

# The Potential of Creatinine-Fibrinogen Ratio Levels as an Indicator of Severe Placenta Abruptio: A Retrospective Case Control Study

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**Purpose:** To compare the relationship between the severity of placenta abruptio and creatinine-fibrinogen ratio (CFR).

**Patients and Methods:** Patients with mild and severe placental abruption were separated. Patients with  $\geq 1$  maternal complications (eg, DIC, hypovolemic shock, blood transfusion, hysterectomy, acute kidney injury, death) were classified as severe placental abruption, while those without were classified as mild. The two groups were compared in terms of hematological parameters and CFR levels at the time of hospital admission.

**Results:** In the study of patients classified by the severity of placental abruption, there were 107 individuals in the mild group and 51 in the severe group. The severe group had elevated creatinine and diminished fibrinogen levels ( $p = 0.001$  and  $p < 0.001$ , respectively). The CFR levels of the severe group was significantly higher ( $p < 0.001$ ). CFR levels were used for ROC analysis to differentiate mild and severe abruptio placenta. CFR had an AUC value of 0.730 ( $p < 0.001$ ). CFR cut-off values were 0.1381 with 64.7% sensitivity and 76.6% specificity. In this analysis, logistic regression revealed significantly greater CFR (OR 1.064, 95% CI: 1.010–1.220;  $p = 0.019$ ).

**Conclusion:** CFR appears to be an effective indicator for predicting severity of placenta abruptio in pregnant women with placental abruption.

