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The Fibrinogen/CRP Ratio as a New Parameter for the Prediction of Disseminated Intravascular Coagulation in Patients with HELLP Syndrome

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ABSTRACT

Background: The syndrome of Hemolysis, elevated Liver enzymes, and Low Platelet count (HELLP) is a life-threatening variant of preeclampsia, and may be accompanied by disseminated intravascular coagulation (DIC). Recently the fibrinogen/C-reactive protein (CRP) ratio has been suggested as a measurement that predicts onset of DIC. The authors sought to analyze the fibrinogen/CRP ratio among obstetric patients who developed DIC due to HELLP syndrome. **Aim:** the aim of this study is to determine if the fibrinogen/C-reactive protein (CRP) ratio could be used as a predictor for disseminated intravascular coagulation in obstetrics patients with the HELLP syndrome. **Patients and Methods:** this study was conducted as a prospective observational study at Ain Shams Maternity Hospital from November 2014 to November 2016 .The study included Patients diagnosed to have Severe Pre Eclamptic Toxemia SPET according to ***ACOG (2013).***Patients was diagnosed with the HELLP syndrome according to the **Martin** classification of HELLP syndrome. **Results:** the results of our study suggest that replacing the use of fibrinogen levels alone with the fibrinogen/CRP ratio would enhance the diagnostic and prognostic power for DIC in patients with HELLP syndrome. **Conclusion:** in light of the physiologic changes of the coagulation cascade during gestation, the International Society on Thrombosis and Hemostasis **ISTH** score could not be implemented in pregnant women alone for the diagnosis and prediction of DIC. **Recommendations:** further evaluation of the fibrinogen/ CRP ratio is required to determine the generalizability of this marker's use in DIC because of causes such as placental abruption, septic abortion, and failed abortion. Furthermore, prospective studies should be performed to determine the best method to predict if there any new method to predict DIC in patients with the HEELP syndrome.

Keywords: HELLP syndrome, fibrinogen, C-reactive protein, pre-eclampsia, DIC

INTRODUCTION

Preeclampsia is a human-pregnancy-specific disease defined as the occurrence of hypertension and significant proteinuria in a previously healthy woman on or after the 20th week of gestation. It occurs in about 2–8% of pregnancies [(1)].

It is the most common medical complication of pregnancy whose incidence has continued to increase worldwide. It is associated with significant maternal morbidity and mortality, accounting for about 50,000 deaths worldwide annually [(2)].

The etiology of preeclampsia is poorly understood, a leading theory is that insufficient spiral artery remodeling in the placenta may result in a hypoxic environment with reperfusion injury and up-regulation of oxidative stress, the pre-eclamptic placenta secretes factors such as inflammatory cytokines and reactive oxygen species into maternal circulation to induce hypertension through local production of vasoconstrictors, notably endothelin-1 [(3)].

Most theories on the etiology of preeclampsia suggest that the disease is a cascade triggered by combination of abnormal maternal inflammatory response, endothelial cell activation/damage with deranged hemodynamic milieu, and deranged immunity [(1)]. The HELLP syndrome is a serious complication in pregnancy characterized by haemolysis (H), elevated liver enzymes (EL) and low platelet count (LP) occurring in 0.5 to 0.9% of all pregnancies and in 10–20% of cases with severe preeclampsia [(4)].

This syndrome usually develops suddenly between 28-36 weeks gestation. Its etiology and pathogenesis are not well understood. Generally, the disorder is considered a placenta-instigated, liver-targeted acute inflammatory condition, with elements of disordered immunological processes the hemolysis which characterizes the syndrome is of microangiopathic origin. Red cells become fragmented as they pass through small vessels with pathological fibrin deposits and damaged endothelium. Obstruction of hepatic blood flow by the same fibrin deposits in hepatic sinusoids results in elevated liver enzymes, and peri portal

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necrosis. In severe cases, intra hepatic hemorrhage, sub capsular hematoma, or even hepatic rupture may occur. Thrombocytopenia, the third aspect of the triad, results from increased consumption and destruction of platelets [5].

