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Assessment of Maternal Hematological Parameters, Kidney and Liver Injury Markers Across Adverse Pregnancy Outcomes: A Cross Sectional Study

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Abstract

Background/Objectives: Adverse pregnancy outcomes (APOs) such as prematurity, low birth weight, stillbirth, and birth defects remain significant global health challenges. While many risk factors are known, APOs encompass a wide range of outcomes with diverse, sometimes poorly understood etiologies. Pregnancy-related acute kidney injury (PR-AKI) and liver injury are particularly associated with increased maternal and fetal mortality. This study investigated the association between hematological parameters, kidney and liver injury markers and adverse pregnancy outcomes. **Methods**: This cross-sectional study involved 714 pregnant women aged 18-40 years, conducted between March 2021 and August 2022. Maternal blood samples were collected before and after delivery to compare hematological parameters. Kidney and liver injury markers were measured using standard methods. The study analyzed the association of these parameters with adverse pregnancy outcomes. **Results**: The median age of participants was 24 years (Q1, Q3: 21, 26). Women with adverse pregnancy outcomes had statistically significant serum creatinine levels [0.52 mg/dL (0.45, 0.58)] compared to those without [0.50 mg/dL (0.44, 0.56)], although the difference was not clinically significant. Elevated AST levels (>90th percentile) were statistically associated with adverse pregnancy outcomes. Pairwise comparisons with Bonferroni corrections revealed significant differences in Hb, WBC, RBC, platelet, and PCV levels before and after delivery ($p<0.05$) in both groups. **Conclusions**: This study highlights a small but significant association of elevated serum creatinine and AST levels with adverse pregnancy outcomes, suggesting their potential role as accessible biomarkers for early risk identification in clinical settings.

Keywords: pregnancy; adverse pregnancy outcomes; liver markers; kidney markers

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1. Introduction

Adverse pregnancy outcomes (APOs), including prematurity, low birth weight, stillbirth, and birth defects, remain significant global health challenges [1]. Over 15 million babies are born prematurely each year worldwide, representing more than 10% of all births [2]. APOs are influenced by various factors, including maternal characteristics, medical conditions, and obstetric complications [3].

Pregnancy induces physiological changes in multiple organ systems, which can exacerbate pre-existing conditions and lead to kidney and liver complications [4–6]. Studies have shown that impaired kidney and liver functions are associated with poor obstetric outcomes, particularly preterm birth, preeclampsia, and fetal growth restriction [7–9]. Liver transaminases (AST, ALT) and kidney markers (creatinine, urea) serve as important indicators of organ function during pregnancy [6–10]. Notably, pregnancy-related acute kidney injury (PR-AKI) is associated with increased maternal and fetal mortality [11]. Hematological parameters also undergo significant changes during pregnancy, known as the physiologic anemia of pregnancy [12,13]. These alterations affect various blood components and are believed to facilitate utero-placental perfusion [14]. Both high and low hemoglobin concentrations have been associated with APOs [15–17].

While previous research has analyzed hematological parameters at specific pregnancy stages, there is a need to monitor these profiles before delivery and during the postpartum period. Moreover, the relationship between hematological parameters, liver and kidney injury markers, and adverse pregnancy outcomes remains unclear. This study aimed to assess the association of kidney and liver injury markers and hematological parameters with adverse pregnancy outcomes, focusing on measurements before delivery and during the postpartum period. By investigating these relationships, we seek to contribute to a better understanding of the complex interplay between maternal physiological changes and pregnancy outcomes.

2. Materials and Methods

This cross-sectional study was part of the larger "Limiting Adverse Birth Outcomes in Resource-Limited Settings" (LABOR) Study [12], a multi-country, prospective, observational cohort study. It was conducted from March 2021 to August 2022 at KLE's Dr. Prabhakar Kore Hospital, Belagavi, Karnataka, India, and approved by the Institutional Ethics Committee KAHER, (KAHER/EC/21-22/002), Belagavi.