**Keywords:** creatinine-fibrinogen ratio, placental abruption, severity of placental abruption

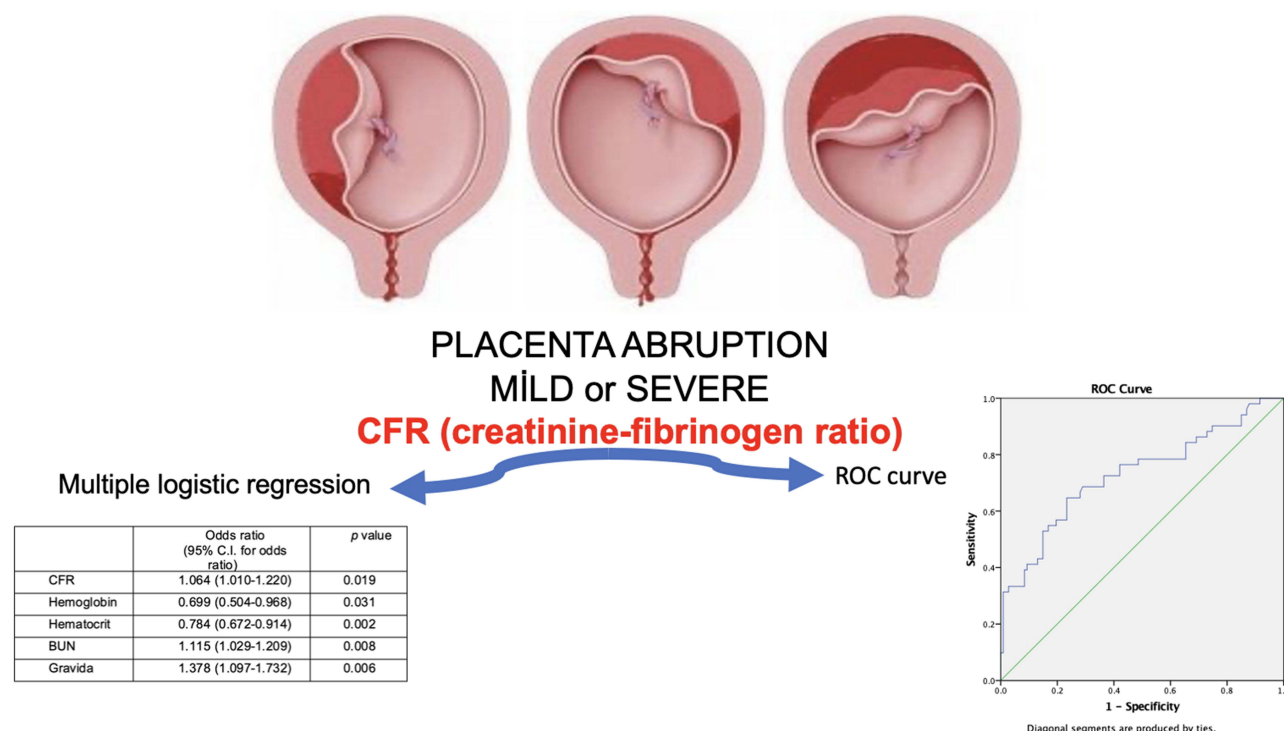
## Introduction

Placental abruption is often characterized as the early detachment of the placenta from the decidua at or beyond 20 weeks of gestation.<sup>1</sup> The overall incidence of placental abruption is approximately 3 to 10 occurrences per 1000 births.<sup>1</sup> Acute placental abruption is a major contributor to maternal morbidity and neonatal morbidity and mortality, especially in preterm case.<sup>2</sup> Mild cases of placental separation may be asymptomatic, however severe ones can present with emergency clinical signs.<sup>3</sup>

It was noted that the placenta was detached from the central region, with the area of separation exceeding 45% in over half of the patients who succumbed to placental abruption.<sup>3</sup> Intrauterine hypoxia is the cause of fetal loss in these instances. Prematurity is the primary cause of fetal fatalities during the postnatal period.<sup>3</sup> In relation to mothers, it can result in severe circumstances such as hypovolemic shock, postpartum hemorrhage, acute renal failure, and disseminated intravascular coagulation (DIC), potentially leading to maternal fatalities.<sup>4</sup>

No laboratory testing or diagnostic techniques exist for the conclusive diagnosis of placental abruption. Nonetheless, some researches have been undertaken to exclude alternative situations and establish baseline data.<sup>5,6</sup> Maternal fibrinogen and creatinine levels change throughout pregnancy. Fibrinogen levels increase to compensate for postpartum blood loss, while creatinine levels decrease due to increased maternal intravascular volume. Fibrinogen has been a significant research topic for its impact on prognosis in postpartum hemorrhage and placental abruption. Increased serum creatinine levels due to placental abruption and hemorrhage pose a risk for acute kidney injury (AKI). Laboratory findings are associated with the

## Graphical Abstract



severity of placental abruption. A minor separation may not affect conventional coagulation assays; nevertheless, more than fifty percent of a placental abruption could lead to DIC. It can progress swiftly, within hours or even minutes, resulting in intrauterine fetal mortality.<sup>7</sup> DIC is a condition resulting from systematically abnormal increases in coagulation and fibrinolytic events.<sup>8</sup> Additionally, AKI is associated with placental abruption due to severe hypovolemia and elevated coagulation factors.<sup>9</sup> A reduction in fibrinogen levels is a criterion for DIC diagnosis, while a raised creatinine level is an essential diagnostic criterion for AKI.<sup>10,11</sup> In addition, decreased fibrinogen levels in individuals with placental abruption appear to be related to the severity of the disease.<sup>12</sup> In literature, there is one study in the literature using the creatinine-to-fibrinogen ratio as a laboratory parameter to predict adverse outcomes of placental abruption.<sup>13</sup>

The diagnosis of placental abruption is most often made clinically based on the classic symptoms of vaginal bleeding and painful uterine contractions. However, abnormal nonstress test findings and ultrasound are also helpful. In our study, we aimed to determine the severity of placental abruption and to investigate the creatinine-to-fibrinogen ratio (CFR) in patients who underwent emergency cesarean delivery with a preliminary diagnosis of placental abruption.

