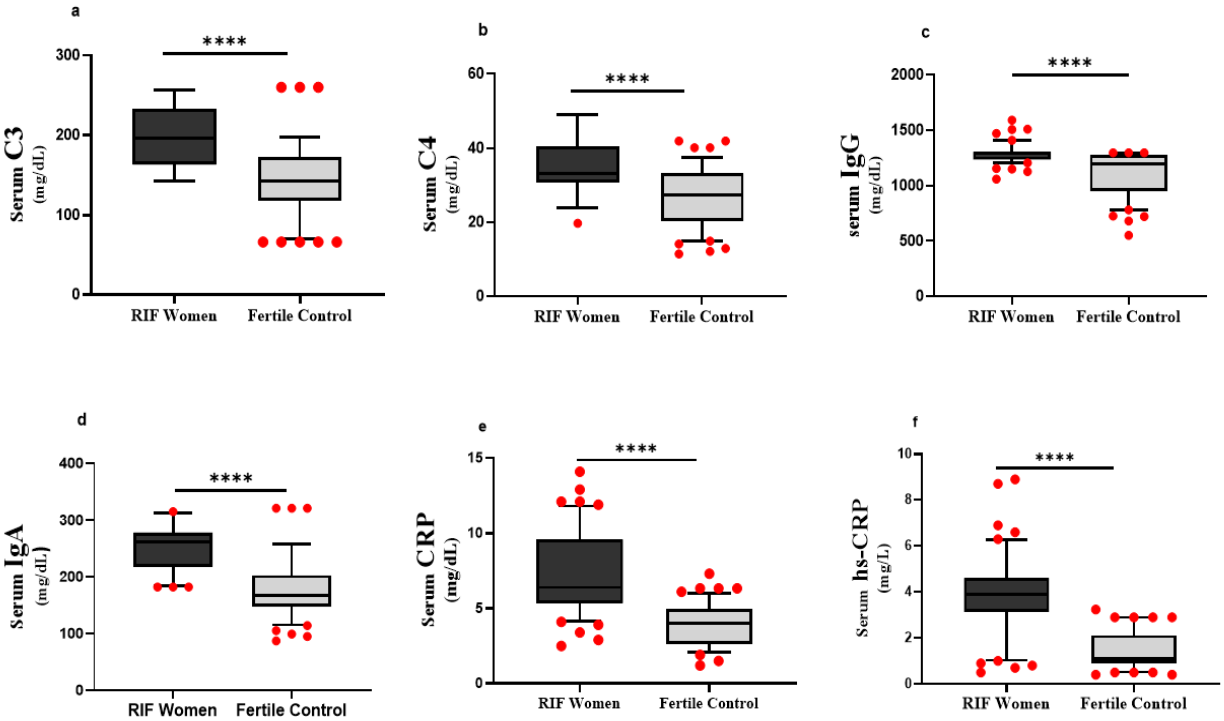
Correlations analysis

In patients with RIF, significant correlation was observed between serum C4 with C3, C3 with CRP and C4 with CRP (r= 0.615, r= 0.401, r= 0.444, respectively, all P<0.05) (Figu. 2a-c). Moreover, BMI in RIF women was significantly associated with CRP levels (r= 0.348, P<0.05) (Fig. 2d). Furthermore, it was found that hs-CRP positively correlated with IgM levels (r=0.295; P=0.044).

In fertile women, there was significant association between IgG with C3, C4 and CRP (r= 0.497, r= 0.336, r= 0.533, respectively, P<0.05) (Fig. 3a-c), and C4 significantly correlated with C3 in fertile women (r= 0.462, P<0.05). Furthermore, a positive significant correlation was found between CRP levels with C3 and C4 (r= 0.743, r= 0.326, respectively, P<0.05) (Fig. 3e-f). In fertile women, BMI was significantly associated with hs-CRP levels, whereas we did not find association BMI with hs-CRP levels in RIF women. Significant positive correlation was found between IgG and IgA (r= 0.505; P=0.002), while no significant was detected between IgG, IgA and IgM in fertile women.

ROC curve analysis

The Receiver Operator Characteristic (ROC) curve analysis for the serum IgG with [AUC: 0.756, (95% CI: 0.661 - 0.850), p<0.0001], serum IgA with [AUC: 0.840, (95% CI: 0.759 - 0.922), p<0.0001], serum C3 with [AUC: 0.781, (95% CI: 0.691- 0.873), p<0.0001] and serum C4 with [AUC: 0.738, (95% CI: 0.642 - 0.836), p<0.0001] showed an excellent discriminatory power, reaffirming the validity of our research. The ROC curve analysis results for serum concentrations of CRP and hs-CRP displayed following results with [AUC: 0.962, (95% CI: 0.931 - 0.994), p<0.0001] and [AUC: 0.994, (95% CI: 0.984 - 1.000), p<0.0001] respectively, which provide an excellent discriminatory power recognizing RIF patients from fertile women (**Fig. 4a-f**).