Anti-angiogenic factors released into maternal blood induce the maternal syndromes. Maternal blood levels of anti-angiogenic soluble Fms like tyrosine kinase 1(sFlt1) are similar, but endoglin and Fas Ligand levels are possibly higher in HELLP than in preeclampsia. These factors trigger the vascular endothelium, resulting in an enhanced inflammatory response which is stronger in HELLP. Activated coagulation and complement, with high levels of activated leucocytes, inflammatory cytokines, TNF-, and active von Willebrand factor, induce thrombotic microangiopathy with platelet-fibrin thrombi in microvessels. The angiopathy results in consumption of circulating platelets, causes hemolysis in affected microvessels and reduces portal blood flow in the liver. Placental Fas Ligand damages hepatocytes, resulting in periportal necrosis. In about one half of women with HELLP, activation of coagulation factors and platelets precipitates disseminated intravascular coagulation, which in a minority becomes uncompensated and contributes to life-threatening multiorgan failure [6].

The mortality rate of women with HELLP syndrome is approximately 1.1%, from 1 to 25 % of affected female develops serious complications such as disseminated intra vascular coagulopathy (DIC), placental abruption, adult respiratory distress syndrome, hepatorenal failure, pulmonary edema, sub capsular hematoma and hepatic rupture. A significant percentage of patients receive blood products [7].

DIC is one of the leading causes for maternal mortality worldwide although DIC results from a wide spread activation of both clotting and fibrinolysis systems leading to: 1) systemic production of fibrin split products, and thrombi that leads to end-organ ischemia; 2) increased vascular permeability due to activation of the kinin system; and 3) microangiopathic hemolysis, during pregnancy hemorrhage is the leading mechanisms for the development DIC [8].

The International Society for Thrombosis and Hemostasis (ISTH) has adopted a score that assists in the diagnosis and the identification of patients at risk for the development of DIC. This score is based on readily available coagulation assays including Prothrombin time PT, Partial thromboplastin time PTT, fibrinogen and D-dimer or fibrin split products. In non-pregnant patients, there is a good correlation between an abnormal score result and the development of DIC [8].

Only 33% of the patients with pregnancy-related conditions that were predisposed to DIC development fulfilled the ISTH criteria regarding the parameter fibrinogen [8].

However, in light of the physiologic changes of the coagulation cascade during gestation, this score could not be implemented in pregnant women, On the other hand, the morbidity and mortality associated with severe hemorrhage and consumption coagulopathy leading to DIC during pregnancy emphasizes the need for the adjustment of this ISTH DIC score to these patients [9].

So a new diagnostic issue: for the author's study population 1056 patients who developed a DIC because of different underlying diseases were selected and investigated regarding coagulation parameters. It turned out that only 8-6% of these patients showed fibrinogen levels under the cutoff value of 100 mg/dL as proposed in the ISTH criteria. Considering fibrinogen as an acute phase reactant it seems to be clear getting elevated in patients with infection and inflammatory disease. A plasma level of fibrinogen that is not adjusted to this acute phase reaction, as in the ISTH criteria, cannot be considered as a useful marker of DIC [10].

AIM OF THE WORK

The aim of this study is to determine if the fibrinogen/C-reactive protein (CRP) ratio could be used as a predictor for disseminated intravascular coagulation in obstetrics patients with the HELLP syndrome.

PATIENTS AND METHODS

1. **Place:**
   Ain Shams Maternity Hospital.
2. **Time:**
   Starts from November 2014 and ends in November 2016.
3. **Type of the study:**
   Prospective observational study.
4. **The inclusion criteria are:**
   - Patients diagnosed to have SPET according to the Diagnostic criteria of pre-eclampsia ***ACOG*** [11].

- Patients with the HELLP syndrome according to **Martin** classification **2013** [12].

5. **The exclusion criteria:**

Any patient with established or diagnosed infection.

Intervention:

After taking informed written consent, the recruited patients were subjected to the following.

1. **Careful and detailed history.**

A. Personal history:

Name, age, occupation, residence and special habits of medical importance.

B. Obstetric history:

First day of last menstrual period for accurate estimation of gestational age and antenatal care.

