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Early Predictors of Neurodevelopmental Adverse Outcome in Term Infants with Postasphyxial Hypoxic Ischemic Encephalopathy

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ABSTRACT

Background: Neonatal brain injury due to intrapartum asphyxia is an important cause of cerebral palsy, mental retardation, and epilepsy. In developing countries, the incidence of post asphyxial neurological damage is particularly high. Despite advances in perinatal care over the past three decades, the incidence of cerebral palsy attributed to birth asphyxia has not changed.

Objectives: To predict the outcome of postasphyxial hypoxic ischemic encephalopathy early in the neonatal period, for proper counseling of the parents, to get benefit in clinical practice and to select patients who will benefit from recent management strategies.

Study Design: This study was conducted on 63 asphyxiated full term newborn infants who developed Hypoxic-Ischemic Encephalopathy (HIE) admitted at Neonatal Intensive Care Unit of Al-Jedaany Hospital, Jeddah, Kingdom Saudi Arabia in the period from May 2006 to January 2008. They were classified according to Sarnat and Sarrnat staging of HIE into the following: 16 with stage I, HIE (Group I), 19 with stage II, HIE (Group II) and 20 with stage III, HIE (Group III). Twenty full term healthy newborn infants, age and weight-matched, were served as a control. All infants were subjected to the following tests: cord blood gases at birth, and Urine sample for testing urinary lactate / creatinine ratio. Also a real-time cranial ultrasonography was done for infants who had HIE. Follow up of the cases was done by the followings: A neurodevelopmental clinical evaluation every three months till the age of one year of life was done for the cases and control infants. An Electroencephalogram (EEG) and auditory brainstem evoked response (ABR) were done at the age of three months and a second ABR at the age of six months for cases with abnormal previous ABR.

Results: Group III (stage III, HIE) has significantly increased initial, maximum and day 7 HIE scores (16.4 ± 3.1, 18.15 ± 2.79 and 13 ± 5.79) respectively compared with group I&II. Also HIE score significantly increased in group II (11.89 ± 2.09, 12.50 ± 2.29 and 5.05 ± 5.03) compared with group I (7.01 ± 1.3, 7.61 ±2.91 and 0). Cord blood metabolic acidemia and the increase of urinary lactate/ creatinine ratio are significantly present in all infants with HIE (groups III, II&I) compared with the control group. Also metabolic acidemia and the increased urinary lactate/ creatinine ratio significantly increase as HIE stages increase. HIE cases with abnormal neurodevelopmental clinical outcome has significant HIE scores [initial (14.51 ± 4.01), maximum (15.60± 4.21) &day 7(9.40± 6.51)], significant metabolic academia (7.04± 0.11) and significant increased lactate / creatinine ratio (3.6± 2.10), compared with HIE cases with normal outcome. Also HIE cases with abnormal ABR have statistically significant abnormal neurodevelopmental outcome while HIE cases with abnormal EEG have no abnormal outcome.

Conclusion: Hypoxic ischemic encephalopathy score, capillary blood gases report, urinary lactate/creatinine ratio and cranial ultrasonographic findings are important early and easily predictors of

perinatal hypoxic ischemic encephalopathy outcome and provides a sliding scale of probabilities that could be used for prognostication and to design eligibility criteria for decision making including neuroprotective therapy.

Keywords: Predictors, HIE, Lactate, creatinine, neurodevelopmental, ABR

Introduction

Perinatal asphyxia and resulting hypoxic ischemic encephalopathy (HIE) occur in 1 to 3 per 1000 births in the United States.[1-3] Higher rates occur in developing countries with limited diagnostic and interventional resources.[1]

Worldwide, 10% to 60% of infants who develop HIE will die and at least 25% of the survivors will have long-term neurodevelopmental sequelae.[2] Hypoxic ischemic encephalopathy is the primary cause of 15% to 28% of cerebral palsy among children.[3]

Perinatal asphyxia progresses to HIE based on the degree of brain injury and resulting clinical presentation. Clinical seizures are the hallmark of resulting encephalopathy following injury.[1,4] Sarnat and Sarnat's criteria for clinical encephalopathy can be used to determine the degree of neuronal injury based on the infant's symptoms.[5] The Sarnat and Sarnats criteria include lethargy, stupor, or coma, with 1 or more of hypotonia, abnormal reflexes (oculomotor or papillary abnormalities), an absent or weak suck, or evidence of seizures.[6]

Parameters that have been used to predict or define perinatal asphyxia include: intrapartum electronic fetal monitoring, fetal or umbilical cord pH measurement, meconium-stained amniotic fluid, Apgar score, hypoxic ischemic encephalopathy (HIE), and major organ disorder. However, no single marker of perinatal asphyxia has shown good predictive efficiency and only a combination of various indices can help in the early diagnosis of perinatal asphyxia.[7,8]

The need for early prediction of outcome is particularly important because of the narrow window of effectiveness and possible side effects of neuro-protective interventions [9]. The realistic window of opportunity for intervention depends on the timing and severity of the primary insult, as well as the type of intervention. Based on animal studies and preliminary clinical experience, the therapeutic window in human neonates seems to be within 1-6 h of birth. Thus, it is important to look for useful predictors early in the course of HIE, preferably within the first 6h after birth [10].

Aim of the Work

To predict the outcome of postasphyxial hypoxic ischemic encephalopathy early in the neonatal period, for proper counseling of the parents, to get benefit in clinical practice and to select patients who will benefit from recent management strategies.