## Material and Methods

This was a 6-year retrospective analysis of cases who were clinically diagnosed with placental abruption between September 2018 and September 2024. Premature placental abruption occurring before the 20th week of gestation, patients with chronic hematological disease, patients using anticoagulant medication, and patients with uterine anomalies, kidney or liver disease, pregnancies resulting from assisted reproductive technology, multiple gestations, smokers and patients diagnosed with chronic abruption or chorioamnionitis were excluded from the study. The required data were collected from electronic database of the hospital. One hundred fifty-eight patients aged 18 to 45 years were enrolled in the study. Patients with placental abruption who had minor placental bleeding on ultrasound and were clinically stable were not included in the study. Patients with clinical symptoms of acute placental abruption who underwent emergency cesarean delivery were included in the study. The diagnosis of placental abruption was validated by the identification of the retroplacental hematoma during the operation.

Patients were divided into two groups as mild and severe placental abruption. Patients with  $\geq 1$  maternal complications such as disseminated intravascular coagulation (DIC), hypovolemic shock, blood transfusion, hysterectomy, acute kidney injury, and fetal death were enrolled in the severe placental abruption group, while those without were enrolled in the mild placental abruption group.<sup>13</sup>

The patients' age, body mass index, gestational age at delivery, gravida, parity number, length of hospital stay, maternal fetal intensive care transfer history was recorded. Birth weight, APGAR score at 1. minutes and 5. minutes, neonatal intensive care unit (NIUC) admission requirements, presence of stillbirth were recorded as fetal outcomes. Laboratory data at the time of the first application before delivery as routine screenings for all admitted patients included hemoglobin (Hb), hematocrit (Htc), white blood cell (WBC), platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine (Cr), mean platelet volume (MPV), fibrinogen and creatinine–fibrinogen ratio (CFR) values were recorded. All data were compared between the groups. Additionally, CFR for severe placental abruption were evaluated.

We employed the Shapiro–Wilk test to determine if the continuous data had a normal distribution. Mean  $\pm$  standard deviation was employed for regularly distributed continuous data, whereas median (interquartile range (IQR)) was utilized for non-normally distributed variables. Categorical variables were recorded as numerical values and percentages. The Mann–Whitney *U*-test was employed for two independent groups without normal distribution, while the Independent Samples *t*-test was utilized when normal distribution was present. The receiver operating characteristic (ROC) curve analysis was employed to ascertain the optimal cut-off values of CFR for the diagnosis of severe abruptio placenta with the highest degree of sensitivity and specificity. A logistic regression analysis was used to investigate the associations between the severity of abruption placenta. The possible risk factors for severity identified with univariate analysis were included in the multiple logistic regression analysis. The odds ratio (OR) and its 95% confidence interval were calculated. We considered  $p < 0.05$  to be statistically significant.

## Results

Our study was conducted with 158 patients. Among the patients grouped according to mild or severe placental abruption, there were 107 patients in mild group, 51 in severe group. Demographic characteristics, obstetrics and fetal outcomes of the patients were shown in Table 1. Hospital stay length and need of maternal intensive care of patients were statistically higher in severe group ( $p < 0.001$ ). Apgar 1. and 5. minute of fetus were statistically lower in severe group ( $p < 0.001$ ). There was no statistically significant in terms of need for neonatal intensive care between groups ( $p = 0.166$ ). Stillbirth was statistically higher in severe group ( $p < 0.001$ ). There was no maternal death in any of our cases.

We showed the laboratory parameters and CFR in Table 2. The severe group exhibited a substantially higher CFR value than the mild group ( $p < 0.001$ ). In addition, hemoglobin, hematocrit, MPV and fibrinogen levels were found to be significantly higher in mild group ( $p < 0.001$ ,  $p < 0.001$ , and  $p = 0.027$   $p < 0.001$ , respectively). There was no statistically significant in terms of platelet between the groups ( $p = 0.199$ ). BUN and creatinine levels were statistically higher in severe group ( $p < 0.001$  and  $p = 0.001$  respectively).