C. Past history:

History of any medical disorder or surgical history.

D. History of the present pregnancy:

Medical or surgical condition to define high risk pregnancy.

2. **Examination of the patients:**
   a) General examination
   b) Abdominal examination
   c) Vaginal examination
   d) Ultrasound examination.
   e) Laboratory investigations.

Full laboratory investigations will be withdrawn from the patients including the following.

- Complete blood picture.
- Liver enzymes (ALT&AST).
- Full coagulation profile (PT, PTT&INR).
- Full renal profile.

Follow-up:

Patients will be observed and will be classified into two groups.

- Group 1: patients will not develop DIC.
- Group 2: Patients who will develop DIC according to the available coagulation assays including Prothrombin time PT, Partial thromboplastin time PTT, fibrinogen and D-dimer or fibrin split products.

The Fibrinogen/C-reactive protein (CRP) ratio was calculated and correlated to the patients who developed DIC in order to determine the cut off value where DIC was developed for the early prediction of DIC in patients with SPET and HELLP syndrome.

Ethics:

The study was approved from the Ethical committee of the Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University.

Sample Size Justification:

Sample size was calculated using the following formula [13]. setting the power (1-β) at 0.8, the type-1 error (α) at 0.05, and the precision at 0.1. Data from a previous relevant study [8] showed that the area under the curve (AUC) for the fibrinogen/CRP ratio as predictor of overt DIC was 0.74 and that the prevalence of overt DIC among women with severe pre-eclampsia and HELLP syndrome in the same study was 11.7%. Calculation according to these values produced a minimal sample size of 84 women.

$$\mathrm{TP} + \mathrm{FN} = Z^2 \times \frac{(SN\ (1 - SN)}{W^2}$$

$$\mathrm{N(sN)} = \frac{\mathrm{TP} + \mathrm{FN}}{P}$$

where,
TP = true positive
FN = false negative
Z = confidence interval distribution value
SN = sensitivity
P = prevalence
W = accuracy

Statistical Methods

Statistical analysis was performed using Microsoft Excel version 2010 and Statistical Package for Social Sciences (SPSS) for Windows version 20.0. Data were described as range, mean and standard deviation (for numeric parametric variables), range, median and interquartile range (for numeric non-parametric variables), or number and percentage (for categorical variables). Difference between two groups was analyzed using independent student's t-test (for numeric parametric variables), Mann-Whitney's U-test (for numeric non-parametric variables), or Chi-squared test (for categorical variables). Receiver operator characteristics (ROC) curves were instructed for measured variables (fibrinogen, CRP and their ratio) as predictors of overt DIC and. Accuracy was expressed in terms of sensitivity, specificity, positive and negative predictive values. Significance level is set at 0.05.

- Probability (P-value)

- P-value ≤0.05 was considered significant.
- P-value ≤0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

Fibrinogen level was found to be decreased with a cut off value less than 100 mg/dl with very high sensitivity and specificity to diagnose DIC.

While CRP level was increased as an acute phase reactant increasing in cases of DIC with high correlation with the occurrence of DIC.

Both fibrinogen and CRP were highly correlated to the other parameters used to diagnose DIC like PT, APTT and D- dimmers.

In our results ,in cases of DIC there were a decrease in the fibrinogen level and increase in the level of the CRP as shown in tables 3 and 4 which cause a decrease in the ratio of the fibrinogen/CRP and the more decease in the ratio increase the sensitivity and the specificity for the prediction of DIC.

DISCUSSION

In the current study the aim was is to determine if the fibrinogen/C-reactive protein (CRP) ratio could be used in obstetrics as a predictor for disseminated intravascular coagulation in obstetrics patients with SPET complicated with the HELLP syndrome and identification of the cut off value of the fibrinogen/C-reactive protein (CRP) ratio to be used as a diagnostic tool to predict DIC and its usage as a prognostic tool in regard to the mortality of the patients having DIC.

From the data this current study have developed a new cut off value for the prediction of DIC which was <2.1, with sensitivity of 81.8% specificity of 93.6 % positive predictive value of 81.8 %, negative predictive value of 93.5% with diagnostic accuracy of 87.4 %.

