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Diagnostic Accuracy of Lactate Dehydrogenase and Serum Creatine Kinase to Detect Prenatal Hypoxia in Term Neonates

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ABSTRACT

Background: Prenatal hypoxia is a condition where the fetus experiences insufficient oxygen levels and it can lead to morbidity and mortality. This study aimed to evaluate the diagnostic efficacy of the serum CK-MB fraction and LDH for the diagnosis of prenatal hypoxia.

Methods: This cross-sectional study was conducted in the Pediatric Department of Central Park Teaching Hospital, Lahore, from June 2022 to February 2024. The study included 240 newborns with signs of hypoxia, using purposive sampling and excluding cases with specific health conditions. Demographics, LDH, and CK-MB levels were analyzed in SPSS for sensitivity, specificity, positive predictive value PPV and negative predictive value (NPV, and diagnostic accuracy, with stratification by neonatal characteristics. The level of significance was set at $p < 0.05$.

Results: The age distribution showed that 63.33% were up to six hours old.CK-MB (sensitivity 93.12%, specificity 66.72%) and LDH (sensitivity 98.40%, specificity 92.31%) PPV 97.42%, NPV 22.15%, and accuracy 92.92%. LDH showed a sensitivity of 98.40%, specificity of 92.31%, PPV of 79.40%, NPV of 57.14%, and accuracy of 78.89% for diagnosing perinatal hypoxia.

Conclusion: Despite CK-MB having higher accuracy, LDH is considered more reliable due to its superior sensitivity and specificity, which are crucial for detecting prenatal hypoxia.

Keywords: Creatine Kinase, Myocardial Form, L-Lactate Dehydrogenase.

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INTRODUCTION

The WHO defines newborn hypoxia as a newborn's inability to start and continue breathing[1]. Neonatal infection and mortality (HIE) are a leading cause of death and morbidity among infants across the globe with rates of 100–250/1000 live births in developing countries and 5–10/1000 live births in industrialized countries[2]. Pakistan is responsible for 7% of the world's newborn mortality and 23% of newborns with birth hypoxia[3]. The size of the issue in Pakistan is shown by these statistics.

APGAR scores that are low and have a history of delayed or absent crying at delivery are commonly used to diagnose prenatal hypoxia. It will be very beneficial if biochemical markers can identify the HIE before clinical symptoms show up[4]. According to the study, the APGAR score should be questioned for assessing hypoxia since it typically does not accurately reflect the level of acidity during birth (analysis of 1110 babies)[5]. Studies have been conducted on newborns who experienced prenatal oxygen deprivation which can result in transient ischemia of the myocardium and myocardial dysfunction. These indicators of hypoxia include CK-MB and LDH[6,7,8]. In research, the specificity and sensitivity for perinatal hypoxia prediction using CK-MB were found to be 28% and 100 %, respectively, whereas those using LDH were 59.18% and 92%. In a newborn who needed resuscitation and had an Apgar score of less than 7, this demonstrated good specificity but extremely low sensitivity[5]. According to another research, the LDH has a sensitivity of 96.3% and a specificity of 87.9%, whereas the CK-MB has a sensitivity of 30% and a specificity of 100 %[9]. The APGAR score and clinical findings will be the gold standard in this investigation. The purpose of the research is to evaluate the investigative precision of blood LDH and CK-MB for perinatal hypoxia prediction in term infants. An earlier and less intrusive technique is needed to anticipate prenatal hypoxia in newborns to reduce the likelihood of it happening. Research has demonstrated that LDH is a more reliable predictor of perinatal hypoxia than CK-MB. However, noteworthy outcomes have been observed in the absence of local proof. Therefore, these markers' implied use in the local setup is not operational. Thus, the goal of this study is to standardize the use of LDH and CK-MB testing for the prediction of early prenatal hypoxia. Furthermore, there is disagreement regarding whether the approach is more trustworthy. Therefore, the goal of this study is to gather local data for future use of more dependable methods in local setups.