**Table 1** Comparison of Patient Characteristics and Clinical Features

| Variables                                            | Mild Group<br>(n=107) | Severe Group<br>(n=51) | p value |
|------------------------------------------------------|-----------------------|------------------------|---------|
| Age (years) (mean $\pm$ S.D.)                        | 28.65 $\pm$ 6.66      | 31.00 $\pm$ 7.22       | 0.053   |
| BMI (kg/m <sup>2</sup> ) (median, IQR)               | 25.18 (4.18)          | 26.23 (2.26)           | 0.140   |
| Gestational age at delivery (week) (mean $\pm$ S.D.) | 33.29 $\pm$ 4.77      | 30.94 $\pm$ 4.77       | 0.004   |
| Gravida (number) (median, IQR)                       | 3 (2)                 | 3 (3)                  | 0.012   |
| Parity (number) (median, IQR)                        | 1 (2)                 | 2 (2)                  | 0.012   |
| Hospital stay (day) (median, IQR)                    | 3 (0)                 | 4 (2)                  | < 0.001 |

(Continued)

**Table 1** (Continued).

| Variables                                      | Mild Group<br>(n=107)    | Severe Group<br>(n=51)   | p value |
|------------------------------------------------|--------------------------|--------------------------|---------|
| Need for maternal intensive care<br>(+)<br>(-) | 0 (0%)<br>107 (100%)     | 22 (43.1%)<br>29 (56.1%) | < 0.001 |
| Hysterectomy<br>(+)<br>(-)                     | 0 (0%)<br>107 (100%)     | 5 (9.8%)<br>46 (90.2%)   | 0.001   |
| Birth weight (grams) (mean ± S.D.)             | 2316.58 ± 979.20         | 1729.50 ± 867.34         | < 0.001 |
| Apgar 1. minute (median, IQR)                  | 8 (1)                    | 5 (8)                    | < 0.001 |
| Apgar 5. minute (median, IQR)                  | 9 (1)                    | 8 (9)                    | < 0.001 |
| Need for neonatal intensive care<br>(+)<br>(-) | 40 (37.4%)<br>67 (62.6%) | 25 (49%)<br>26 (51%)     | 0.166   |
| Stillbirth<br>(+)<br>(-)                       | 5 (4.7%)<br>102 (95.3%)  | 15 (29.4%)<br>36 (70.6%) | < 0.001 |

**Abbreviations:** mean ± S.D, mean ± standard deviation; IQR, interquartile range; BMI, body mass index.

**Table 2** Comparison of Laboratory Data

|                                                | Mild Group<br>(n=107) | Severe Group<br>(n=51) | P value |
|------------------------------------------------|-----------------------|------------------------|---------|
| Hemoglobin (g/dL) (median, IQR)                | 11.4 (1.8)            | 9.4 (2.2)              | < 0.001 |
| Hematocrit (%) (median, IQR)                   | 34.2 (5.2)            | 28.8 (7.1)             | < 0.001 |
| White blood cell count (×10 /L) (median, IQR)  | 11.2 (3.75)           | 12.9 (7.4)             | < 0.001 |
| Platelet count (× 10 /L) (mean ± S.D.)         | 226.88 ± 70.20        | 208.59 ± 88.46         | 0.199   |
| Aspartate aminotransferase (U/L) (median, IQR) | 21 (13)               | 23 (14)                | 0.779   |
| Alanine aminotransferase (U/L) (median, IQR)   | 12 (8)                | 12 (8)                 | 0.639   |
| BUN (mg/dL) (median, IQR)                      | 14 (7)                | 18 (10)                | < 0.001 |
| Creatinine (mg/dL) (median, IQR)               | 0.44 (0.18)           | 0.52 (0.26)            | 0.001   |
| MPV (fL) (median, IQR)                         | 9.5 (2.1)             | 8.9 (1.2)              | 0.027   |
| Fibrinogen (g/L) (mean ± S.D.) (median, IQR)   | 4.15 ± 1.10           | 3.18 ± 1.59            | < 0.001 |
| CFR (median, IQR)                              | 0.110 (0.052)         | 0.155 (0.193)          | < 0.001 |

**Abbreviations:** mean ± S.D, mean ± standard deviation; IQR, interquartile range; BUN, Blood urea nitrogen; MPV, Mean Platelet Volume; fL, femtoliter; g/dL, grams per deciliter; U/L, units per liter; mg/dL, milligrams per deciliter; g/L, grams per liter; CFR, creatinine–fibrinogen ratio.