Many different studies were performed in order to predict DIC in different types of diseases in order to try to decrease the morbidity and mortality of DIC and its effect on patients.

Kim *et al.* [10] recruited 1056 patients where 535 of the was with overt DIC and in agreement to this study they detected that Use of the Fibrinogen/CRP Ratio instead of Fibrinogen Increases the Prognostic Power of DIC and also inagreement with this study showed that a low fibrinogen/CRP ratio was highly correlated with a high DIC score. But in contrast to this study the patient was on a wider scale including numerous causes of DIC not only the HELLP syndrome.

Kim et al. [10] in agreement with this study cutoff value of 100 mg/dl for fibrinogen has been suggested to show the consumption of coagulation factors and also we have shown here that the CRP was increased in the patients with high DIC scores. CRP was highly elevated in the DIC patients.

In contrast to this study the previous study was a retrospective study while the current study was a prospective observational study.

Windsperger and Lehner in another study [8] recruited 111 patients with HELLP syndrome, his results were in agreement with this study which prove that the implementation of the fibrinogen/CRP ratio within patients with hemolysis, elevated liver enzymes, and low platelet count syndrome is a good diagnostic and prognostic factor for the occurrence of disseminated intravascular coagulation **.**

In agreement to this study it was found that the fibrinogen/CRP ratio was markedly lower in patients with overt DIC, with decrease in the level of fibrinogen and increase in the level of the CRP[8].

Comment:

The presence of decreased fibrinogen levels according to the ISTH criteria has generally lost its validity as an indicator of DIC. Our study demonstrated that the fibrinogen/CRP ratio could be used instead. This parameter differed by a statistically significant degree in pregnant women with HELLP syndrome and overt DIC vs those with HELLP syndrome alone.

Logistic regression and ROC analysis demonstrated that the fibrinogen/CRP. Ratio predicted DIC more accurately than fibrinogen levels.

Study limitations:

Even though the CRP level was well correlated with the fibrinogen level, we could not compare the fibrinogen kinetics with the CRP kinetics during acute synthesis of these proteins. It is known that the serum level of CRP rises significantly within 12 h after an acute inflammatory insult, reaching the maximum levels within 2–5 days [13] and it is also known that after injury plasma fibrinogen rises gradually and is sustained at the post

injury level [14]. Even though both proteins are increased during the acute phase, we cannot confirm the increment amount of both these parameters according to the acute inflammatory response. Therefore, the fibrinogen/CRP ratio may not reflect accurate consumption of fibrinogen.

CONCLUSION

In light of the physiologic changes of the coagulation cascade during gestation, the ISTH score could not be implemented in pregnant women alone for the diagnosis and prediction of DIC.The results of our study suggest that replacing the use of fibrinogen levels alone with the fibrinogen/CRP ratio would enhance the diagnostic and prognostic power for DIC in patients with HELLP syndrome.

RECOMMENDATIONS

Further evaluation of the fibrinogen/ CRP ratio is required to determine the generalizability of this marker's use in DIC because of causes such as placental abruption, septic abortion, and failed abortion.

Furthermore, prospective studies should be performed to determine the best method to predict if there any new method to predict DIC in patients with the HEELP syndrome.