METHODS

The research was conducted following the clearance by the ethical committee of the hospital. Patients were scheduled to attend the Central Park Teaching Hospital, Lahore pediatric department between June 2022 to February 2024 ethical approval number CPMC.IRB-No 1465. The study employed a cross-sectional design to recruit newborns. The sample size was calculated using a statistical power calculator, considering a 95% confidence level and a 23% expected prevalence of perinatal hypoxia [9]. Prenatal hypoxia is expected to account for 240 instances with a 95% confidence level, while perinatal hypoxia is expected to account for 23% of cases. The LDH test's sensitivity is 59.18% with a 13% margin of error, and the specificity of the test is 92%[10]. This research comprised newborns of either gender who had delayed crying at delivery (shut off after two minutes) neonates aged 6 hours fall into the category, which was considered to be signs of suffocation. The study excluded neonates having a history of mother's coagulation abnormalities (aPTT> 20 seconds, PT> 15 seconds), drug addiction, septicemia, extremely low birth weight neonates (<2000 grams), congenital deformity, and other conditions. It was conducted in the emergency pediatrics department of Central Park Teaching Hospital, Lahore with 240 babies who fulfilled the inclusion criteria. The parents approved the treatment to be carried out. Name, gender, age (in hours), gestational age, and birth weight were the demographic data that was collected. Using a 3cc BD syringe, blood was drawn in an aseptic manner.

The hospital's pathology lab examined the samples to check for LDH and CK-MB. On 2 milliliters of clotted blood, samples were examined using auto analyzers and reagent kits. Subjects were classified as either negative or positive for both indicators after reports were evaluated. Neonatal were then brought into the NICU. The cut-off values used to detect prenatal hypoxia in the study were LDH ≥ 400 IU/L and CK-MB ≥ 10 IU/L. The neonate was verified as either positive or negative if prenatal hypoxia occurred. Every detail was documented on proforma. SPSS version 24 was used for the data analysis, and standard proforma was used to record all results. For the quantitative characteristics like birth weight, and gestational age, there was a mean & a standard deviation. Frequency and percentages were used for (CK-MB, LDH, and actual development). Qualitative factors 2x2 tables were used to calculate the specificity, sensitivity, PPV, NPV, and diagnostic accuracy of the CK-MB and LDH tests. When analyzing the data, consideration was given to the neonate's age, gestational age, gender, and birth weight. Using 2x2 tables created following stratification, the LDH and CK-MB specificity, sensitivity, PPV, NPV, and diagnostic accuracy were determined.

RESULTS

Table 1: Demographics Characteristics of the Study Participants (n=240)

Variable	Category	Mean ± SD / Frequency (%)
Age (Hours)	≤ 6 hours	153 (63.75%)
	> 6 hours	87 (36.25%)
Gestational Age (Weeks)	37-38	190 (79.17%)
	> 38	50 (20.83%)
Birth Weight (Kg)	-	Mean ± SD: 2.95 ± 0.45 Kg
Gender	Female	147 (61.25%)
	Male	93 (38.75%)
Prenatal Hypoxia (Gold Standard)	Yes	233 (97%)
	No	7 (2.92%)
CK-MB (≥ 10 IU/L)	Hypoxia	221 (92.08%)
	No Hypoxia	19 (7.92%)
LDH (≥ 400 IU/L)	Hypoxia	187 (77.92%)
	No Hypoxia	53 (22.08%)

The mean ± SD was estimated as 5.60 +1.79 hours. The distribution of age reveals that 63.33% were up to 6 hours and 36.67% were more than 6 hours (n=153 and n=87 respectively). According to gender distribution, there were 61.25% of girls and 38.75 % of men (n = 147). Weight at birth (kg): 2.74±0.46 kg. **Table 1**.

Figure 1 shows that the computed gestational age was 79.17 percent (n = 190) for those who were between 37 and 38 weeks and 20.83 percent (n = 50) for those who were above 38 weeks. On the gold standard, the frequency of prenatal hypoxia was found in 97 percent of cases, whereas 2.5 percent of cases showed no evidence of perinatal hypoxia (n = 233 and n= 7respectively). 92.08% (n=221) of the cases of prenatal hypoxia on CK-MB were documented, whereas 7.92% (n=19) of the cases showed no evidence of perinatal hypoxia. 22.08% (n=53) showed no evidence of prenatal hypoxia, whereas 77.92% (n=187) had a frequency of perinatal hypoxia on LDH. Serum CK-MB fraction was found to have a sensitivity of 93.12%, specificity of 66.76 %, PPV of 97.42%, NPV of 22.15%, and a diagnostic accuracy rate of 92.92% when using 2x2 analysis as the gold standard for diagnosing perinatal hypoxia in term neonates. **Tables 2** and **3** display the table.