Patients and Methods

This study was conducted on 63 asphyxiated full term newborn infants who developed HIE admitted at Neonatal Intensive Care Unit of Al-Jedaany Hospital, Jeddah, Kingdom Saudi Arabia in the period from May 2006 to

January 2008. All survived infants were followed up for at least one year after hospital discharge. The diagnosis of perinatal asphyxia was made on clinical signs during the early hours after birth together with abnormal acid-base status and a history of documented abnormal Cardiotocography (CTG) during the first and second stages of labor. The studied infants were classified on the basis of Sarnat and Sarnat staging of HIE [(5)] into the following 3 groups;

Group I (stage I HIE) included 16 newborn infants who have hyperalertness, hyperreflexia and tachycardia, Group II (stage II HIE) included 19 newborn infants who have lethargy, hyporeflexia, bradycardia, hypotonia, weak suckling & Moro reflexes and convulsions and Group III (stage III HIE) included 28 newborn infants who have stupor, profound hypotonia, hypothermia, absent suckling & Moro reflexes, apnea and frequent seizures with or without coma. Twenty healthy full term newborn infants, age and weight matched with the diseased groups, served as control. *For asphyxia groups*; term newborn infants completed their 37th week of gestation, with Apgar score <7 at 5 min, umbilical artery acidemia pH< 7.20) and/or base deficit >12mmol/L, and clinical signs of asphyxia were included in the study. *For control group*,newborn infants with no maternal illness, normal CTG study during the first stage of labor, arterial cord blood pH>7.20 with base deficit <10.0, Apgar score >7 at 5min, and uneventful clinical course during the first 3 days of life were included in the study. Infants with Gestational age < 37 weeks (as the neurological complications of prematurity may interfere with the results), presence of perinatal infection, congenital anomalies or metabolic disorders and those who did not complete the course of the follow up were excluded from the study. Eight infants from stage III group died in the first 24 hours of life due to multiple organ failure syndromes, so excluded from the study due to the need for follow up.

CTG or the external fetal cardiac monitoring, was done routinely for all women in labor and was considered abnormal (non-reassurance) if any of the following was present for any time interval: Fetal tachycardia > 160/min, fetal bradycardia<120/min, absence of beat-to-beat variation, or late deceleration.

Our study was approved by the clinical committee of the hospital and performed according to ethical procedures.

All studied infants and controls were subjected to complete physical and neurological examination daily for at least 7 days using HIE score proposed by *Thompson et al,*[(11)] who have developed a clinical assessment score of 9 signs (Table 1). They claimed that the parents of an asphyxiated infant who scores a maximum of 10 or less and is normal by day 7 can be assured of a normal neurological outcome, while those with scores higher than 15 and remain abnormal after day 7 must have a guarded prognosis. Laboratory investigations included; cord blood gases at birth, complete Blood count, blood glucose and serum electrolytes and urine sample for testing urinary lactate / creatinine ratio. Also real-time cranial ultrasonography was done for infants who have HIE. A) Acid-Base Analysis; arterial cord blood samples were collected from double clamped umbilical cord, anaerobically, using heparinized disposable syringes (5ml syringe washed by 1000IU/ml heparin). Air bubbles were removed immediately, and the samples were analyzed by (CIBA CORNING 238 pH/Blood Gas Analyzer – Bayer, Germany).It directly measures pH, pO2, pCO2, bicarbonate and base excess. B) Urinary Lactate / Creatinine Ratio; for determination of urinary lactate / creatinine ratio, a pediatric urine bag is perfectly fitted to the genitalia of the newborn for collection of

early spot urine sample. i) *Urinary creatinine measurement* [12]*;* kinetic determination of creatinine without deproteinization. The complex formed by creatinine and picric acid in an alkaline medium is measured for one minute. ii) *Urinary lactate measurement* [13]*;* the concentration of lactate in the sample is determined by Colorimetric method. C) Cranial Ultrasonography; we performed real-time cranial ultrasonography within 24 hours, 48 to 72 hours, and 10 days after birth in the infants with perinatal asphyxia, using a 5- or 7.5-MHz sector transducer (SSD 630, Aloka, Tokyo, Japan).[14] Ultrasonographic findings of increased echogenicity within the cerebral cortical parenchyma, basal ganglia, and thalamus or the presence of encephalomalacia were considered abnormal [15].

Follow up of the 55 survived cases was done as the following; a neurodevelopmental clinical evaluation every three months till the age of one year of life was done for the cases and control infants, an Electroencephalogram (EEG) and auditory brainstem evoked response (ABR) were done at the age of three months and a second ABR at the age of six months for cases with abnormal previous ABR.

The neurodevelopmental outcome was classified as favorable outcome {defined as normal neurologic development or only mild impairment (slight abnormalities in muscle tone and reflexes)}; and adverse outcome {defined as impairment resulting in death, severe cerebral palsy, developmental delay, blindness, deafness, spasticity or seizure disorder}[16].

Statistical methods; Continuous data were expressed as mean ± SD. Student's t test was used for comparison between two means. Nominal data were expressed as number and percent. The differences between the groups were evaluated using the Chi-square X^2 test. Correlation coefficient tests are used test how variables are related. One way ANOVA test was done for comparison between two groups. Sensitivity (Sn), Specificity (Sp), Positive predictive value (PPV) and Negative predictive value (NPV) were also computed for each test. The significance level for all tests was defined at as a P value <0.05.

Results

According to Sarnat and Sarnat staging of HIE, the study included 16 newborn infants with stage I, HIE (group I), 19 newborn infants with stage II, HIE(group II) and 20 newborn infants with stage III, HIE(group III), and 20 healthy full term newborn infants as control. All study infants were age and weight matched with no statistical difference regarding their gestational age and the birth weight. Table 2 compares the HIE score in relation to the disease groups. It shows that Group III has significantly increased (initial, maximum and day 7 HIE scores) compared with group II&I. Also HIE score significantly increased in group II compared with group I. Table 3 showed cord blood metabolic acidemia and the increase of urinary lactate/ creatinin ratio are significantly present in all infants with HIE (groups III, II&I) compared with the control group. Also metabolic acidemia and the increased urinary lactate/ creatinin ratio significantly increase as HIE stages increase. Table 4 & Figure 1 represent the relationship between the different variables and the neurodevelopmental Outcomes among the studied HIE cases. It shows that HIE cases with abnormal outcome has a significant HIE scores (initial, maximum &day 7) and significant metabolic academia and increased lactate / creatinin ratio, compared with HIE cases with normal outcome ($p< 0.001$). Table 5 and Figures 2, 3, & 4 showed a significant positive correlation between lactate/ creatinine ratio and initial