REFERENCES

1. **Eiland E, Nzerue C, and Faulkner M(2012):** Preeclampsia.Journal of Pregnancy.DOI:10.1155/2012/586578.
2. **WHO,** Recommendations for Prevention and Treatment of Preeclampsia and Eclampsia 2011, WHO Department of Maternal and Child Health, Geneva, Switzerland.
3. **Wong F and Cox B(2014):** Proteomics Analysis of Preeclampsia, a Systematic Review of Maternal and Fetal Compartments. J Proteomics Bioinform S10: 001. doi:10.4172/jpb.S10-001.
4. **Haram K, Svendsen E, and Abildgaard U(2009):** The HELLP syndrome: Clinical issues and management. BMC Pregnancy and Childbirth , 9(8): 1-15.
5. **Hemant K S, Chabi S, Frey D(2009):** Hellpsyndrome,JObstetGynecol India , 59(1): 30-40.
6. **Abildgaard U and Heimdal K(2013):** Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP) European Journal of Obstetrics & Gynecology and Reproductive Biology,166(2):117-123.
7. **Gupta T, Gupta N, Jain J, Gupta S, Bhatia P and Bagla J(2013):** Maternal and perinatal outcome in patients with severe pre eclampsia/ eclampsia with and without HELLP Syndrome.Journal of Universal College of Medical Sciences., 104: 7- 12.
8. **Windsperger K, Lehner R(2013):** The fibrinogen/CRP ratio as a new parameter for the diagnosis of disseminated intravascular coagulation in patients with HELLP syndrome and as a predictive factor for neonatal outcome. Am J ObstetGynecol ,208:118.e1-7.
9. **Erez O, Novack L, Weisel, KB, Dukler D, Press F, ZlotnikA,Than NG, Tomer A, Mazor M(2014):** DIG Score in Pregnant Women - A Population Based Modification of the International Society on Thrombosis and Hemostasis Score. Plos One, 9: 1-10.
10. **Kim HK, Lee DS, Kang SH, Kim JQ, Park SY, Cho HI(2007):** Utility of the Fibrinogen/C-Reactive Protein Ratio for the Diagnosis of Disseminated Intravascular Coagulation, ActaHaematol .,117:34–39.
11. **The American college of obstetricians and Gynecologists(2013):** Hypertension in Pregnancy.OBSTETRICS& GYNECOLOGY,122(5): 1122-1131.
12. **Martin J(2013):** Milestones in the quest for best management of patients with HELLP syndrome (microangiopathic hemolytic anemia, hepatic dysfunction, thrombocytopenia). International Journal of Gynecology and Obstetrics ,121 : 202–207.
13. **Johnson A(1999):**: Proteins; in Burtis C (ed): Tietz Textbook of Clinical Chemistry, ed 3. Philadelphia, Saunders, pp 477–540.
14. **Thompson C, Blumenstock FA, Saba TM, Feustel PJ, Kaplan JE, Fortune JB, Hough L, Gray V(1989):**: Plasma fibronectin synthesis in normal and injured humans as determined by stable isotope incorporation. J Clin Invest ., 84: 1226–1235.

Table (1): Descriptive data of the study group

	Range	Mean±SD
Age (years)	18-42	29.21±5.13
GA (weeks)	26-40	33.17±2.85
Parity		
Multi- para	60	71.43%
Prim gravida	24	28.57%

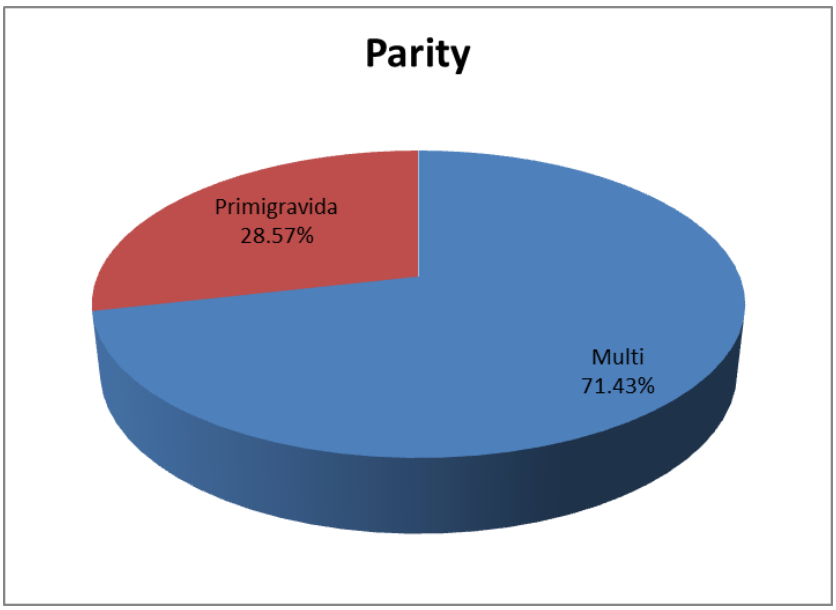

Figure (1): Pie chart parity distribution of the study group.