This site analysis included 714 women aged 18-40 years with intrauterine singleton pregnancies who provided written informed consent. Its sample size was preset by the parent, multi-country protocol. Women were screened upon presenting for delivery at the hospital. We recorded composite adverse events for mothers (death, hemorrhage, hypertensive disorders, or infection) and fetuses/newborns (intrapartum stillbirth, neonatal death, encephalopathy, or sepsis) attributable to the intrapartum period.

"Adverse pregnancy outcomes" (APOs) were defined as low birth weight, preterm birth, or stillbirth. Normal births without these complications were categorized as "no APOs." Maternal characteristics recorded included age, gestational age, height, weight, systolic and diastolic blood pressure (SBP, DBP). Body mass index (BMI) was calculated using pre-pregnancy weight (kg) divided by height squared (m^2).

The study excluded women with multiple pregnancies, those admitted for elective caesarean without comorbidities, those unable to provide informed consent, and any participants with social or medical conditions deemed unsafe or unfeasible for participation by study staff.

2.1. Sample Collection and Biochemical Analysis

Blood samples were collected from women under aseptic conditions from a large peripheral vein at hospital admission and after delivery, following approved standard operating procedures. Sample collection, processing, and result reporting adhered to good clinical laboratory practice standards.

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Pre-delivery, 5 ml of blood was collected: 2 ml in EDTA for complete blood count (CBC) and 3 ml in a Serum Separation Tube (SST). The SST sample was allowed to clot for one hour, then centrifuged at 3000 rpm for 10 minutes at room temperature to separate serum. This serum was used to measure electrolytes, kidney, and liver injury markers. Post-delivery, an additional 2 ml of blood was collected in EDTA for CBC.

Biochemical assays were performed using a Cobas 6000 analyzer. The following methods were employed: Aspartate and alanine aminotransferases were measured by enzymatic method (UV with P5P); sodium, potassium, chloride, and bicarbonate by ion selective electrode indirect method; creatinine by enzymatic IFCC-IDMS method; and urea by urease UV enzymatic method. Complete Blood Count was measured by using haematology analyser (Beckman coulter LH 780 haematology analyser).

2.2. Statistical Analysis

Continuous variables (e.g., age, Hb, SBP, DBP) were summarized using Mean(SD) or Median (Q1, Q3), depending on data normality assessed by the Kolmogorov-Smirnov test. Categorical variables (e.g., stillbirth, preterm birth, low birth weight) were summarized using frequencies and percentages. Comparisons of maternal characteristics and kidney injury markers between groups with and without adverse pregnancy outcomes were conducted using the Mann-Whitney U test. Chi-Square tests were used to assess associations between liver injury markers and adverse pregnancy outcomes. Odds Ratios (OR) with 95% confidence intervals were reported. Two-way Repeated Measures Analysis of Variance (RM-ANOVA) was employed to compare trends in hematological parameters over time (before and after delivery) across groups. All statistical analyses were performed using SPSS version 16.0, with a P-value less than 0.05 considered statistically significant.

3. Results

3.1. Demographic and Clinical Characteristics

A total of 714 pregnant women were included in the study; demographic and clinical variables of the study population are presented in Table 1. The median age of the women in this study was 24 (Q1, Q3:21,26) years. Within the composite adverse pregnancy outcome, the proportion of LBW was higher [17.23 % (95%CI: 17.15,23.15)] when compared to PTB and stillbirth [6.89% (95%CI: 5.14,9.01) and 0.84% (95%CI: 0.31,1.82) respectively]. Maternal BMI was found to be associated with APOs. However, there was no clinical difference observed between other maternal characteristics and adverse pregnancy outcomes.

Table 1. Maternal Characteristics and Adverse pregnancy outcomes.