HIE Score. There is a significant negative correlation between lactate/creatinine ratio and pH, BD & Hco_3. On the other hand there is no significant correlation between lactate / creatinine ratio and maximum HIE Score & HIE Score on day 7. Table 6 showed that there is a highly significant difference between cases with normal and with abnormal cranial sonar as regards to initial HIE score , maximum HIE score and HIE score on day 7($p<0.001$) . There is significant difference between cases with normal and with abnormal cranial sonar as regards to pH, BD and HCO_3 ($p<0.05$). There is no significant difference as regard to urinary creatinine, lactate and lactate / creatinine ratio ($p>0.05$). Table 7 showed that there is a highly statistical significant increase in the mean initial HIE score and lactate/creatinine ratio in cases with abnormal ABR. There is a statistical significant increase in maximum HIE score, HIE score on day 7 and BD in cases with abnormal ABR. There is a statistical significant decrease in pH in cases with abnormal ABR. There is no statistical significant decrease in HCO_3 in cases with abnormal ABR. As regard EEG findings, there is no significant difference in mean initial HIE score, maximum HIE score, HIE score on day 7, pH and BD ratio in cases with abnormal EEG compared to cases with normal EEG . While there is a significant difference in mean HCO_3 in cases with abnormal EEG compared to cases with normal EEG. Table 8 represents the findings of ABR & EEG in relation to the neurodevelopmental outcome of HIE cases. It shows that HIE cases with abnormal ABR have statistically significant abnormal neurodevelopmental outcome while HIE cases with abnormal EEG have no abnormal outcome.

Discussion

Asphyxia remains one of the main causes of later disability in term infants. Despite many publications identifying possible predictors of outcome in this population of interest, little is known about the long-term neurodevelopmental outcome of asphyxiated term neonates [17]. In our study we used Hypoxic-ischemic encephalopathy score postulated by Thompson et al., [11] for clinical evaluation of full term newborn infants who developed hypoxic-ischemic encephalopathy to be used in prediction of neurodevelopmental outcome at 1 year of age. Our results demonstrated that a significant increase in HIE score [initial score, maximum score, and score on day 7 onwards ($P<0.001$)] when HIE stage progress from mild to severe. A highly significant increase in HIE score (initial, maximum and score on day 7 onwards) in newborn infant with abnormal outcome at 1 year of age when compared with infants with normal outcome ($P<0.001$). The positive predictive value and the negative predictive value of both initial and maximum HIE score were 74.1 % and 78.2 % respectively with a sensitivity and specificity of 90.4 % and 51.9 % respectively. While the positive predictive value and negative predictive value of HIE score on day 7 onwards were 90.8 % and 82 % respectively with a sensitivity and specificity of 88.2 % and 48.1 % , respectively. Our results are concomitant with Thompson et al., [11] who found that the maximum HIE score had a positive predictive value of 92 % and a negative predictive value of 82 % for abnormal outcome, with a sensitivity and specificity of 71 % and 96 %, respectively. Thompson et al., [11] also found that, when predictors were assessed in combination, an infant with maximum HIE score and who remained abnormal after day 7 had a 92 % chance of being abnormal and all infants who peaked below 16 and who were normal by day 7 were normal at one year of age (negative predictive value 100%) with sensitivity and specificity of 100% and 93% respectively. Our results disagree with Thompson et al., [11] who

stated that all infants whose score had returned to 0 by day 7 were normal (the negative predictive value was 100% for an abnormal score on day 7).

In our result, 19 % of infants whose score had returned to 0 by day 7 had abnormal outcome at one year of age. This finding is compared with Caravale et al., [18] who found that 4 of 28 infants (14%) who were normalized at day 7 had abnormal outcome at one year of age. However this difference may be attributed to different sample size, different standard level of care in different countries and also the abnormal outcome may be caused by other causes unrelated to hypoxic-ischemic insult. Our results are also consistent with Thompson et al., [11] as regards to good correlation between the range of HIE score and the stage of HIE.

We found that: infants in the stage I had maximum HIE score of 9 or less, infants in stage II had maximum HIE score of 10-14, and infants in stage III had maximum HIE score more than 14. In our study, we found that 15% of infants whose maximum HIE score fell outside these ranges. Also, 2 infants in stage I HIE with scores of 10 and 17 (the later was under effect of muscle relaxants), 3 infants in stage II HIE with scores of 8, 15, and 17 and 2 infants in stage III HIE with scores of 12, 13. This means that maximum HIE score correlates well with Sarnat and Sarnat staging of HIE.

Our results are consistent with Sarnat and Sarnat [5] and Dilenge et al., [16] who found that the persistence of grade 2 or 3 encephalopathy after 7 days carried a less favorable prognosis. However, we are partially in disagreement with them as regards to the outcome of stage I HIE. While they confirm that the outcome of stage I HIE is always favorable, we found that 13% of infants of stage I had abnormal outcome. This finding is consistent with Ezgu et al., [19] who found one of the three infants of stage I HIE who continue follow up till 1 year of age, had abnormal outcome. He found that the infant had abnormal EEG finding and a neuron-specific enolase level greater than the cutoff value. We also found that the two of 16 infants with stage I HIE who had abnormal outcome were having lactate/creatinine ratio greater than the cut off value. This result was supported by Caravale et al., [18] who found that 14% of infants with grade I HIE at 48 hours developed abnormal outcome, 33% of grade II HIE developed abnormal outcome at one year of age. At the same time 100% of infants with grade III HIE at day 7 developed abnormal outcome at one year of age.

