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Predictors of Feto-Maternal Outcome in Pregnancies Complicated by Hepatic Dysfunction: Observational Study in a Tertiary Care Hospital in Punjab

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ABSTRACT

Introduction: The spectrum of hepatic dysfunction complicating pregnancy has varied underlying etiologies and is associated with grave feto-maternal prognosis. There is an imperative need to identify individuals at risk and recognize factors predicting poor outcome in order to improve maternal survival. There is paucity of literature published about predictors of survival and utility of low cost, easily available biochemical and hematological investigations as reliable tools for feto-maternal prognostication.

Aim: The present study aims to analyze maternal and fetal outcome in pregnancies complicated by hepatic dysfunction and to evaluate various clinico-demographic, biochemical and hematological variables as reliable tools for predicting feto-maternal outcome in such pregnancies.

Materials and methods: It was a prospective observational study in 118 antenatal women with hepatic dysfunction in pregnancy. Clinico-demographic, biochemical and hematological variables were analyzed. Common laboratory parameters across underlying etiologies of hepatic dysfunction were compared using appropriate statistical methods and their predictive performance as feto-maternal adverse outcome predictors was analyzed.

Results: Pre-eclampsia (42.4%) was the most common underlying etiology of hepatic dysfunction. Maternal mortality rate was 5.9%. Neonatal intensive care was required in 27.6% babies. Presence of coagulopathy, elevated serum bilirubin levels and thrombocytopenia were associated with grave feto-maternal prognosis.

Conclusion: Total serum bilirubin and international normalized ratio are important predictors of feto-maternal outcome.

Keywords: Hepatic dysfunction; Bilirubin; Feto-maternal outcome.

INTRODUCTION

Hepatic dysfunction is a common disorder, complicating around 3-5% of pregnancies.[1] The incidence varies from 0.1% in developed countries to 3-20% in developing countries. It is an important cause of feto-maternal morbidity and mortality, accounting for 60% of perinatal mortality and 14% of maternal mortality. **Table 1** enlists the commonly encountered spectrum of hepatic dysfunction in pregnancy. Postpartum haemorrhage (PPH), hepatic encephalopathy, disseminated intravascular coagulation (DIC), septicemia, placental abruption, renal dysfunction and multi organ dysfunction are the commonly

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Table 1
Classification of liver diseases in pregnancy[2]

Type of liver disease	*Common examples*
Pregnancy Specific Liver Diseases [PsLD]	
	Intrahepatic cholestasis of pregnancy (IHCP) Hyperemesis gravidarum Pre-eclamptic toxemia of pregnancy HELLP syndrome Acute fatty liver of pregnancy (AFLP)
Liver diseases co-incidental to pregnancy and exacerbated during pregnancy	
	Acute viral hepatitis Gall stones
Pre-existing liver diseases unrelated to pregnancy	
	Portal hypertension Wilson's disease Chronic hepatitis

observed maternal complications. Fetal complications include intra-uterine fetal death, still births, meconium staining of amniotic fluid, fetal distress and perinatal transmission of viral hepatitis from mother to fetus.[3,4]

Due to a significant degree of overlap in clinical and laboratory parameters amongst different causes of liver disease in pregnancy, the diagnosis of underlying etiology can be challenging. In resource constrained set up of developing countries, harnessing adequate multidisciplinary support can be difficult at times. Therefore, we need to improve clinical skills along with utilization of the easily available hematological and biochemical variables for guidance of health care workers involved at the grassroot level. There are limited studies available for prediction of feto-maternal prognosis using commonly available laboratory tests.

The present study focuses on the utility of commonly available blood investigations as reliable tools which would enable obstetricians in resource poor settings to identify patients who survive with supportive care and those who require advanced care and /or referral to liver centers.