*) Mann–Whitney U test median; Min – Max (10th – 90th)
****p<0.0001

Figure 1. Comparative analysis of serum concentrations of complement components C3, C4, IgG, IgA, CRP and hs- CRP in the RIF and control women.

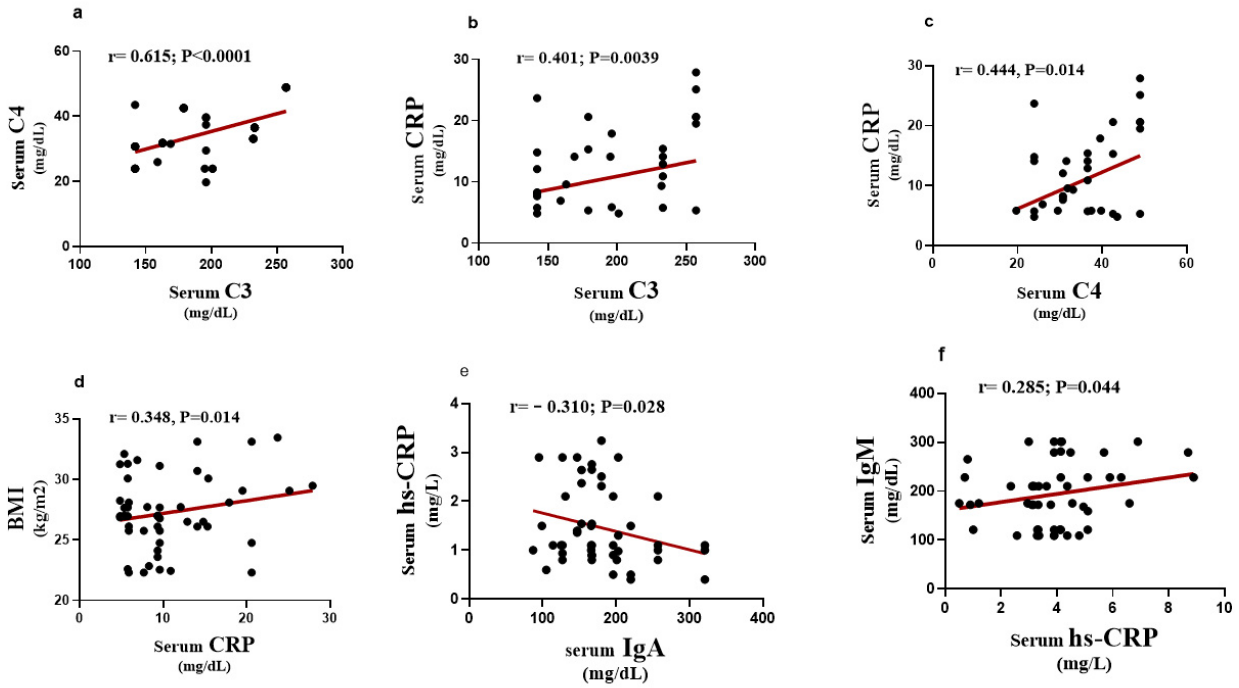


Figure 2. Correlation between complement components, immunoglobulins and CRP level in women with RIF