As regards to arterial blood gas reports, our finding showed a significant metabolic acidemia in all stages of HIE when compared with control group ($P<0.001$). Moreover, a significant metabolic acidemia in HIE cases with abnormal outcome when compared with HIE cases with normal outcome ($P<0.001$). The positive predictive value and the negative predictive value of pH were 72.1% and 71.5% respectively with sensitivity and specificity of 88.2% and 49.1% respectively. These results are consistent with Toh, [20] who found significant metabolic academia in cases of abnormal outcome compared with cases of normal outcome ($P<0.001$).The positive predictive value and the negative predictive value of pH <7.1 were 93.8% and 69.2% respectively with sensitivity and specificity of 78.9% and 90% respectively. Our results are also in accordance of Malin and his colleagues[21] who concluded that Low arterial cord pH showed strong, consistent, and temporal associations with clinically important neonatal outcomes that are biologically plausible. These data can be used to inform clinical management and justify the use of arterial cord pH as an important outcome measure alongside

neonatal morbidity and mortality in obstetric trials.

The above results disagree with Socol et al., [22] who stated that neither low umbilical cord arterial pH nor higher base deficit was predictive of chronic neurologic disability. Also they found that there was no difference in umbilical cord arterial blood gas measurements between infants who were subsequently normal versus those with cerebral palsy.

Our results showed that the mean urinary lactate excretion was highly significantly increased in all stages of HIE compared with control group ($P < 0.001$). The urinary lactate / creatinine ratio showed highly significant increase in all stages of HIE compared with control group ($P < 0.001$). The mean lactate/creatinine ratio showed highly significant increase in HIE cases of abnormal outcome compared with HIE cases with normal outcome ($P < 0.001$). One explanation of these striking differences in lactate excretion and lactate/creatinine ratio in urine of different groups is that lactate is used as an alternative energy substrate in infants with normal outcome [23]. The positive predictive value and the negative predictive value of lactate/creatinine ratio were 71.2% and 63.1% respectively with sensitivity and specificity of 78.3% and 54.1% respectively. These results are in agreement with and supported by the findings of Liu et al.,[24] who concluded that early measurement of both urinary S100B protein level and lactate/creatinine ratio in the urine of newborns with HIE is a practical convenient and sensitive way to improve diagnosis on the third day of life and prognostic prediction of HIE.

Our results also in agreement with Huang et al., [13] , who studied the ratio of urinary lactate / creatinine in a group of non-asphyxiated infants and a group of asphyxiated infants , who were further subdivided into two subgroups, one who developed HIE and the other did not develop HIE. They found that the lactate / creatinine ratio increased as HIE worsened. Furthermore, they found that lactate / creatinine ratio was also significantly related to the neurodevelopmental outcome at one year of age. Huang et al., [13] measured urinary lactate and creatinine by proton nuclear magnetic resonance spectroscopy, while we measured these compounds by biochemical methods in our study.

Lactate/creatinine ratio has significant positive correlation with initial HIE and base deficit (BD), a significant negative correlation with PH and serum HCO_3 levels and no significant correlation with maximum HIE and score on day 7. Although these results are important because they help us to predict outcome of HIE early in the neonatal period to counsel the parents and to select newborn infant with HIE who will gain benefit from continuous medical support, many infants with HIE invariably have oliguria which impede early urine sampling.

In our study, abnormal sonographic findings (30 infants with Brain edema and 3 infants with intraventricular hemorrhage) were detected in 24 newborn infants with abnormal outcome and 9 newborn infants with normal outcome. On the other hand, normal sonographic findings were detected in 12 newborn infants with normal outcome and in 7 newborn infants with abnormal outcome. The positive predictive value and the negative predictive value of cranial sonographic findings were 78.1% and 58.3% respectively with sensitivity and specificity of 73.3% and 64.1% respectively. This results are consistent with Jongeling et al., [25] they found that severe edema on ultrasound had a positive predictive value and a negative predictive value of 83 % and 82 % respectively with sensitivity and specificity of 63 % and 93 % respectively. These results also are supported

by Caravale et al., [18] who concluded that both the 48 hours and 7 day head ultrasounds correlated well with developmental outcome at one year of age. The 7 day ultrasound was more sensitive in predicting abnormal development. A normal scan at 48 hours was more predictive of a normal outcome compared with the ultrasound scan at 7 days. Our results disagree with Ezgu et al.,[19] who found that ultrasonographic findings did not seem to predict the grade of encephalopathy or the outcome. In our study, when there were abnormal ultrasonograpic findings, there were significant increase in HIE score, BD, and significant decrease in PH and HCO_3 findings. On the other hand there was no significant difference in lactate/creatinine ratio in urine in cases with abnormal ultrasonograpic findings.

Our cases were followed up every 3 months till the age of one year. Our follow up was clinically and neurophysiologically using auditory evoked response (ABR) and EEG. ABR is the preferred screening method to evaluate hearing loss in neonatal intensive care unit graduate as evoked otoacoustic emissions (EOAE) is more likely to be affected by debris or fluid in the external ear and middle ear. Furthermore, EOAE is unable to detect some forms of sensorineural hearing loss. Infants with abnormal ABR screening should have follow up testing. This is done within two weeks after their test in case of bilateral affection and within 3 months in unilateral affection [26]. In our study using ABR , 43.7% of cases of HIE experienced transient hearing loss at the age of 3 months, However only 12.5% of cases had persistent hearing impairment at the age of 6 months. These findings are similar to the findings shown by Jiang et al [27] who found that 34.4% of babies after hypoxia-ischemia had peripheral hearing impairment. The impairment gradually recovered after the first day. By one month, only about 10% of babies had persistent impairment. However it is not known how hearing changes during the neonatal period after perinatal hypoxia-ischemia. Yasuhara et al [28] reported that 66.7% of the babies with severe hypoxia-ischemia demonstrated hearing threshold elevation while Hecox and Cone [29] found that peripheral hearing impairment occurred in 20% of babies within three months after the onset of hypoxia-ischemia occurring. The significant differences in the reported prevalence of hearing impairment are partly related to the differences in the population studied and the time after birth when the subjects were studied [30]. Hatakeda et al.,[31] reported that the brain stem function testing at a discharge from NICU is important for the neurophysiological prognosis of the patients and the ABR test with the reference range defined here can be a useful tool.