ROC analysis was performed using CFR levels to separate mild and severe abruptio placenta groups. The AUC value for CFR was found as 0.730 ( $p < 0.001$ ). The CFR cut-off values were 0.1381, exhibiting 64.7% sensitivity and 76.6% specificity (Table 3 and Figure 1).

**Table 3** Cut-off Points Analysis of CFR Values to Determine Severe Abruption Placenta

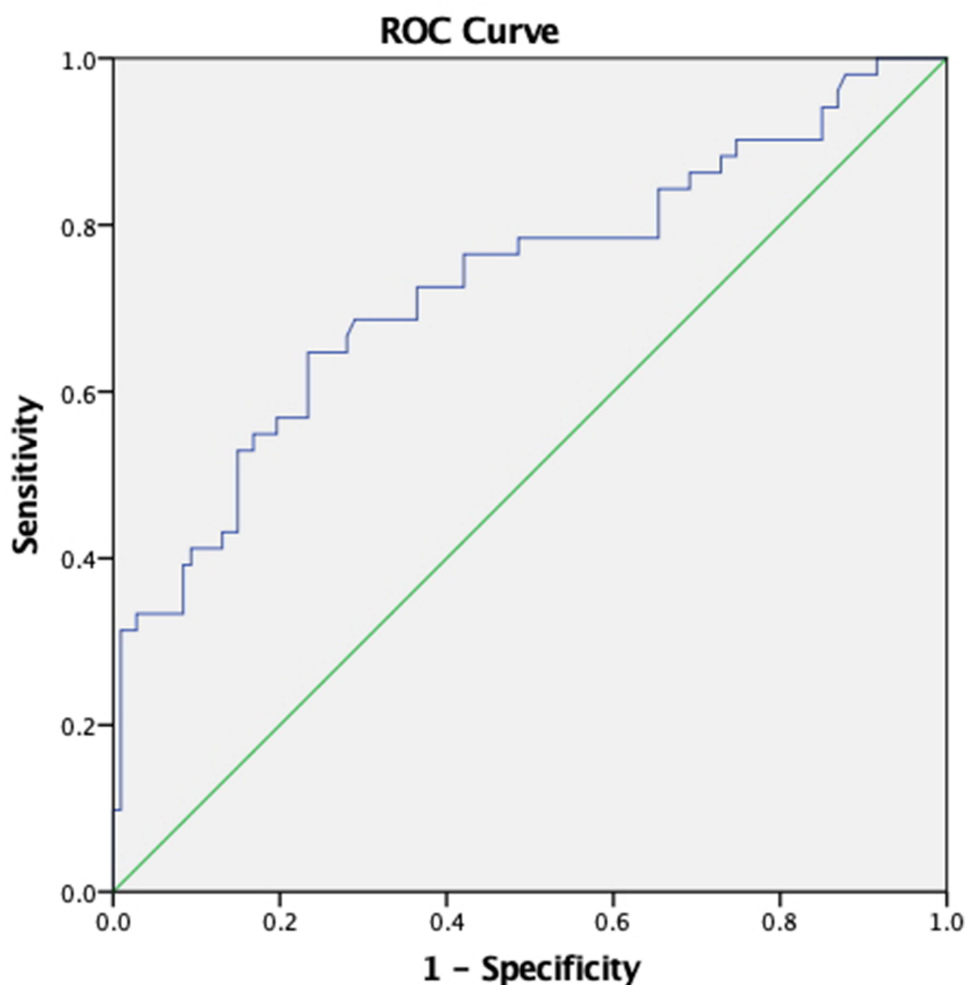
|     | Cut Point | AUC   | p       | Sensitivity 95% CI | Specificity 95% CI | PPV 95% CI       | NPV 95% CI       |
|-----|-----------|-------|---------|--------------------|--------------------|------------------|------------------|
| CFR | 0.1381    | 0.730 | < 0.001 | 64.7 (50.1–77.6)   | 76.6 (67.5–84.3)   | 56.9 (47.0–66.3) | 82.0 (75.6–87.0) |

**Abbreviations:** AUC, area under curve; CFR, creatinine–fibrinogen ratio; PPV, Positive predictive value; NPV, Negative predictive value.