Maternal characteristics	Adverse pregnancy outcomes				Mann-Whitney U statistic	p-value
	No ([median(Q_1,Q_3)]	n	Yes [(median,(Q_1,Q_3)]	n		
Maternal age (years)	24(22, 26)	568	23(21, 26)	143	38689.50	0.379
BMI (kg/m2)	24.6(22.3, 26.9)	571	23.1(21.4, 26.2)	142	33541.50	0.001*
Gestational age at delivery (weeks)	39(38, 40)	568	37(36, 38)	143	16791.50	<0.001*
Systolic Blood Pressure (mmHg)	120(110, 120)	571	120(112, 120)	143	37744.50	0.138
Diastolic Blood Pressure (mmHg)	80(70, 80)	571	80(70, 80)	143	39095.50	0.396
Maternal weight (Kg)	58(52, 64)	571	54(49, 60)	143	31200.00	<0.001*
Maternal height (cm)	152(150, 155)	571	152(150, 154)	143	32593.50	<0.001*

*statistically significant.

3.2. Association Between Kidney Injury Markers and Adverse Pregnancy Outcomes

The average levels of creatinine were moderately elevated in adverse pregnancy outcomes group 0.52 (0.45,0.58) when compared to the group without adverse pregnancy events 0.50 (0.44,0.56). Man-Whitney U test was used to compare the average kidney injury and liver injury markers across

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groups with adverse and normal pregnancy outcomes. None of the other kidney injury markers were found to be statistically significant as outlined in Table 2.

Table 2. Association between average kidney injury markers and adverse pregnancy outcomes.

Parameters	Adverse pregnancy outcome				Mann-Whitney U statistic	p-value
	Yes		No			
	Median (Q1,Q3)	n	Median (Q1,Q3)	n		
Urea (mg/dL)	12(10, 15)	141	12(10, 14)	562	36754.5	0.17
Creatinine (mg/dL)	0.52((0.45, 0.58)	141	0.50(0.44, 0.56)	562	34356.5	0.015*
Sodium (mEq/L)	136(134, 138)	141	136(134, 138)	562	39139	0.82
Potassium (mEq/L)	4.15(3.78, 4.80)	141	4.11(3.79, 4.54)	562	37679.5	0.36
Chloride (mEq/L)	100.0 (98, 102)	141	100.0 (98.0, 102.0)	562	38352.5	0.55
Bicarbonate (mmol/L)	18.0 (16.0, 20.0)	141	18.0 (16.0, 19.0)	562	38332.5	0.54

* Statistically significant.

3.3. Association Between Liver Injury Markers and Adverse Pregnancy Outcomes

For AST levels, 16.4% of women with adverse pregnancy outcomes had elevated AST (>90th percentile) compared to 7.1% of women without adverse outcomes. The odds of experiencing an adverse pregnancy outcome were 2.57 times higher among mothers with AST >90th percentile compared to those with AST ≤90th percentile [OR: 2.57 (95% CI: 1.48, 4.45)]. Regarding ALT levels, 13.6% of women with adverse pregnancy outcomes had elevated ALT (>90th percentile) compared to 9.1% of women without adverse outcomes. The odds of experiencing an adverse pregnancy outcome were 1.57 times higher among mothers with ALT >90th percentile compared to those with ALT ≤90th percentile [OR: 1.57 (95% CI: 0.90, 2.76)]. However, no statistically significant association was observed between ALT levels and adverse pregnancy outcomes as presented in Table 3.

Table 3. Association of Serum Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels across adverse pregnancy outcomes.

Parameters	Adverse pregnancy outcomes		Chi-Square test statistic	OR (95% CI)	p-value
	Yes	No			
	n (%)	n(%)			
ALT(U/L) (≤90thpercentile)	121(86.4)	511(90.9)	2.524	ref	0.112
ALT(U/L) (>90th percentile)	19(13.6)	51(9.1)		1.57(0.90,2.76)	
AST(U/L) (≤90thpercentile)	117(83.6)	522(92.9)	11.895	ref	0.001*
AST(U/L) (>90th percentile)	23(16.4)	40(7.1)		2.57(1.48,4.45)	

* Statistically significant.