AIM OF THE STUDY

1. To analyze maternal and fetal outcome in pregnancies complicated by hepatic dysfunction
2. To evaluate clinico-demographic, biochemical and hematological variables as reliable tools for predicting feto-maternal outcome in affected pregnancies

MATERIALS AND METHODS

The present study was a prospective study conducted in the department of Obstetrics and Gynecology and General Medicine at Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, which is a government hospital providing tertiary level of health care. The study was conducted over a period of 1 year from 1st January 2018 till 31st December 2018 with a sample size of 3822 antenatal women. Prior approval was taken by the institutional ethical committee and subjects were recruited from out patients as well as from wards in the hospital after informed written consent.

Inclusion Criteria

All antenatal patients, irrespective of period of gestation, with hepatic dysfunction who consented to be a part of the study were recruited. Hepatic dysfunction was defined as total serum bilirubin (TSB) > 1 mg/dL, serum aspartate transaminase (AST) > 40 IU/L, serum alanine transaminase (ALT) > 40 IU/L.

Exclusion Criteria

Women who did not give informed consent for the study or those with onset of hepatic dysfunction in post partum period were excluded from the study.

A detailed history was taken regarding demographic profile, last menstrual period, parity, gestational age, signs and symptoms, relevant past obstetric history. Any history of blood transfusion/fever/pruritis/

vomiting were recorded. This was followed by a thorough general physical examination, systemic and obstetric examination. The women were also referred for a consultation with physician. Investigations included complete hemogram, liver function tests, coagulation profile, viral serology (HbsAg, Anti HAV IgM, Anti HCVab, Anti HEV IgM), renal function tests and ultrasonography of whole abdomen and pelvis. All investigations were done free of cost under Janani Shishu Surakhsha Yojna. The women were managed as per standard treatment protocols and feto-maternal outcomes assessed. A post natal follow-up was done after discharge until 2 weeks irrespective of outcome.

STATISTICAL ANALYSIS

Data was analyzed using SPSS 20.0 statistical software. Various underlying clinico-demographic, biochemical and hematological variables were analyzed for their predictive efficacy as reliable tools in feto-maternal prognostication. Continuous variables were expressed as mean and standard deviation. The laboratory parameters were assessed using Kruskal–Wallis test with p values <0.05 considered as statistically significant. Bivariate analysis of demographic and laboratory characteristics was done, with death as outcome of interest. Receiver operating characteristic (ROC) curves were plotted for TSB , AST, ALT, INR, platelet counts (PLT) and hemoglobin (Hb), and their predictive performance as feto-maternal adverse outcome predictors was analyzed. Association of maternal co-morbidities and risk factors with maternal adversities was analyzed using Odds ratio (OR).

RESULTS

Table 2 shows the demographic characteristics of study population. 118/3822 [3.1%] women had abnormal liver function tests in pregnancy. Most of the patients (66.9%) delivered vaginally. Associated medical complications were anemia (44.1%), diabetes (5.9%), obesity (5.1%) and hypothyroidism (4.2%). One woman had co-existing peri-partum cardiomyopathy. The most common underlying etiology of hepatic dysfunction was hypertension in pregnancy (61.9%) followed by viral hepatitis (20.3%) with Hepatitis B (33.3%), Hepatitis C (29.2%), Hepatitis E (16.7%), Hepatitis A (12.5%) and hepatitis B-C co-infection (8.3%). Hepatic dysfunction due to hyperemesis gravidarum was seen in one patient who presented with intractable vomiting at 16 weeks of pregnancy and was managed conservatively and discharged in healthy condition.

Table 2

Clinico-demographic profile of the patients (N = 118)

	Parameter	N (%)	Mean	S.D. (Range)
Age (years)	<25 25-30 30-35 >35	71 (60.2%) 31 (26.3%) 12 (10.2%) 4 (3.4%)	25.18	4.290 (18-38)
Parity	Primiparous Multiparous	94 (79.7%) 24 (20.3%)	-	-
Booking status	Booked Un-booked	40 (33.9%) 78 (66.1%)	-	-
Fetus number	Singleton Multiple	109 (92.4%) 9 (7.6%)	-	-
Etiology of hepatic dysfunction	Pre-eclampsia Eclampsia HELLP syndrome Viral hepatits Pregnancy cholestasis Chronic liver disease Sepsis Hyper emesis Gravidarum	50 (42.4%) 16 (13.6%) 7 (5.9%) 24 (20.3%) 16 (13.6%) 1 (0.8%) 3 (2.5%) 1 (0.8%)	-	-