Table (2): DIC distribution of the study group.

DIC	Range	Mean±SD
DIC	22	26.2%
Not DIC	62	73.8%
Total	84	100%

Table (2) shows that 22 patients suffered From DIC (26.2%) and 62 patients did not suffer from DIC (73.8%).

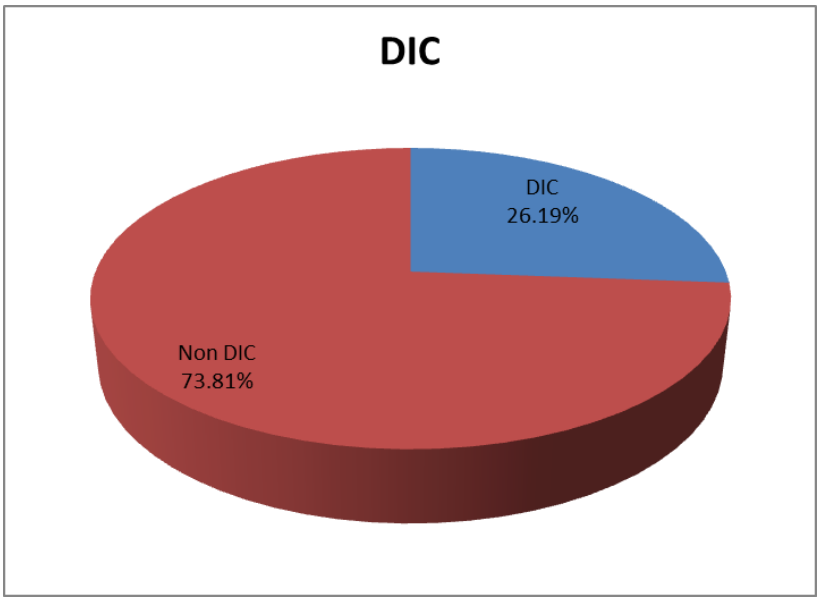

Figure (2): Pie chart DIC distribution of the study group.

Table (3): Comparison between DIC and non DIC according to fibrinogen.

Fibrinogen	DIC		t-test	
	DIC (n=22)	Non DIC (n=62)	t	p-value
Mean±SD	154.68±28.73	295.85±82.28	-8.386	<0.001
Range	100-200	181-577		

Table (3) shows highly statistically significant difference between DIC and non DIC according fibrinogen.