3.4. Haematological Parameters and Adverse Pregnancy Outcomes

Two-way Repeated Measures Analysis of Variance (RM-ANOVA) was used to compare trends in hematological parameters over time (before and after delivery) across groups, as presented in Table 4. A statistically significant interaction between time points and adverse pregnancy outcomes was observed for Hb, PCV, and RBCs ($p<0.05$). Other parameters did not show statistically significant interactions. After conducting pairwise comparisons within each group and implementing Bonferroni corrections, we found that Hb, WBC, RBC, platelet, and PCV levels were significantly different before and after delivery ($p<0.05$). Specifically, average platelet levels decreased after delivery compared to before delivery, while average WBC levels increased after delivery compared to before delivery. No significant differences were observed in the average levels of MCV, MCH, MCHC, and RDW before and after delivery.

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Table 4. Comparison of haematological parameters before and after delivery among normal and adverse pregnancy outcomes.

Haematological parameters	Adverse pregnancy outcome	Sample size (n)	Time period		Mean Difference (95% CI)	Interaction F-value (p-value)
			Before delivery	After delivery		
Hb (gms %)	Yes	141	11.7(1.45)	10.8(1.41)	0.89 (0.702, 1.07)	5.52(0.019*)
	No	564	11.6(1.41)	10.5(1.39)	1.14 (1.04, 1.23)	
Total (WBC) count (10^ 3/ µL)	Yes	141	16.0(4.48)	17.9(4.56)	-1.89(-2.60, -1.18)	0.19(0.65)
	No	564	15.6(4.24)	17.7(4.66)	-2.07(-2.43, -1.72)	
Platelets count (10^3 µL)	Yes	141	228.8(59.91)	216.9(52.35)	11.92 (6.60, 17.24)	1.12(0.29)
	No	564	225.0(66.91)	216.3(60.89)	8.71 (6.05, 11.37)	
RBC count (10^ 6/ µL)	Yes	141	4.20(0.53)	3.86(0.54)	0.33 (0.26, 0.40)	4.54(0.03*)
	No	564	4.23(0.47)	3.81(0.50)	0.41 (0.384, 0.45)	
PCV (%)	Yes	141	36.2(4.05)	33.2(4.14)	3.04 (2.45, 3.63)	4.42(0.036*)
	No	564	36.1(3.93)	32.4(4.08)	3.75 (3.45, 4.04)	
MCV (fl)	Yes	141	86.7(7.98)	86.3(7.68)	0.37 (0.03, 0.72)	0.21(0.64)
	No	564	86.7(7.55)	85.2(7.67)	0.46 (0.29, 0.63)	
MCH (pg)	Yes	141	28.1(3.13)	28.2(3.08)	-0.14 (-0.25, -0.04)	3.2(0.08)
	No	564	27.7(3.04)	27.7(3.03)	-0.03 (-0.09, 0.01)	
MCHC (g/dL)	Yes	141	32.3(1.02)	32.6(1.07)	-0.31 (-0.44, -0.18)	1.35(0.24)
	No	564	32.2(1.12)	32.5(1.03)	-0.22 (-0.29, -0.16)	
RDW (%)	Yes	141	15.9(3.52)	15.8(3.55)	0.13 (-0.08, 0.36)	0.62(0.43)
	No	564	16.1(3.38)	16.1(3.65)	0.03 (-0.07, 0.14)	

* Statistically significant.