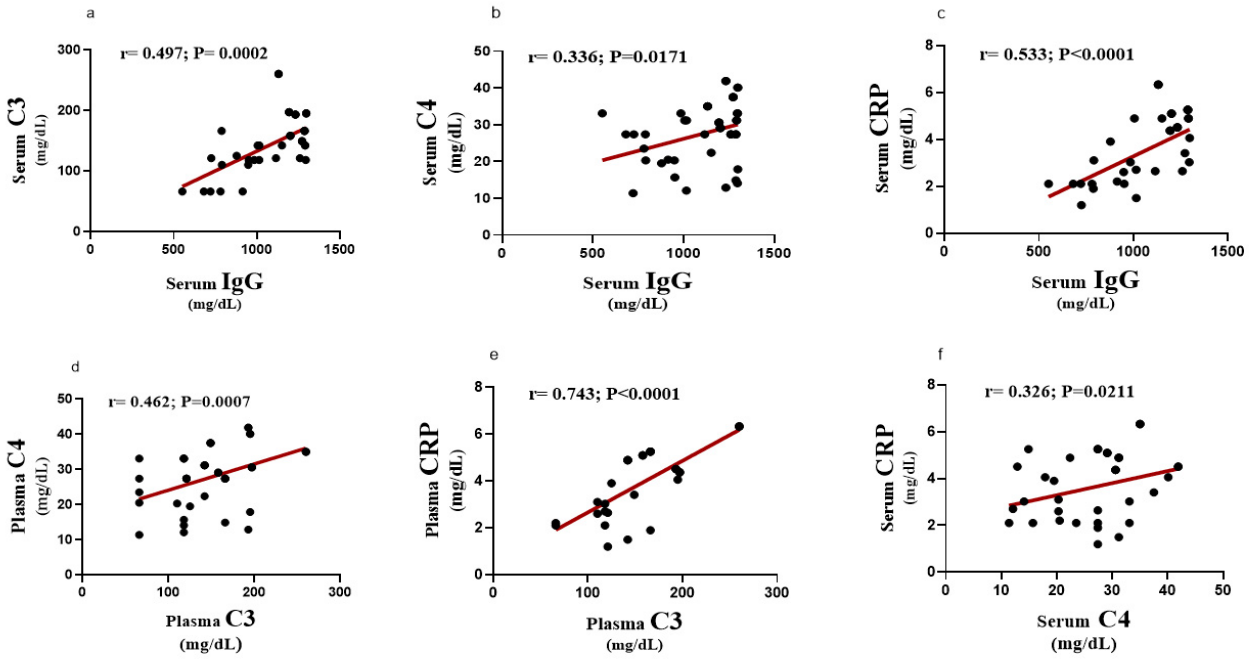


Figure 3. Correlation between complement components, immunoglobulins and CRP levels in fertile women

Using ROC curve analysis, the sensitivity and specificity and cut-off point were calculated and the data are presented in Table 2. It was found that CRP and Vit-D3 had higher sensitivity and specificity for detecting and differentiating RIF from fertile women with 94% sensitivity and 92% specificity with cut-off point 5.3 mg/dL for CRP and 70% sensitivity and 90% specificity with cut-off point 46.5 ng/mL.

Discussion

RIF presents significant challenges in reproductive health, necessitating thorough diagnostics, management, and prevention strategies. Recent studies suggest a potential link between RIF and hyperactivation of the complement system, evidenced by elevated levels of complement proteins C3 and C4, as well as high-sensitivity C-reactive protein (hs-CRP), immunoglobulin

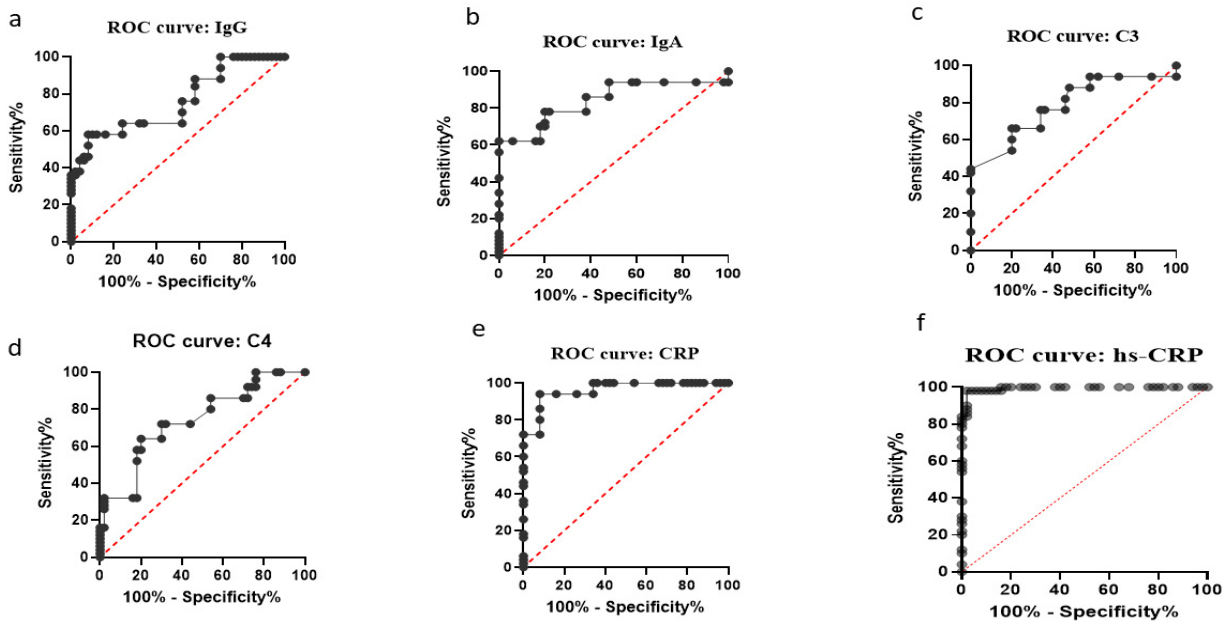


Figure 4. Receiver Operating Characteristic (ROC) analysis highlighting the variables that differentiate between RIF and healthy fertile controls