In this analysis, logistic regression revealed significantly greater CFR (OR 1.064, 95% CI: 1.010–1.220;  $p=0.019$ ), hemoglobin (OR 0.699, 95% CI: 0.504–0.968;  $p=0.031$ ), hematocrit (OR 0.784, 95% CI: 0.672–0.914;  $p=0.002$ ), BUN levels (OR 1.115, 95% CI: 1.029–1.209;  $p=0.008$ ) and gravida (OR 1.378 95% CI: 1.097–1.732;  $p=0.002$ ) in the severe placenta abruption than mild placenta abruption (Table 4).

## Discussion

Laboratory findings play an important role in the severity of placental abruption. In our study, we found a significantly higher CFR value in the severe abruption placenta group than in the mild group ( $p<0.001$ ). In the ROC analysis using CFR levels, we found the AUC value for CFR to be 0.730 ( $p<0.001$ ). As a result of logistic regression, we found a significantly greater CFR (OR 1.064, 95% CI: 1.010–1.220;  $p=0.019$ ) in severe placental abruption than in mild placental abruption.



**Figure 1** The ROC curve analysis to investigate the value of creatinine–fibrinogen ratio in severe placenta abruption.

**Table 4** Multiple Logistic Regression Analysis of Factors Related to the Severity of Abruptio Placenta

|            | <b>Odds Ratio<br/>(95% C.I. for Odds Ratio)</b> | <b>p value</b> |
|------------|-------------------------------------------------|----------------|
| CFR        | 1.064 (1.010–1.220)                             | 0.019          |
| Hemoglobin | 0.699 (0.504–0.968)                             | 0.031          |
| Hematocrit | 0.784 (0.672–0.914)                             | 0.002          |
| BUN        | 1.115 (1.029–1.209)                             | 0.008          |
| Gravida    | 1.378 (1.097–1.732)                             | 0.006          |

**Abbreviations:** CFR, creatinine–fibrinogen ratio; BUN, Blood urea nitrogen; MPV, Mean Platelet Volume.

Premature separation of the placenta after the 20th gestational week of pregnancy is called placental abruption.<sup>14</sup> The pathogenesis of placenta abruptio is intricate, and the precise mechanisms that underlie this severe obstetric complication have yet to be fully understood. Nevertheless, the primary risk factors were identified as hypertensive disorders of pregnancy, chronic renal disease, autoimmune conditions, cocaine dependency, trauma, preterm premature rupture of membranes, and chorioamnionitis. Additionally, a cascade of events that results in placenta abruptio may be initiated by injury of placenta, compromised placental perfusion, tissue hypoxia, and modified inflammatory processes.<sup>15</sup> Thrombin is a pivotal factor in the clinical signs of abruption and may potentially play a role in its development.<sup>16</sup>

Patients who experience an acute abruption typically exhibit the sudden onset of uterine contractions, mild to moderate abdominal pain, and vaginal bleeding.<sup>9</sup> The three predominant placental sites for abruption are retroplacental, subchorionic, and preplacental,<sup>17</sup> however, these discoveries are not apparent in all instances.<sup>18</sup> Morbidity and mortality for the fetus in placental abruption depend on the severity of the separation and the gestational age, while for the mother, it is directly proportional to the severity of the separation.<sup>18,19</sup> Excessive hemorrhage and disseminated intravascular coagulation are severe maternal outcomes of placental abruption. These complications may result in acute renal failure, adult respiratory distress syndrome, multiorgan failure, and shock, and might potentially lead to postpartum hysterectomy or, in rare instances, maternal mortality.<sup>9,20</sup>

The degree of placental separation is correlated with laboratory parameters. A moderate degree of separation may not correlate with abnormalities in standard hemostasis testing, however a separation exceeding 50% can result in DIC.<sup>7</sup> Fibrinogen levels are one of the hematological tests that most accurately correlate with the amount of bleeding in patients who develop DIC and require transfusion.<sup>12</sup> Fibrinogen levels below 2 g/L show a 100% positive predictive value for predicting the severity of postpartum hemorrhage, whereas levels  $\geq 4$  g/L demonstrate a negative predictive value of 79%.<sup>6</sup> In our study, there was statistically significant in terms of initial fibrinogen levels between the mild and severe groups. In severe group it was lower due to the consumption of fibrinogen in homeostasis.