Contd…

	Parameter	N (%)	Mean	S.D. (Range)
Gestational age at delivery (weeks)	<28 28-<32 32-<36 36-<40 >/=40	5 (4.2%) 13 (11.0%) 18 (15.3%) 53 (44.9%) 23 (19.5%)	36.33	4.037
Mode of delivery	Miscarriage Vaginal Cesarean section Expired Undelivered Improved Undelivered	2 (1.7%) 79 (66.9%) 33 (28%) 2 (1.7%) 2 (1.7%)	-	-
Co-existing pathology	Anemia Thyroid Diabetes Obesity Peri-partum cardiomyopathy	52 (44.1%) 5 (4.2%) 7 (5.9%) 6 (5.1%) 1 (0.8%)	-	-

Table 3 enlists the common clinical features in women with hepatic dysfunction. Prevalence of jaundice among antenatal women was 0.99% (38/3822). Other symptoms were pruritis, gastro-intestinal symptoms and headache. Ascites, hepatomegaly, abdominal tenderness, pedal edema and scratch marks were commonly seen signs and symptoms. Overall, the most common complication was postpartum hemorrhage (21.2%) followed by placental abruption (10.5%) and renal dysfunction [8.5%]. The latter two were mainly observed in pregnancy induced hypertension and sepsis groups. Hepatic encephalopathy (3.4%), DIC (2.5%) and fulminant hepatitis (1.7%) were also observed. Thirty-three (28%) patients received transfusion of blood/blood components .

Table 3

Signs, symptoms and complications of hepatic dysfunction in the present study

Signs and symptoms	N (% patients)
Pruritis	22 (18.6%)
Gastro-intestinal symptoms	20 (16.9%)
Jaundice	38 (32.2%)
Headache	13 (11%)
Ascites	18 (15.3%)
Scratch marks	10 (8.5%)
Hepatomegaly	17 (14.4%)
Abdominal tenderness	32 (27.1%)
Edema	41 (34.7%)
Complications	
PPH	25 (21.2%)
Abruptio placentae	10 (8.5%)
Renal dysfunction	8 (6.8%)
Hepatic encephalopathy	4 (3.4%)
DIC	3 (2.5%)
Fulminant Hepatitis	2 (1.7%)
Septicemia	1 (0.8%)
Transfusions	
Whole blood (WB)	17 (14.4%)
Fresh Frozen Plasma (FFP)	4 (3.4%)
Platlet concentrates (PRP)	2 (1.7%)
Whole blood + FFP	7 (5.9%)
WB + PRP	3 (2.5%)

Laboratory Markers

Table 4 lists the laboratory parameters observed. TSB was >/= 10 mg /dL in 9 (7.6%) subjects. Mean TSB was 4.48 (SD: 3.03) with highest levels seen in sepsis (12.42 ± 8.09). INR was highest in sepsis (2.17 ± 0.058) and HELLP syndrome (2.057 ± 0.11). Mean PLT counts (1.07 ± 1.23) and mean Hb% (7.33 ± 1.66) were lowest in patients with HELLP syndrome. Serum lactate dehydrogenase (LDH) levels were highest in patients with HELLP syndrome. Levels of TSB and INR across various underlying etiologies of hepatic dysfunction in pregnancy were statistically significant (p = 0.00) [Kruskal –Wallis test]. TSB levels were directly related to maternal mortality (TSB >/= 10mg/dl in 6 of 7 patients who expired). Higher TSB and INR levels and low Hb% values had significant correlation with maternal mortality (p values : 0.000, 0.001 and 0.003 respectively) (Bivariate analysis) (Table 5). However laboratory values