EEG was done to every case survived at the age of 3 months .EEG was abnormal in 85.3% of cases. Of the 3 cases who developed epilepsy, one case had normal EEG. Three of cases with normal EEG (60%) had normal outcome. On the other hand, 10 of cases of Abnormal EEG (34.5%) developed abnormal outcome. Ezgu et al., [19] found that among the 19 babies with HIE whom were investigated by EEG in the first 72 hours of life, only one baby had an abnormal outcome who had a normal EEG test and only one baby had a favorable outcome who had an abnormal EEG findings. EEG changes can be valuable in identifying infants at high risk for subsequent brain damage, but the interpretation of neonatal EEGs can vary and requires considerable experience [32]. Hendrick et al., 2004[33] indicate that the course of Amplitude-Integrated EEG (aEEG) patterns adds to the prognostic value of aEEG monitoring in asphyxiated infants. Spontaneous recovery of severely abnormal aEEG patterns is not uncommon.

Ong et al., 2009 [34] concluded that, There was no added advantage in combining EEG or

Ultrasonographic parameters over a clinical neurological scoring system alone in predicting the outcome of asphyxiated term newborns.

All cases of persistent hearing loss fitted hearing aid at 6 months of age and all of them got obvious improvement in hearing .All cases of abnormal outcome were put under physiotherapy and all of them got great benefit on follow up.

Conclusion

Hypoxic ischemic encephalopathy score, cord blood gases report, urinary lactate/creatinine ratio and cranial ultrasongraphy findings are important early and easily predictors of perinatal hypoxic ischemic encephalopathy outcome and provide a sliding scale of probabilities that could be used for prognostication and to design eligibility criteria for decision making including neuroprotective therapy.

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References

1. Wyatt JS, Gluckman PD, Liu PY, Azzopardi D, Ballard R, Edwards AD,et al. Determinants of outcomes after head cooling for neonatal encephalopathy. Pediatrics. 2007; 119:912-921.
2. Jacobs SE, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2007;(4): CD003311.
3. Rutherford MA, Azzopardi D, Whitelaw A, Cowan F, Renowden S, Edwards AD, et al. Mild hypothermia and the distribution of cerebral lesions in neonates with hypoxic—ischemic encephalopathy. Pediatrics. 2005; 116:1001-1006.
4. Perlman JM. Intervention strategies for neonatal hypoxic—ischemic cerebral injury. Clin Ther. 2006; 28:1353-1365.
5. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet. 2005; 365:663-670.
6. Ghosh B, Mittal S, Kumar S, Dadhwal V. Prediction of perinatal asphyxia with nucleated red blood cells in cord blood of newborns. Int J Gynaecol Obstet. 2003; 81: 267 – 271.
7. Volpe JJ. Hypoxic-ischemic encephalopathy. In: Volpe JJ, ed. Neurology of the Newborn. 4th ed. Philadelphia: WB Saunders. 2001; 217 – 394.
8. Vannucci RC and Perlman JM. Interventions for perinatal hypoxic – Ischemic encephalopathy. *Pediatrics.* 1997; 100:1004–1014.
9. Cheung PY, and Robertson CMT. Predicting the outcome of term neonates

with intrapartum asphyxia. *Acta Pediatrics.* 2000; 89:262-271.

10. Sarnat HB and Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electro-encephalographic study. *Arch neurol. 1976;* 33: 696-705.

11. Thompson CM, Puterman AS, Linley LL, Hann FM, van der Elst CW, Molteno CD, et al. The value of a scoring system for hypoxic–ischemic encephalopathy in predicting neurodevelopmenal outcome. *Acta Pediatr.* 1997; 86:757-761.

12. Houot O. Interpretation of clinical laboratory tests. In: Siest G, Henny J, Schiele F, Young D (eds), Biochemical publications. 1985; 220–234.

13. Huang CC, Wang ST, Chang YC, Lin KP, Wu PL. Measurement of the urinary lactate: Creatinine ratio for the early identification of newborn infants at risk for hypoxic ischemic encephalopathy. *N Engl J Med*. 1999; 341: 328-335.

14. Siegel MJ, Shackelford GD, Perlman JM, Fulling KH. Hypoxic-ischemic encephalopathy in term infants: diagnosis and prognosis evaluated by ultrasound. *Radiology.* 1984; 152:395-9.

15. Amiel-Tison C, Grenier A. Neurological assessment during the first year of life. New York: Oxford University Press, 1986.

16. Dilenge M, Majnemer A and Shevell M. long-term developmental outcome of asphyxiated term neonates. *J child Neurol.*. 2001; 16: 781–792.

17. Aurora S and Snyder E Y. Perinatal asphyxia. In: Cloherty J P, Eichenwald E C and Stark A R (eds.), *Manual of Neonatal Care,* 5th edition, Lippincott-wiliams and wilkims, Philadelphia. 2004; 536-555.

18. Carvale B, Allemand F and Libenson M. Factors predictive of seizures and neurologic outcome in perinatal depression. *Pediatr Neurol*. 2003; 29: 18 – 25.

19. Ezgü FS, Atalay Y, Gücüyener K, Tunç S, Koç E, Ergenekon E, et al. Neuron-specific enolase levels and neuroimaging in asphyxiated term newborns. *J Child Neurol.* 2002; 17: 824-829.

20. Toh VC. Early predictors of adverse outcome in term infants with post-asphyxial hypoxic-ischemic encephalopathy within 4 hours of birth. *Acta Paediatr*. 2000; 89:343-347.

21. Malin GL, Morris RK and Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis. 2010; May 13;340:c1471.

22. Socol ML, Garcia PM, Riter S. Depressed APGAR scores, acid-base status, and neurologic outcome. *Am J obstet Gynecol.*. 1994; 170: 991–999.

23. Volpe J. Hypoxic ischemic encephalopathy. In: Volpe J (ed.), *Neurology of the Newborn.* 3rd edition, W.B. Saunders, Philadelphia. 1995; p.250.

24. Li Liu, Chong-xun Zheng, Shu-feng Peng, Hong-yan Zhou, Zu-you Su, Li He, et al. Evaluation of Urinary S100B Protein Level and Lactate/Creatinine Ratio for Early Diagnosis and Prognostic Prediction of Neonatal Hypoxic-Ischemic Encephalopathy. Neonatology. 2010; 97:41-44.