Table 2. Calculated Sensitivity, specificity, cut-off point, LR and Youden's index for measured factors according ROC analysis

Biomarker	AUC (95% CI)	Sensitivity	Specificity	Cut-off point	Likelihood ratio (LR)	Youden's index
IgG	0.756 0.661 - 0.850	64%	76%	1234 mg/dL	2.67	0.40
IgA	0.840 0.759 - 0.922	78%	80%	204 mg/dL	3.95	0.58
C3	0.781 0.691- 0.873	76%	66%	167 mg/dL	2.23	0.42
C4	0.738 0.642 - 0.836	64%	80%	30.65 mg/dL	3.20	0.44
CRP	0.962 0.931 - 0.994	94%	92%	5.30 mg/dL	11.75	0.86
hs-CRP	0.994 0.984 - 1.000	98%	98%	2.92 mg/dL	49	0.87

G (IgG), and immunoglobulin A (IgA). Serum samples from RIF patients demonstrated significantly higher concentrations of these markers compared to a control group of healthy fertile women. This observation is consistent with prior research highlighting complement activity and hypergammaglobulinemia in women experiencing recurrent infertility issues. Importantly, findings by Koshak et al. indicate that women diagnosed with unexplained female infertility (UFI) also show increased levels of C3, C4, and IgG. This underscores a critical avenue for future investigation into the mechanisms underlying these immunological factors and their potential correlations with RIF (4).

Accumulating data demonstrated that during pregnancy, women experience immune system changes to support healthy gestation, including modifications in immune cells and cytokines. Research shows that the complement system is important for immunomodulation during pregnancy. In this regard, Kimura et al. demonstrated that C3-deficient mice can prevent fetal loss, unlike those lacking C4 or C5. In humans, a complete complement system is essential for host defense,fetal survival, and optimizing placental development. Regulating this system at the placental interface is important from the early stages of pregnancy, as some complement activation occurs normally

throughout gestation (9-11).

In a recent study conducted by Amjadi et al (12), it was revealed that the expression of IL-11 is elevated in patients with polycystic ovary syndrome (PCOS). This increase may exacerbate the C3 component of the complement system, leading to enhanced complement activation that can hinder the implantation process. The complement cascade is triggered by increased production of C3 by endometrial cells, resulting in the formation of the membrane attack complex (MAC). Consequently, cell death occurs as the MAC infiltrates the membranes of endometrial cells, inducing apoptosis (12). In recent study by Zhou et al. (13). they reported that the levels of C3 and C4 were elevated in serum and decidual tissues of women with unexplained recurrent spontaneous abortion (URSA) than control women. In a relevant investigation, Banadakoppa et al (14). demonstrated that serum concentrations of C5a were markedly elevated in women experiencing spontaneous abortion (SA) as well as those undergoing elective abortion (EA). Further examination revealed three fold downregulation of CD46 and CD55 expression in the decidual tissue of women with spontaneous abortion. This notable decrease in CD46 expression may play a crucial role in the C5-mediated complement activation implicated in spontaneous abortion pathology (14). Huang et al. (2) found that C3 and C4 expression were significantly higher in RIFpatients compared to control and recurrent miscarriage (RM) patients. They suggested that RIF uniquely affects uterine receptivity, with overexpression of C3 promoting cell lysis through the membrane attack complex, while the decay-accelerating factor (DAF) inhibits this effect. In addition, He et al (15). documented that the levels of complement component C3 and C4 were at their nadir during the initial stages of pregnancy, exhibiting a progressive increase correlating with advancing gestational age. Specifically, they reported C3 levels at 93.5 ± 27.1 mg/dL and C4 levels at 35.7 ± 10.2 mg/dL in early pregnancy. In contrast, our findings revealed that C3 levels were approximately twice as high as those identified by He et al., while C4 levels remained statistically similar. Previous studies have indicated that excessive complement activation in serum may be implicated in the development and progression of implantation defects and miscarriage, particularly when complement regulatory proteins are inadequate or downregulated (13, 14, 16). Nevertheless, the elevated complement levels observed in our study could signify an early immune response phase, where these components have not yet reached their depletion threshold.