Table 4

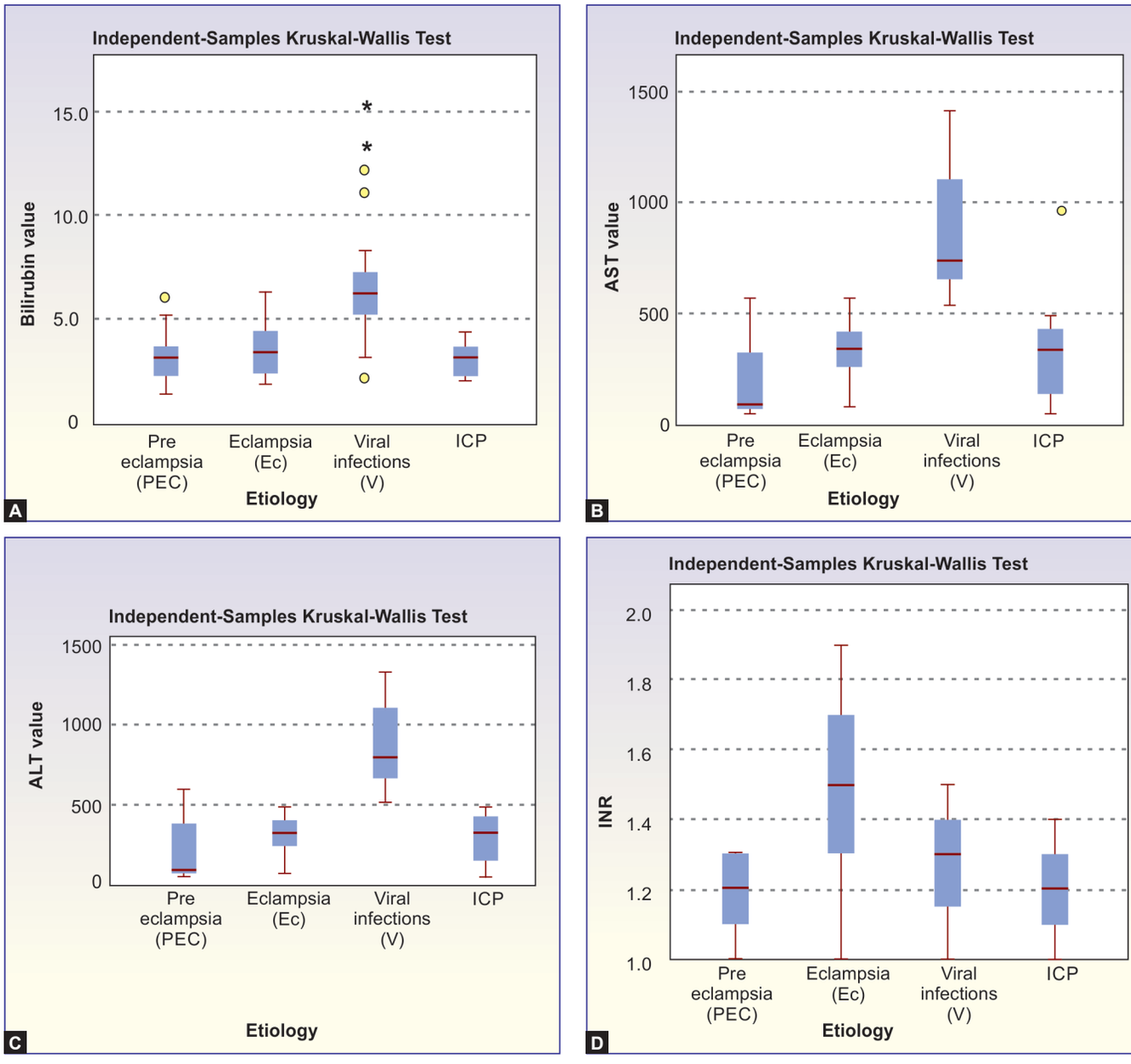
Laboratory investigations in different aetiologies (N =118)