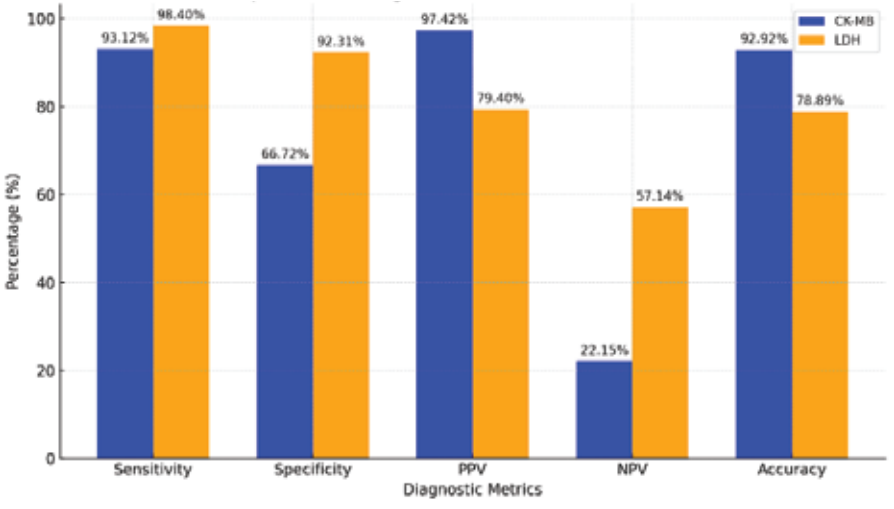

Figure 1: Comparison of Diagnostic Of CK-MB and LDH

Table 2: CK-MB And LDH: Test\S Sensitivity, Specificity, PPV, NPV

CK-MB	Perinatal Hypoxia		Total	**Sensitivity=**93.12%
	Yes	**No**		**Specificity=**66.72%
≥ 10 IU/L	233	3	236	**PPV=**97.42%
< 10 IU/L	7	1	8	**NPV=**22.15%
Total	240	4	244	**Accuracy=**92.92%
LDH	**Perinatal Hypoxia**		**Total**	**Sensitivity=**98.40%
	Yes	**No**		**Specificity=**92.31%
≥ 400 IU/L	233	2	235	**PPV=**97.42%
< 400 IU/L	7	5	12	**NPV=**22.15%
Total	240	7	247	**Accuracy=**92.92%

Table 3: Stratification Of CK-MB and LDH W.R.T Different Variables!

Variables		Sensitivity	Specificity	PPV	NPV	Accuracy
Serum Creatine Kinase						
Age	≤6 h	100%	50%	98.67%	100%	89.68%
	>6 h	82.56%	100 %	100 %	12.74 %	82.95%
Gender	Male	82.44%	50%	96.5%	12.74 %	82.92%
	Female	100 %	100 %	100 %	100 %	98.63%
Gestational Age	37 to 38 weeks	91. 8%	66.76 %	97.84%	22.15%	90.15%
	>38 weeks	100 %	0.0%	100 %	0.0%	100 %
Birth Weight	<2.5 kilograms	100 %	0.0%	94.15%	0.0%	94.15%
	>2.5 kilograms	91.23%	100 %	100 %	22.15%	91.42%
Lactate Dehydrogenase						
Age	≤6 h	100 %	100 %	100 %	100 %	100 %
	>6 h	93.15%	0%	43.53%	0%	43.15%
Gender	Male	96.5%	12.74 %	82.44%	50%	82.92%
	Female	97.42%	5.82%	73.17 %	66.76 %	75.43%
Gestational Age	37-38 weeks	97.83%	7.69%	73.77%	57.14%	73.16%
	>38 weeks	100 %	0.0%	100 %	0.0%	100 %
Birth Weight	up to 2.5 kg	100 %	100 %	100 %	100 %	94. 61%
	>2.5 kg	97.17%	4.00%	68.21%	40%	67.31%

Using gold standard clinical findings, the precision of LDH's perinatal hypoxia diagnosis in term newborns was tested and determined to be sensitivity of 98.40, specificity of 92.31%, PPV of 79.00%, NPV of 57.14% and 78.05% accuracy. When analyzing the data, consideration was given to the ninth table in the series, which includes the neonate's age, sex, gestational age, and birth weight. **Table 3** displays the 2x2 tables that were created following stratification and used to compute the specificity, sensitivity, PPV, and NPV.