25. Jongeling BR, Badawi N, Kurinczuk JJ, Thonell S, Watson L, Dixon G, et al. Cranial ultrasound as a predictor of outcome in term newborn encephalopathy. *Pediatr Neurol.* 2002; 26: 37-42.

26. Stewart J E and Stolz JW. Hearing loss in neonatal intensive care unit graduates. In: Cloherty J.P, Eichenwald E.C, and Stark AR (eds.), *Manual of neonatal care*, 5th edition, lippincott Williams & Wilkins, Philadelphia. 2004; P: 683-685.

27. Jiang ZD, Brosi DM, Li ZH, Chen C, Wilkinson AR. Brainstem auditory function at term in preterm babies with and without perinatal complications. *Pediatric Research.* 2005; 58 (6): 1164–1169.

28. Yasuhara A, Kinoshita Y, Hori A, Iwase S, Kobayashi Y. Auditory brainstem response in neonates with asphyxia and intracranial haemorrhage. *Eur J Pediatr.* 1986; 145: 347–350.

29. Hecox K and Cone B. Prognostic importance of brainstem auditory evoked response after asphyxia. *Neurology*. 1981; 31: 1429-1433.

30. Jiang ZD, Wang J, Brosi DM, Shao XM, Wilkinson AR. One-third of term babies after perinatal hypoxia-ischemia have transient hearing impairment: dynamic change in hearing threshold during the neonatal period. *Acta Paediatr.* 2004; 93: 82–87.

31. Hatakeda N, Kuroda M, Igaki A, Fujii S, Inuzumi K, Wada Y, Koshiba M. [Reference range of the auditory brainstem response for the patients in the NICU]. Rinsho Byori. 2011; Feb; 59(2):134-7.

32. Hellstrom-WL, Rosen I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. *Arch Dis child fetal Neonatal Ed.* 1995; 72: 34–38.

33. Hendrik J. Ter Horst, Constanze Sommer, Klasien A. Bergman, Johanna M. Fock, Tiemen W. Van Weerden, and Arend F. Bos Prognostic Significance of Amplitude-Integrated EEG during the First 72 Hours after Birth in Severely Asphyxiated Neonates. Pediatr Res. 2004; 55: 1026–1033.

34. Ong LC, Kanaheswari Y, Chandran V, Rohana J, Yong SC, Boo NY. The usefulness of early ultrasonography, electroencephalography and clinical parameters in predicting adverse outcomes in asphyxiated term infants. Singapore Med J. 2009; Jul;50(7):705-9.

Table 1: HIE score proposed by Thompson et al. [11]

Sign	0	1	2	3
Tone	Normal	Hypertonia	Hyportonia	Flaccid
Consciousness	Normal	Hyperalert , stare	Lethargic	Comatosed
Fits	Normal	infrequent < 3day	frequent > 2/day	
Posture	Normal	Fisting / cycling	Strong, distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent± bites	
Respiration	Normal	Hyperventilation	Brief apnea	(Apnoea)
Fontanelle	Normal	Full not tense	Tense	

Table 2: Hypoxic ischemic encephalopathy (HIE) score among different groups

Studied group / Variables	Group I N = 16	Group II N = 19	Group III N = 20	F	P
initial HIE score ***X ± SD***	**7.01± 1.3**	**11.89 ± 2.09**	**16.4 ± 3.1**	**5.11**	**< 0.001**
maximum HIE score **X ± SD**	**7.61 ±2.91**	**12.50 ± 2.29**	**18.15 ± 2.79**	**6.09**	**< 0.001**
HIE score on day 7 ***X ± SD***	**0**	**5.05 ± 5.03**	**13 ± 5.79**	**4.38**	**< 0.001**

Table 3: Mean cord blood PH, HCO_3, BD, Creatinine (U), Lactate (U) and Urinary Lactate / Creatinine ratio among studied groups

Studied group / Variables	Group I (N = 16)	Group II (N = 19)	Group III (N = 20)	Control (N= 20)	F	P
PH						
Range	**7.1-7.2**	**7.0-7.18**	**6.76-7.16**	**7.20-7.38**	**2.81**	**< 0.05**
X ± SD	**7.11± 0.07**	**7.1± 0.06**	**6.90± 0.09**	**7.27± 0.06**		
HCO_3(mmol/L)						
Range	**9 - 13**	**9.2- 13**	**4.3- 12**	**13.3- 16**	**5.39**	**< 0.001**
X ± SD	**9.01± 1.7**	**9.3± 2.1**	**7.11± 2.69**	**14. 1± 3.1**		
BD (mmol/L)						
Range	**5.1-15.5**	**8-20**	**10.7-29.1**	**1.5-12.1**	**6.29**	**< 0.001**
X ± SD	**11.9± 2.90**	**13.1± 3.30**	**16.9± 4.03**	**6.1± 2.90**		
Creatinine(U)(mg/l)						
Range	**380-950**	**380-950**	**410-900**	**340-900**	**2.03**	**>0.05**
X ± SD	**601.1±181.1**	**690.2±207.1**	**630.1±170.1**	**649.3±150.1**		
Lactate(U)(mg/l)						
Range	**360-3200**	**680-3250**	**490-9200**	**28-93**	**16.01**	**<0.001**
X ± SD	**1201±860.1**	**1799±730.1**	**2050± 1820**	**65.1± 18.05**		
Urinary Lactate /Creatinine Ratio						
Range	**0.71-5.85**	**0.89-6.34**	**1.38-10.45**	**0.05-0.17**	**8.80**	**<0.001**

X ± SD	**2.01± 1.3**	**3.30± 1.39**	**4.1± 2.70**	**0.12± 0.04**		

PH = negative logarithm of hydrogen ion concentration **HCO_3**= serum bicarbonate **BD** = base deficit **Creatinine (U)** = urinary creatinin. **Lactate (U)** = urinary lactate**.**