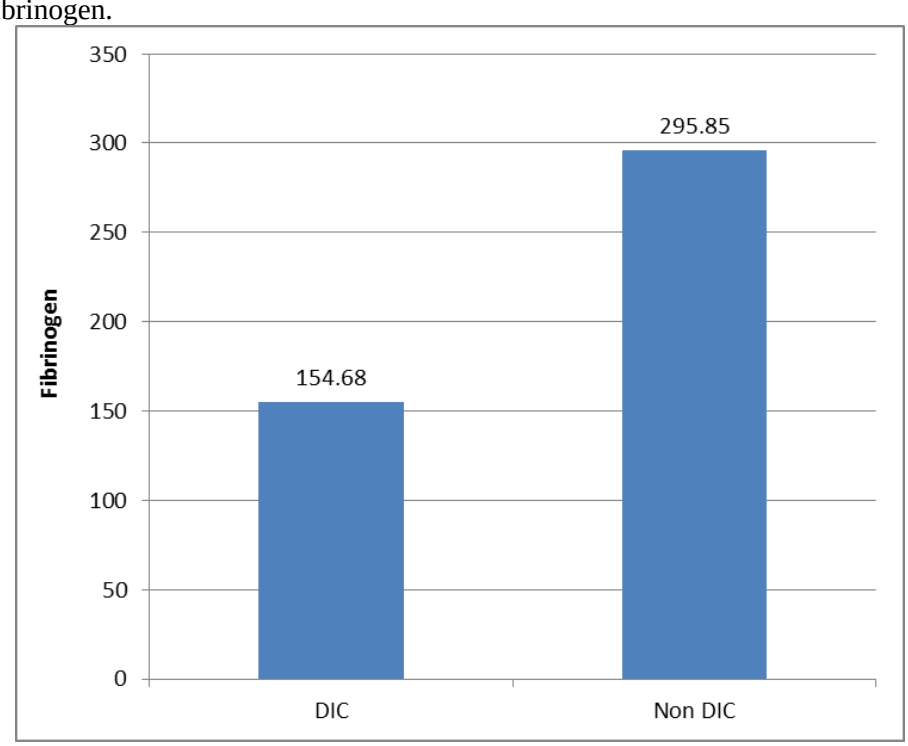

Figure (3): Comparison between DIC and non DIC according fibrinogen.

Table (4): Comparison between DIC and non DIC according CRP.

CRP	DIC		t-test	
	DIC (n=22)	Non DIC (n=62)	t	p-value
Mean±SD	76.85±29.47	26.17±4.07	8.605	<0.001
Range	12-95	5.5-112		

Table (4) shows highly statistically significant difference between DIC and non DIC according CRP.

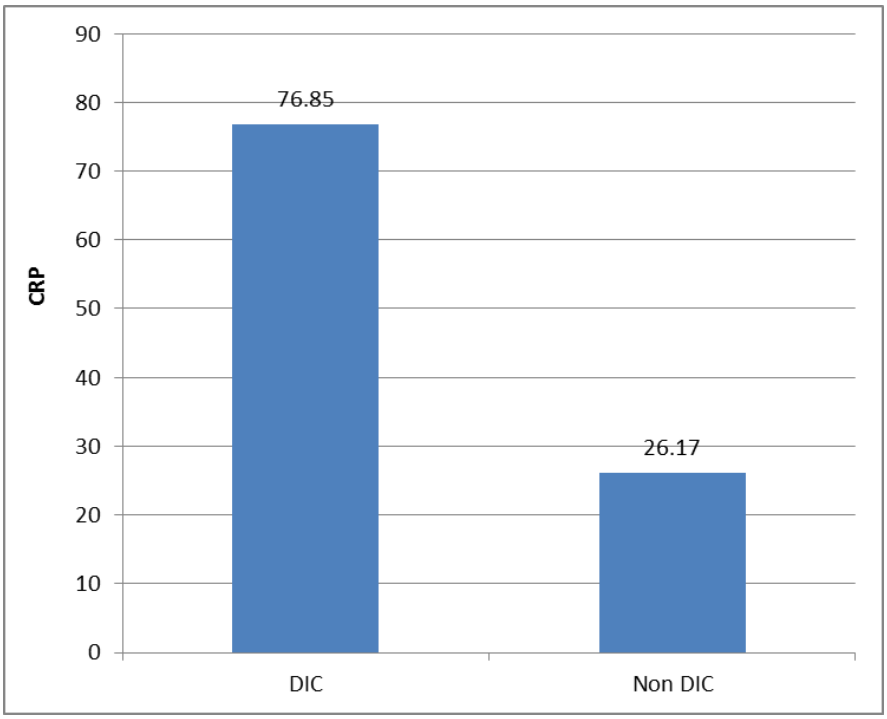

Figure (4): Comparison between DIC and non DIC according CRP.

Table (5): Comparison between DIC and non DIC according Fibrinogen /CRP ratio.

FIB/CRP ratio	DIC		t-test	
	DIC (n=22)	Non DIC (n=62)	t	p-value
Mean±SD	3.92±5.34	26.10±6.28	-4.176	<0.001
Range	1.45-15.9	1.8-105		

Table (5) shows highly statistically significant difference between DIC and non DIC according FIB/CRP ratio.