DISCUSSION

Research revealed that when it comes to predicting prenatal hypoxia, LDH is more reliable than CK-MB. However, noteworthy outcomes have been observed in the absence of local proof. Therefore, these markers' implied use in the local setup is not operationalc[11,12,13]. Therefore, the goal of this work was to design a protocol for early prenatal hypoxia prediction using CS-MB and LDH. Furthermore, there is disagreement regarding whether the approach is more trustworthy. The purpose of the research was to gather local data so that future local setups may use a more trustworthy approach. The age distribution in our study indicates that 36.67% (n=87) had more than 6 hours, and 63.33% (n=153) had up to 6 hours. The mean±SD was 38.75 % (n=93) of the hours, estimated as 5.60+1.79, were spent by men, and 61.25% (n=147) by women. Serum creatine kinase muscle brain fraction was found to have an accuracy rate of 92.92%, a sensitivity of 93.12%, a specificity of 66.76 %, PPV of 97.42%, and NPV of 22.15% the diagnosis of perinatal hypoxia in term neonates (with the use of clinical findings as the gold standard). Using clinical evidence as the gold standard, the accuracy rate of LDH for perinatal hypoxia in term newborns was shown to be 78.89%, with a specificity of 98.40%, specificity of 92.31%, PPV of 79.40%, and NPV of 57.14%.

According to earlier research, the sensitivity and

specificity of LDH were 92% and 59.18% for the prediction of neonatal hypoxia, compared to 28% and 100 % for CK-MB. In a newborn who needed resuscitation and had an Apgar score of less than 7, this demonstrated good specificity but extremely low sensitivity [14]. According to another research, the LDH has a sensitivity of 96.3% and a specificity of 88.9%, whereas the CK-MB has a sensitivity of 30% and a specificity of 100 % [18]. This study's findings are similar to ours. Another study examined the relationship between the degree of perinatal hypoxia and laboratory indicators of heart damage, as well as the investigative usefulness of a series of assessments in the retrospective analysis of birth hypoxia [19]. Moreover, the cut-off Creatine Kinase-MB value of more than 92.6 U/L showed 82% of both specificity and sensitivity after 8 hours[18]. CK-MB scores 80.34 percent for positive predictive values and 81.63 percent for negative predictive values. A 24-hour period of more than 60 U/L of CKMB has a 95.83 percent specificity cut-off value and a 58.33 percent sensitivity 69.70 % NPV and a 93.33 % PPV. A threshold LDH value of greater than 580 U/L had 100 percent sensitivity and 87 percent specificity at 72 hours[20]. LDH has an 89.29% chance of being beneficial and a 100 % chance of being detrimental. Based on the neonate's clinical features and history, LDH and CKMB level analysis at 8 and 24 hours of life may distinguish between a non-hypoxia and a hypoxia newborn. LDH performs diagnostically better than CK-MB and the studies similarly compatible with the results of our investigation[14,15,16,17].

The findings of this study align with existing literature, underscoring the critical role of CK-MB and LDH as diagnostic markers for perinatal hypoxia. The higher sensitivity of LDH (98.40%) compared to CK-MB (93.12%) corroborates studies suggesting its superior reliability in identifying hypoxic states in neonates. However, CK-MB demonstrated a higher positive predictive value (97.42%), reflecting its accuracy in confirming cases of hypoxia. These differences may highlight variations in the metabolic and enzymatic response of neonates to hypoxic stress[23]. Studies emphasize the utility of biochemical markers like LDH and CK-MB in the early diagnosis of hypoxic-ischemic encephalopathy, especially in settings with limited access to advanced diagnostic tools[24]. The importance of inflammatory markers in understanding the outcomes of perinatal hypoxia, which may complement CK-MB and LDH measurements[25].

CONCLUSION

Findings showed that the diagnosis of perinatal hypoxia was mainly done through clinical findings. While CK-MB and LDH both detected hypoxia, LDH proved more reliable because of its greater sensitivity and specificity. The analysis also recognized the impact of gestational age, birth weight, and neonatal age as relevant diagnostic factors. These results reveal that LDH is a more reliable biomarker for perinatal hypoxia than CK-MB.

LIST OF ABBRIVIATIONS

CK-MB - Creatine Kinase-MB
LDH - Lactate Dehydrogenase
TP - True Positive
FP - False Positive
FN - False Negative
TN - True Negative
NPV - Negative Predictive Value
PPV - Positive Predictive Value
NICU - Neonatal Intensive Care Unit
aPTT - Activated Partial Thromboplastin Time
PT - Prothrombin Time
SD - Standard Deviation
N - Total Number of Cases

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CONFLICT OF INTEREST

None

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AUTHORS' CONTRIBUTIONS

All authors contributed equally.

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