In addition, acute tubular and cortical necrosis may occur in the kidney due to acute hypovolemia in placental abruption.<sup>9</sup> This may cause an increase in creatinine levels in this patient group in direct proportion to the severity of placental abruption. There was also statistically significant in terms of initial creatinine levels between the mild and severe groups in our study. The creatinine levels were higher in severe group because of hypovolemia.

In the literature, Özkavak et al reported that both fibrinogen and creatinine were used to determine the severity of placental abruption, but a cut-off value was not determined for these two values, and CFR could be a practical and cost-effective marker for the adverse outcomes of placental abruptio and by performing ROC analysis, they found reliable sensitivity and specificity for the defined cut-off value.<sup>13</sup> In our study, CFR values were compared to determine the severity of placenta abruptio. There was a statistically significant difference in CFR values between mild and severe groups. We also found a 0.1381 cut-off value in the current study to determine the severity of abruptio placenta. (AUC=0.730,  $p<0.001$ ). This cut-off value has 64.7% sensitivity and 76.6% specificity.

In a recent study, Loyd et al evaluated hyperfibrinolysis and dysfibrinogenemia in acute obstetric coagulopathy during postpartum hemorrhage (PPH).<sup>21</sup> Most women exhibited normal hemostasis during PPH, but a small number of women

developed severe early hemostatic impairment that can lead to extensive PPH, according to their report. They determined that 12 out of 518 individuals (2.3%) exhibited a specific coagulopathy, characterized by extensive hyperfibrinolysis. In our study we excluded patients with hematological disease but there may be specific coagulopathies as reported above and may be undiagnosed, unknown to the patient. This situation could also be another way of explanation of higher CFR in patients with severe placental abruption.

Su et al conducted an analysis of the predictive value of before the delivery laboratory test results concerning the severity of placental abruption and pregnancy outcome.<sup>22</sup> Their findings indicated that the severity of placental abruption was correlated with before the delivery routine blood, biochemical, and coagulation parameters. Placental abruption may manifest as either overt bleeding or covert hemorrhage. Hemorrhage involves a decrease in blood volume, regardless of its classification. Subsequent to acute short-term blood loss, white blood cell counts increase, whereas hemoglobin levels, erythrocyte volume, platelet count, and serum albumin levels decrease, along with additional stress-related responses. Blood clots that develop between the placenta's surface and the uterine wall include increased levels of thrombin and tissue factors, which activate coagulation system. Nevertheless, patients with a separated placenta are unable to deliver promptly, and the continuous influx of thrombin and tissue factor can stimulate the coagulation and fibrinolytic processes, potentially leading to DIC. The fibrinogen and D-dimer levels in the degree III abruption group were significantly reduced, which elucidated the low-coagulation state observed in this group of patients.<sup>22</sup> In our study, similar to studies in the literature, decreased fibrinogen was found in the severe placental abruption group. Although the treatment of serious complications such as DIC due to placental abruption is done supportively, the data in our study may be a warning for clinicians about the serious complications of placental abruption.

While the strength of our study is being the second study comparing CFR values according to the severity of placental abruption, its limitation is retrospective design.

## Conclusion

In patients with a definitive diagnosis or strong suspicion of placental abruption, the severity of the condition can be first assessed using these laboratory indices. CFR seems to be a potential and significant predictor of disease severity in women with placental abruption.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author Dr. Fikriye Işıl Adıgüzel on reasonable request.

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Clinical Research Ethics Committee of Health Sciences University Adana City Training and Research Hospital in 05/12/2024 (decision number 256). Written informed consent was obtained from all individual participants included in the study.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This research received no external funding.

## Disclosure

The authors report no conflicts of interest in this work.

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