Table 4: Relation between different variables and neurodevelopmental Outcome among the studied HIE cases

Outcome / variable	Normal (N = 22) $\bar{X}$ ± SD	Abnormal (N = 33) $\bar{X}$ ± SD	t	P
Initial HIE score	**8.78± 2.70**	**14.51 ± 4.01**	**5.89**	**< 0.001**
Maximum HIE score	**9.82± 3.80**	**15.60± 4.21**	**5.19**	**< 0.001**
HIE Score on day 7	**1.37± 3.92**	**9.40± 6.51**	**5.41**	**< 0.001**
pH	**7.18± 0.05**	**7.04± 0.11**	**6.29**	**< 0.001**
HCO_3	**14.3± 2.03**	**10.41± 3.20**	**5.91**	**< 0.001**
BD	**12.40± 3.20**	**15.90± 4.13**	**5.44**	**< 0.001**
L / cr. ratio	**1.65± 1.88**	**3.6± 2.10**	**4.33**	**< 0.001**

Table 5: Correlation coefficient (r) of lactate/creatinine ratio and different variables

L / cr. ratio / Variable	R	P
Initial HIE Score	**0.2531**	**< 0.05 ***
Maximum HIE Score	**0.2120**	**> 0.05**
HIE Score on day 7	**0.2076**	**> 0.05**
pH	**-0.2730**	**< 0.05 ***
BD	**-0.2870**	**< 0.05 ***
HCO_3	**-0.3040**	**< 0.05 ***

* Critical value = 0.2276

Table 6: Relationship between cranial sonographic findings and different variables

Cranial sonar / Variable	Normal (N = 22) $\bar{X}$ ± SD	Abnormal (N = 33) $\bar{X}$ ± SD	T	P
Initial HIE score	**9.82± 3.30**	**13.8 ± 3.81**	**3.49**	**< 0.01**
Maximum HIE score	**10.30 ± 3.41**	**15.41± 5.09**	**4.30**	**< 0.01**
HIE Score on day 7	**3.3± 4.61**	**7.88± 7.32**	**2.91**	**< 0.01**
pH	**7.13± 0.07**	**7.03± 0.13**	**2.21**	**< 0.05**
BD	**12.40± 3.20**	**14.63± 5.21**	**2.05**	**< 0.05**
HCO_3	**10.41± 2.71**	**8.41± 3.71**	**2.06**	**< 0.05**
Creatinine	**1.03 ± 0.19**	**1.06 ± 0.31**	**0.6**	**> 0.05**
Lactate	**1801.5 ± 1881.5**	**1699.1 ± 868.13**	**0.22**	**> 0.05**
Lactate/Creatinine Ratio	**2.35 ± 2.10**	**3.02 ± 1.71**	**0.49**	**> 0.05**

Table 7: Relation between ABR, EEG results and different variables

Variables	ABR		EEG	
	Normal (No=21)	Abnormal (No= 13)	Normal (No=5)	Abnormal (No=29)
Initial HIE Score				
X ± SD	8.3± 2.7	11.21 ± 2.7	9± 2.13	9.69 ± 3.1
t	2.55		0.51	
P	< 0.01		> 0.05	
Maximum HIE Score				
X ± SD	9.20± 3.2	11.99± 3.2	9± 2.13	10.21± 3.4
t	2.51		0.89	
P	< 0.05		> 0.05	
HIE Score on day 7				
X ± SD	1.3± 3.7	4.91± 4.7	2.01± 4.01	2.61± 4.3
t	2.09		0.41	
P	< 0.05		> 0.05	
pH				
X ± SD	7.13± 0.06	7.10± 0.07	7.17± 0.04	7.16± 0.07
t	2.48		0.65	
P	< 0.05		> 0.05	
HCO_3				
X ± SD	11.8± 2.1	9.39± 2.2	10.7± 0.8	8.1± 2.3
t	1.58		2.49	
P	> 0.05		< 0.05	
BD				
X ± SD	12.4± 3.3	14.6± 2.5	12.3± 2.14	15.3± 3.3
T	2.01		1.33	
P	< 0.05		> 0.05	
Lactate/creatinine ratio				
X ± SD	1.89± 1.3	3.41± 1.2	1.88± 0.5	2.44± 1.4
t	3.19		1.40	
P	< 0.01		> 0.05	

ABR= auditory brainstem evoked response **EEG** = electroencephalogram

Table 8: Relation between ABR, EEG findings and the neurodevlelopmental outcome

Outcome / Variables	Normal N	%	Abnormal N	%	Total N	%	Adjusted x^2	P
ABR								
Normal	19	90.5%	2	9.5%	21	61.7 %	11.31	<0.001
Abnormal	3	25%	10	77.0%	13	38.3 %		
EEG								
Normal	3	60.0 %	2	40%	5	14.7%	0.02	>0.05
Abnormal	19	65.5%	10	34.5%	29	85.3%		