4. Discussion

4.1. The Main Findings

In this large cross-sectional study of women presenting for delivery at KLE's Dr. Prabhakar Kore Hospital, Belagavi, Karnataka, we assessed the relationship between hematological parameters, kidney and liver injury markers, and adverse pregnancy outcomes. We found that creatinine levels were significantly elevated in those with adverse pregnancy outcomes, including preterm birth, compared to those with no adverse outcomes. However, no significant differences in creatinine were observed in cases of stillbirth or low birth weight. Elevated AST levels (above the 90th percentile) were also significantly associated with adverse outcomes, while urea, electrolytes, and ALT did not show significant differences. Hemoglobin concentration varied significantly, but other hematological parameters were not statistically significant.

Pregnancy-related acute kidney injury is a serious complication associated with increased maternal and fetal mortality, as well as adverse maternal and fetal outcomes [13]. Creatinine, a metabolic by-product of creatine, is continually generated within the body and efficiently filtered and eliminated by the kidneys. It serves as a crucial biomarker for assessing kidney and muscle health. Elevated serum creatinine levels may indicate potential kidney dysfunction, as the kidneys may struggle to clear creatinine effectively [4].

In this study, we found a statistically significant association between creatinine levels and adverse pregnancy outcomes. Similar elevations were noted in specific outcomes like preterm birth, with creatinine levels showing statistically significant differences. However, no significant differences were found in stillbirth and low birth weight cases. Our findings align with recent studies by Yalamati et al. and Deng et al., which identified an association between elevated serum creatinine (≥ 0.8 mg/dl) and adverse pregnancy outcomes [14,15]. Additionally, Harel et al. showed that pre-pregnancy kidney dysfunction conferred an increased risk of preterm birth [16]. In contrast, Champion et al. found no association between creatinine levels and adverse pregnancy outcomes in women with gestational diabetes when levels were below 1.2 mg/dL [17]. It is important to note that physiological changes during pregnancy affect serum creatinine levels. Typically, serum creatinine decreases due to increased fluid volumes [18]. rapidly declining in the first trimester, stabilizing in

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the second, and gradually increasing in the third trimester, eventually returning to pre-pregnancy levels [19].

Urea, the metabolic end product of nitrogen-containing compounds like proteins and nitrogen bases, is produced in the liver through the urea cycle and filtered by the kidneys [20]. The present study observed no association between urea levels and adverse pregnancy outcomes. Similar results were reported by Ambad et al., who found that while concentrations of urea, creatinine, and uric acid were increased in eclampsia compared to normal women, the increases in serum urea and creatinine levels in pre-eclampsia were not significant [21]. Our study revealed no statistically significant relationship between electrolytes and adverse pregnancy outcomes. These results differ from previous study that demonstrated an association between electrolytes and preeclampsia [22].

Regarding liver enzymes, we found an association between elevated levels of AST and adverse pregnancy outcomes. However, we did not find any association between ALT levels and adverse pregnancy outcomes. These findings contrast with a study by Losy et al., which showed no association of AST and ALT with adverse pregnancy outcomes [23]. Additionally, a study in the USA found that among patients with preeclampsia, elevated liver enzymes were not independently associated with an increased risk of adverse maternal or neonatal outcomes. Conversely, another study indicated that elevated liver enzymes were linked to a higher likelihood of maternal and fetal complications [24]. A systematic review by Thangaratinam et al. further demonstrated that increased levels of liver enzymes were associated with an increased risk of maternal and fetal complications [20].

Pregnancy typically leads to a 50% increase in plasma volume, while red cell mass also increases, but relatively less in comparison. This results in a decrease in hemoglobin (Hb) concentration during pregnancy, causing dilutional anemia. Despite experiencing a decrease in Hb during the second trimester, its levels tend to stabilize during the third trimester [25]. In our study, we found significant variation in hemoglobin concentration. The interaction between time points and adverse pregnancy outcomes showed significant differences for levels of Hb, PCV, and RBCs. We also observed that average platelet levels decreased after delivery compared to before delivery, while average WBC levels increased. No differences were observed in the average levels of MCV, MCH, MCHC, and RDW before and after delivery. However, the interaction between time points and adverse pregnancy outcomes was not statistically significant for these parameters.