Etiology →	**Pre-eclampsia (N = 50)**	**Eclampsia (N = 16)**	**HELLP (N = 7)**	**Viral hepatitis (N = 24)**	**IHCP (N = 16)**	**Sepsis**
Parameter ↓						
S. Bilirubin						
<5 mg/dL	47 (94%)	13 (81.25%)	3 (42.8%)	5 (20.8%)	16 (100%)	1
5-<10 mg/dL	3 (6%)	3 (18.75%)	1 (4.4%)	15 (62.5%)	-	-
10-<15 mg/dL	-	-	3 (42.8%)	3 (12.5%)	-	1
>15 mg/dL	-	-	-	1 (4.2%)	-	1
Mean ± SD	3.11 ± 0.99	3.77 ± 1.49	7.54 ± 3.95	6.93 ± 3.09	3.13 ± 0.82	12.42 ± 8.08
AST						
<100 IU/l	29 (58%)	2 (12.5%)	-	-	4 (25%)	1
100-<500 IU/l	20 (40%)	13 (81.25%)	7 (100%)	-	12 (75%)	1
500-<1000 IU/l	1 (2%)	1 (6.25%)	-	17 (70.8%)	-	1
>/=1000 IU/l	-	-	-	7 (29.2%)	-	-
Mean ± SD	183.46 ± 147.78	319.94 ± 136.44	331.43 ± 86.25	856.92 ± 280.22	329.63 ± 230.06	362.67 ± 316.61
ALT						
<100 IU/l	27 (54%)	2 (12.5%)	1 (14.3%)	-	4 (25%)	1
100-<500 IU/l	22 (44%)	14 (87.5%)	6 (85.7%)	-	12 (75%)	1
500-<1000 IU/l	1 (2%)	-	-	17 (70.8%)	-	1
>/=1000 IU/l	-	-	-	7 (29.2%)	-	-
Mean ± SD	206.26 ± 167.60	307.50 ± 120.46	342.86 ± 62.91	854.33 ± 248.03	301.13 ± 156.16	370.00 ± 370.41
Platelet Count						
<50,000/mm^3	-	1 (6.25%)	4 (57.14%)	-	-	-
50,000-<1 lac /mm^3	1 (2%)	-	-	1 (4.2%)	1 (6.25%)	1
1-<1.5 lac/mm^3	22 (44%)	9 (56.25%)	2 (28.57%)	14 (58.3%)	7 (43.75%)	1
>/=1.5 lac/mm^3	27 (54%)	6 (37.5%)	1 (14.28%)	9 (37.5%)	8 (50%)	1
Mean ± SD Hb (gm%)	2.52 ± 1.34	2.15 ± 1.51	1.07 ± 1.23	2.19 ± 1.44	2.36 ± 1.49	1.90 ± 1.40
<4	2 (4%)	0	0	0	0	
4-<7	5 (10%)	4 (25%)	4 (57.1%)	3 (12.5%)	1 (6.25%)	
7-<10	25 (50%)	7 (43.75%)	3 (42.9%)	14 (16.7%)	4 (25%)	
>/=10	18 (36%)	5 (31.25%)	0	7 (70.8%)	11 (68.75%)	
Mean ± S.D	9.36 ± 2.30	8.38 ± 2.33	7.33 ± 1.66	9.15 ± 2.40	10.49 ± 2.02	

Table 5

Bivariate analysis of demographic and laboratory characteristics with mortality as primary outcome (*p* value < 0.05 significant)

Variable	*Alive* *Mean ± S.D.*	*Dead* *Mean ± S.D.*	*P value*
Age	25.11 ± 4.337	26.29 ± 3.546	0.221
TSB	3.960 ± 2.0433	12.686 ± 4.3472	0.000
Thrombocytopenia	2.292 ± 1.39	2.171 ± 1.82	0.378
Anemia	9.350 ± 2.26	6.300 ± 1.70	0.001
INR	1.299 ± 0.269	1.771 ± 0.431	0.003
AST	364.53 ± 310.787	526.29 ± 414.207	0.379
ALT	372.66 ± 303.097	521.29 ± 374.030	0.254