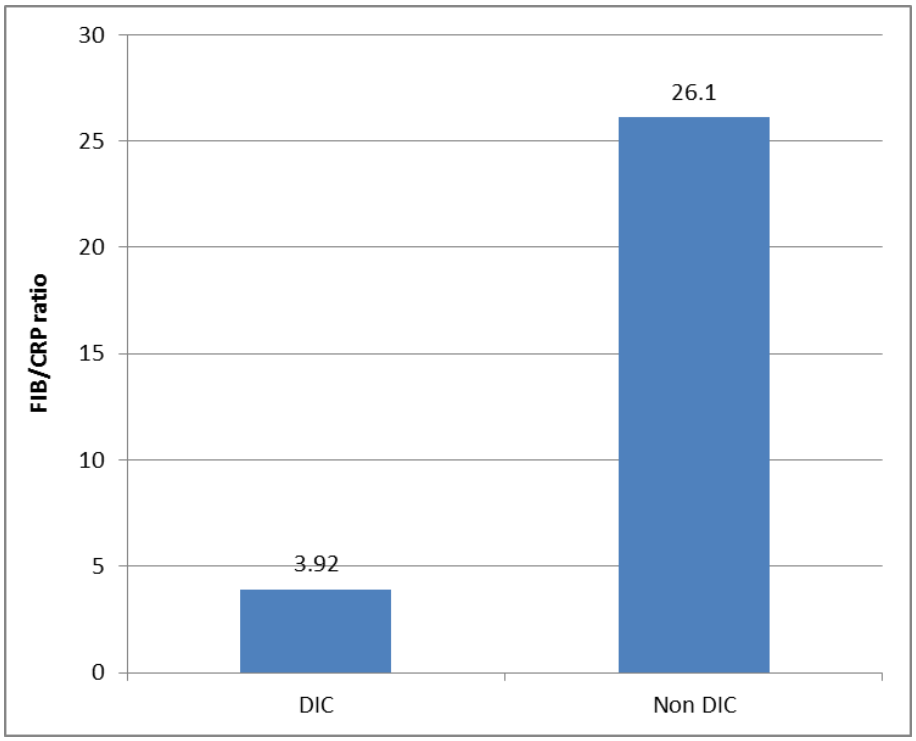

Figure (5): Comparison between DIC and non DIC Fibrinogen /CRP ratio.

Table (6): Diagnostic Performance of DIC and Non DIC in Discrimination of Fibrinogen/CRP ratio.

Cut-off.	Sen.	Spe.	PPV	NPV	Accuracy
≤2.1	81.8%	93.6%	81.8%	93.5%	87.4%

Receiver operating characteristics (ROC) curve was used to define the best cut off value of fibrinogen/CRP ratio which was <2.1, with sensitivity of 81.8% specificity of 93.6 % positive predictive value of 81.8 %, negative predictive value of 93.5% with diagnostic accuracy of 87.4 %.

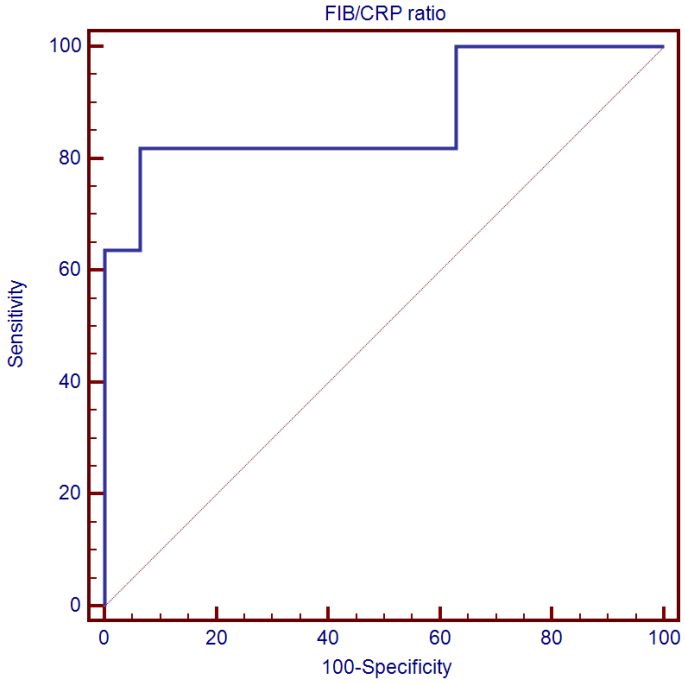

Figure (6): Sensitivity and specificity between DIC and Non DIC in Discrimination of Fibrinogen/CRP ratio.