Studies have shown associations between hematological parameters and adverse pregnancy outcomes [26]. Conversely, Mensah et al found no association between haematological indices and birth weight.[27] MM Hana et al. observed decreases in RBC, HCT, MPV, and MCH in the 2nd trimester, followed by increases in the 3rd trimester. MCV, MCHC, and RDW increased in the 2nd trimester and decreased in the 3rd trimester. Comparing the 3rd to the 1st trimester, MCV increased while RBC, HCT, MCH, and MCHC decreased. Post-delivery, RBC, HCT, MCV, MCH, and MPV decreased while MCHC, RDW, and PLT levels increased [28]. Aligning with our findings, Shigemi et al. found no significant association between white blood cell count and maternal adverse outcomes on the day following operative vaginal delivery [29]. Similarly, Dahlstrom et al. showed no significant change in platelet count after vaginal delivery. However, after caesarean sections, they observed a median decrease of 12.5% in platelet count on the first postoperative day and a median increase of 5% on the third postoperative day [30].

Numerous diagnostic biomarkers for adverse pregnancy outcomes have been identified to date. However, many of these biomarkers remain underutilized in clinical settings, particularly in regions like India, due to their reliance on advanced laboratory facilities. In such contexts, simple and cost-effective biomarkers are essential. Maternal serum levels of creatinine, blood urea, AST, ALT, and various hematological parameters represent readily available biomolecules that show promise for the early prediction of adverse pregnancy outcomes. These markers offer potential for widespread clinical application, especially in resource-limited settings, due to their accessibility and relatively low cost of measurement.

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4.2. Limitations

The study focused on a specific set of hematological and biochemical markers. Other potential markers related to adverse pregnancy outcomes, such as inflammatory markers or specific proteins, were not included, potentially missing important aspects of the complex interaction between maternal health and fetal outcomes. Additionally, the study did not extensively explore external factors such as socio-economic status, environmental exposures, or genetic factors, which could contribute to adverse pregnancy outcomes. These factors might confound the observed associations. The study's cross-sectional design restricts the ability to demonstrate causal relationships between the markers and outcomes. In order to understand the dynamic changes in hematological and biochemical markers throughout pregnancy, longitudinal studies would be more beneficial.

Furthermore, as the study was conducted in a single center, the generalizability of the findings to other populations or settings may be limited. The timing of pre-delivery sample collection at hospital admission may have varied in gestational age across participants, potentially introducing variability in the results. Additionally, the lack of pre-pregnancy baseline measurements makes it challenging to fully assess the impact of pregnancy on these markers. These limitations highlight the need for future research to include multi-center designs, standardized timing of sample collection, and pre-pregnancy baseline data to provide a more comprehensive understanding of the relationship between these biomarkers and adverse pregnancy outcomes.

5. Conclusions

Our study reveals a marginal yet significant difference in creatinine levels between groups with and without adverse pregnancy outcomes. although the difference was not clinically significant. Additionally, elevated AST levels were found to be associated with adverse pregnancy outcomes, while other liver and kidney markers did not show statistically significant associations.

Notably, we observed statistically significant interactions between time points (before and after delivery) and adverse pregnancy outcomes for Hb, PCV, and RBCs ($p<0.05$), while other hematological parameters did not show significant interactions. These findings underscore the importance of longitudinal monitoring of specific biomarkers for early identification and management of women at risk of adverse pregnancy outcomes. The observed associations, particularly with creatinine and AST levels, as well as the dynamic changes in certain hematological parameters, suggest potential avenues for developing personalized antenatal care strategies. However, given the study's limitations, further research is warranted to validate these findings in larger, more diverse cohorts. Future studies should also explore additional biomarkers and consider pre-pregnancy baselines to enhance predictive accuracy. Such comprehensive investigations could significantly contribute to improving maternal and fetal outcomes through early risk identification and targeted interventions.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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