Figs 1A to D: Difference in distribution of lab parameters: TSB, AST, ALT, INR, across various underlying etiologies of hepatic dysfunction in pregnancy: (A) Distribution of TSB; (B) Distribution of AST; (C) Distribution of ALT; (D) Distribution of INR across PEC, EC, V, ICP groups. Using Kruskal–Wallis test (level of significance: $p < 0.050$), difference in TSB, AST, ALT and INR values across above underlying etiologies of hepatic dysfunction in pregnancy were found to be statistically significant with p values 0.000

of PLT and Hb % levels were not significant statistically as prognostic markers (ROC analysis) (Figs 1A to D).

Fetal Complications (Table 6)

Prematurity (35.4%) was the most common fetal complication followed by low birth weight (14.2%), fetal growth restriction (9.4%) and meconium stained liquor (8.7%). IHCP had good feto-maternal prognosis with 87.5% (14/16) patients having term delivery. Two patients, one with hepatitis B infection and another with fulminant hepatitis due to HEV infection suffered miscarriage. NICU admission was 27.6% and 9 babies (7.1%) had early neonatal deaths. Overall pregnant patients with IHCP had better fetal outcome.

Table 6

Feto-maternal outcomes in patients with hepatic dysfunction in pregnancy

Etiology → Outcome ↓	Pre-eclampsia	Eclampsia	HELLP syndrome	Viral hepatitis	IHCP	Chronic liver disease	Sepsis	Hyperemesis Gravidarum	Total
Maternal Outcome	(50)	(16)	(7)	(24)	(16)	(1)	(3)	(1)	(118)
ICU	-	3 (18.8%)	6 (85.7%)	8 (33.3%)	-	-	3 (100%)	-	20 (16.9%)
Cesarean	13 (26%	8 (50%)	3 (43%)	2 (8.3%)	6 (38%)	-	1 (33.3%)	-	33 (28%)
Near Miss	2 (4%)	15 (93.7%)	5 (71.4%)	5 (20.8%)	-	-	1 (33.3%)	-	28 (23.7%)
Death	-	1 (6.3%)	2 (28.6%)	2 (8.3%)	-	-	2 (66.7%)	-	7 (5.9%)
Fetal outcome	51	18	8	26	18	1	4	1	127
Multiple pregnancy	1	2	1	2	2	-	1	-	9
Pre-term	6 (12 %)	14 (78%)	4 (50%)	18 (69%)	2 (11%)	1	-	-	45 (35.4%)
LBW	3 (5.9%)	4 (22.2%)	2 (25%)	8 (30.8%)	1 (5.6%)	-	-	-	18 (14.2%)
FGR	5 (9.8%)	3 (16.7%)	2 (25%)	1 (3.8%)	-	-	1	-	12 (9.4%)
Still birth	-	1	1	-	-		-	-	2 (1.6%)
Abortion	-	-	-	2	-	-	-	-	2
IUFD	2	2	-	1	-	-	1	-	6 (4.7%)
MSL	6	4	-	-	1	-	-	-	11 (8.7%)
NICU admissions	6	6	5	15	2	1	-	-	35 (27.6%)
Neonatal Death	-	-	1	7 (27%)	-	1	-	-	9 (7.1%)

Maternal Complications (Table 6)

20 women (16.9%) required ICU admission. 7 maternal deaths were noted (5.9%), 1 in eclampsia group and 2 each in HELLP syndrome, viral infections and sepsis groups. The underlying cause of maternal mortality was hepatic encephalopathy in 3 patients, DIC in 2 patients, septicemia with multi organ dysfunction and fulminant hepatitis in 1 patient each. Mortality rates were as high as 75% in patients with hepatic encephalopathy, followed by 66% in those with DIC and 50% in those with septicemia and fulminant hepatitis. Coagulopathy (odds ratio OR: 16.2), hyperbilirubinemia (OR: 12.2) and thrombocytopenia (OR: 10.8) were associated with adverse maternal outcomes . Diabetes (OR: 3.41) and anemia (OR: 2.23) were also associated with adverse maternal outcome (Table 7). Figure 2 (A-D) depicts the performance of TSB and INR in predicting the maternal and fetal outcome.