In the context of endometriosis (EM), dysregulation of the complement system plays a pivotal role in its pathogenesis. Specific complement components, including C3, C4A, C7, factor D, factor B, factor H, and mannose-associated serine protease 1 (MASP), exhibit differential expression patterns in EM tissues as opposed to normal uterine tissues. Notably, single nucleotide polymorphisms (SNPs) in the C3 gene have been associated with an elevated risk of developing EM and related infertility issues (17). C3 levels are notably upregulated in EM, with TNF-α and IL-1β produced by EM tissue identified as key stimulators of this enhancement. Moreover, comparative analyses reveal significantly higher concentrations of C3 and C4 in the peritoneal fluid of women diagnosed with EM compared to those without the condition (17).Our results indicated that the levels of CRP increased in RIF women, providing of inflammation response in RIF patients. In recent study by Huang and colleagues reported that enhanced CRP and C3 were associated with preterm birth in pregnant women. Their result suggested that C3 enhanced in PTB and these results are concomitant with prevuoius results indicated that C3 overexpression and high serum levels at early pregnancy have adverse effect on implantation and pregnancy outcome (18).

In the present study, the serum levels of IgG and IgA significantly enhanced in women with RIF. In similar study, Koshak et al (4). reported that the levels of IgG and IgA increase in women with URI and they suggested that preconception hypergammaglobulinemia as a risk factor for low pregnancy rates with IVF. Danaii et al. (19). found that women experiencing recurrent pregnancy loss (RPL) had higher IgG levels compared to normal pregnant women. Additionally, both the proportion of IL-10+ CD19+ B cells and the levels of IL-10 in serum and the culture medium of stimulated B cells were significantly reduced. Their results suggested that IL-10 may enhance pregnancy outcomes by regulating autoantibody production. Patients with more miscarriages often exhibit lower levels of these B cells producing IL-10 and higher autoantibody levels (19).

Recent studies have introduced new inflammatory and Ig biomarker for diagnosing advance stage of endometriosis (EM). Kokot et al. reported that the levels of IgG and hs-CRP significantly enhanced in the serum of women with advance EM. Moreover, serum CRP natively correlated with IgG in women with advance EM. Their ROC curve analysis indicated that IgG cut-off point was 1010 mg/dL that was similar to our results (1234 mg/dL), but our AUC, sensitivity and specificity were 0.756, 64% and 76%. However, cut-off point for hs-CRP was 2.5 and AUC, sensitivity and specificity were for hs-CRP were 0.680, 51% and 89%, respectiverly. (20). Unlike Kokot study's, our cut-off was upper limit of hs-CRP physiological range and it could be used as discriminating biomarker for women with RIF. ROC analysis also revealed that cut-off point for IgA, C3 and C4 were upper limits of reference range and they could be useful to be applied in clinical diagnostic and prognosis.

This study faced significant limitations, primarily the omission of assessments related to blood white blood cell (WBC) counts and key inflammatory cytokines,

specifically interleukin-6 (IL-6) and interleukin-1 (IL-1). Additionally, the research did not evaluate gene expression in endometrial tissue or peripheral blood mononuclear cells (PBMC), which are critical for elucidating the immunological mechanisms underlying RIF and its regulatory pathways. Another limitation was that the cross-sectional design prevented us to draw clear conclusions about the causality between elevated immune markers and RIF. The small sample size (n = 100) may reduce statistical power and increase the risk of overfitting. Additionally, although efforts were made to control for confounding factors, variables such as BMI may still influence the results. These limitations might affect the validity and generalizability of the findings.

In summary, our study demonstrated that women experiencing RIF have markedly elevated serum concentrations of complement proteins C3 and C4, alongside increased immunoglobulin levels (IgG and IgA) and heightened markers of inflammation, specifically CRP and hs-CRP, compared to a control group. Within the RIF cohort, we observed a strong positive correlation between C3, C4, and hs-CRP levels. In contrast, significant associations between IgG and complement proteins were primarily evident in the control subjects. These results suggest that systemic immune activation and inflammation may play a role in the mechanisms underlying implantation failure. Notably, C3 and hs-CRP emerged as having the highest diagnostic potential, underscoring their utility in multi-marker screening approaches. To further substantiate these findings and examine the potential for targeted complement modulation to enhance implantation success, additional longitudinal and mechanistic studies are warranted.

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Conflict of interest

The authors declare that there is no conflict of interest.

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