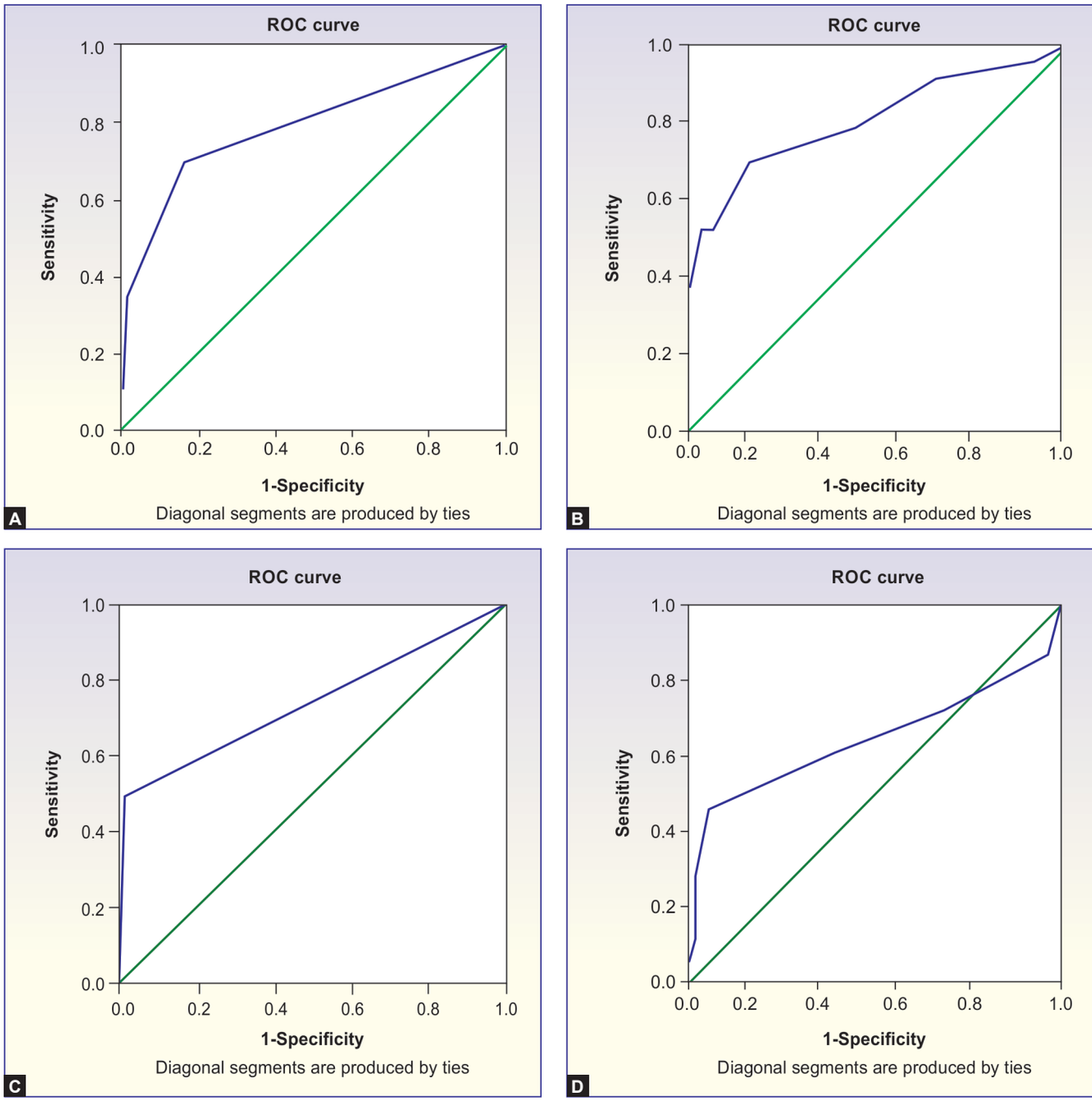
Table 7

Risk factors in maternal outcome

S.No.	*Maternal Risk factor*	*Adverse maternal outcome odds ratio*
1.	Primigravida	1.27
2.	Diabetes	3.41
4.	Anemia	2.23
5.	Serum bilirubin	12.2
6.	Thrombocytopenia	10.8
7.	Obesity	0.81
8.	Coagulopathy	16.2

DISCUSSION

We found an overall prevalence of hepatic dysfunction in pregnancy to be as high as 3.1% with pre-eclampsia in 1.3% women. This corroborates with the prevalence observed by other investigators.[5-7] We found a 0.99% prevalence of jaundice in antenatal population, which is similar to that observed by Satia et al (0.81%).[8]



Figs 2A to D: ROC curves showing predictive performance of maternal: (A) Serum total bilrubin; (B) INR in predicting maternal adversities; (C) Serum total bilirubin; (D) INR in predicting fetal adversities

Majority of patients with hepatic dysfunction presented to us in third trimester (109; 92.4%) and higher number of feto-maternal complications were also seen during this period. As we are the only government tertiary care referral hospital, most of our patients are referred late and many as complicated cases.

Our maternal mortality was 5.9% with majority of deaths in women <30 years (6/7; 85.7%). This may be a confounder as majority of subjects in the present study were younger than 25 years. Reddy et al found a higher maternal mortality (16.6%).[6] This may be because of older age of mothers in their study as compared to ours.

IHCP was found majorly in third trimester of pregnancy whereas viral hepatitis was equally distributed throughout pregnancy. Feto maternal complications were lesser in IHCP as compared to other etiologies of liver dysfunction. This is similar to findings of other researchers.[5]

On analysis of laboratory markers as predictors of feto-maternal outcome, TSB and INR were found to be superior to Hb% and platelet counts; TSB being better than INR (Figs 2C and D). Murali et al[9] and Suresh et al[12] also found similar predictive values. We suggest that women with altered TSB +/- INR should be closely observed and considered for referral to higher centers. Due to involvement of multiple systems, it is essential that we provide these women with multidisciplinary care to cause an impact in preventing feto-maternal morbidity and mortality.[10,11]

Low maternal Hb% values are known to be associated with poor feto-maternal outcome. In our subjects also, we found a lower Hb% in women with adverse outcome. To test the same we performed ROC analysis of maternal Hb% and platelet levels, but the results were not statistically significant. Therefore, the efficiency of Hb% values as a predictor of feto-maternal outcome could not be statistically validated in our study. Likewise, though thrombocytopenia was found to be associated with poor feto-maternal outcome, yet its predictive efficiency in determining outcome too could not be validated in the present study. ALT and AST were not found to score good as outcome predictors, however asymptomatic rise should prompt investigation even in the presence of normal TSB.

Limitation of the Study

The most important is the single center study.

CONCLUSION

Hepatic dysfunction in pregnancy is responsible for significant feto maternal mortality and morbidity. TSB and INR are important laboratory markers in prognostication of women with hepatic dysfunction in pregnancy. They can be used to help health care workers in peripheral health centres to identify patients who require referral/advanced care. Multi-centric studies across other geographical areas are needed to further evaluate the efficiency of these variables as tools for prognostication and outcome prediction.

Abbrevations

TSB: Serum Total Bilirubin; HBSAg: Hepatitis B Surface Antigen; HCV Ab: Hepatitis C virus antibody; HEV: Hepatitis E Virus; PLT: platelet; Hb: hemoglobin; LDH: Lactate Dehydrogenase; ROC: Receiver Operating Characteristic curve; AUROC: Area Under Receiver Operating Characteristic Curve; SD: Standard Deviation; PIH:Pregnancy Induced Hypertension; DIC: Disseminated Intravascular Coagulation; NICU: Neonatal Intensive Care Unit; ICU: Intensive Care Unit

Source of Support

Nil

Conflict of Interest

There are no conflict of interest.

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