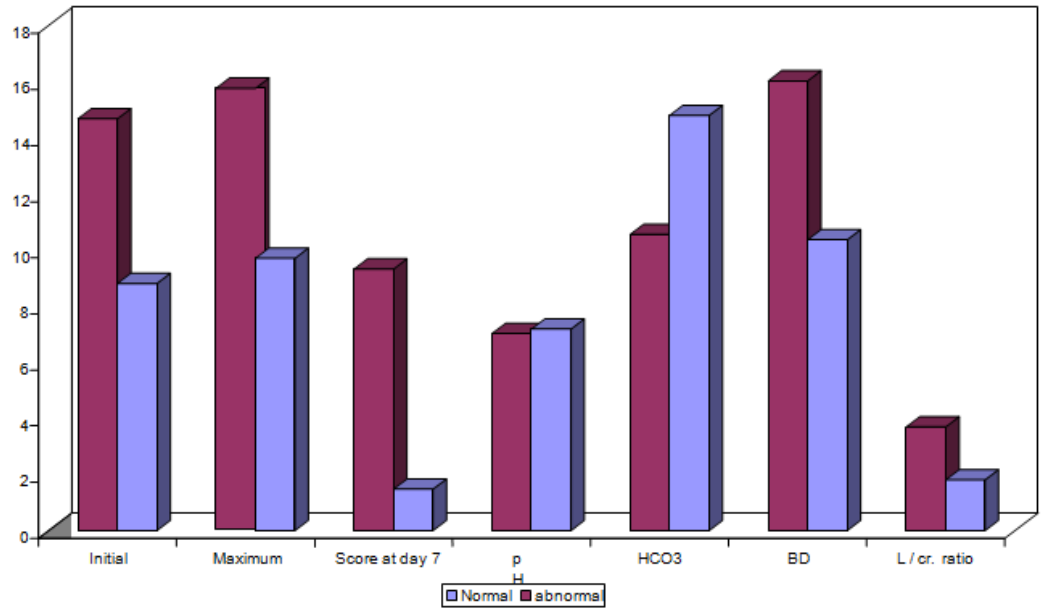

Figure 1: Means of different variables among the studied groups in relation to Outcome

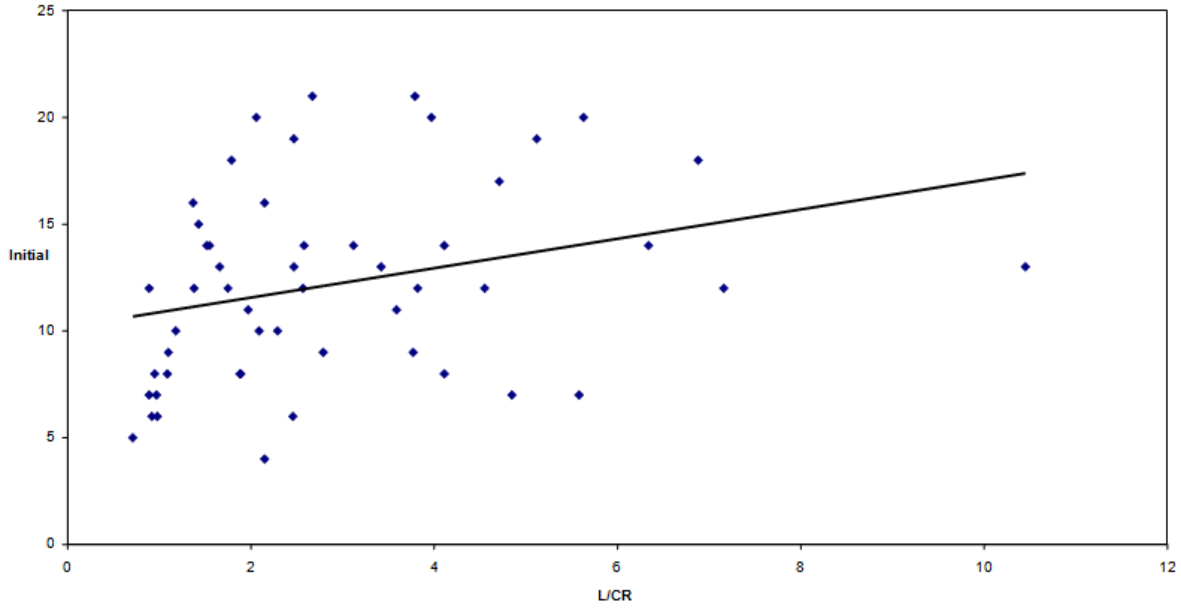

Figure 2: Correlation coeffecient btween initial HIE score and lactate creatinine ratio among the studied groups

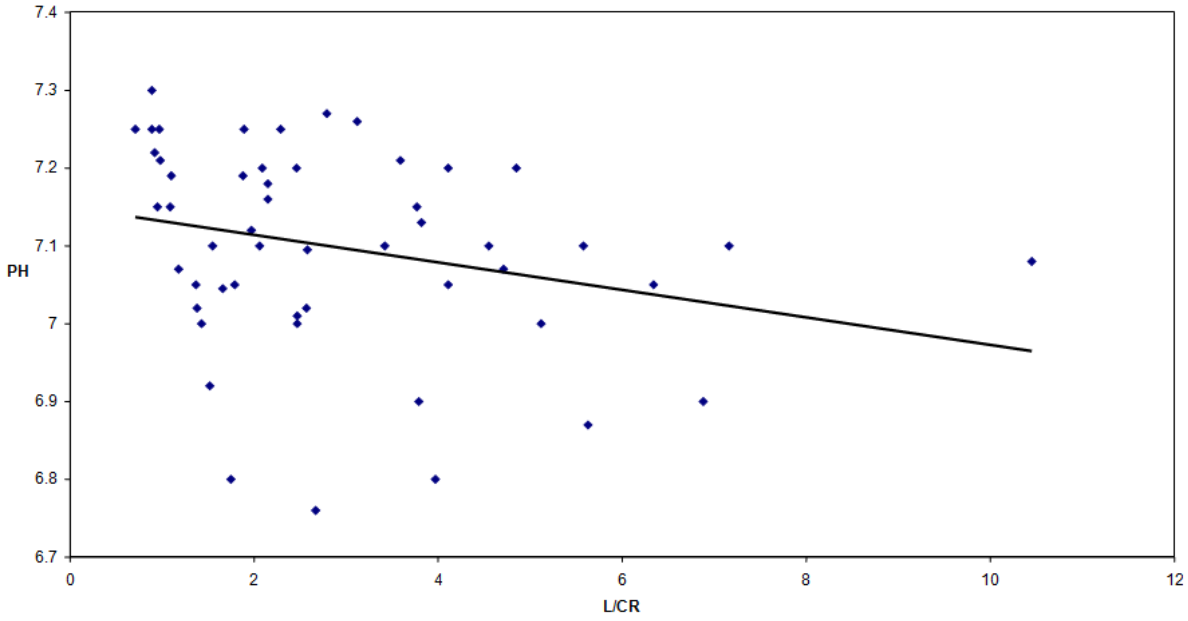

Figure 3: Correlation coeffecient btween pH and lactate / creatinine ratio among the studied groups

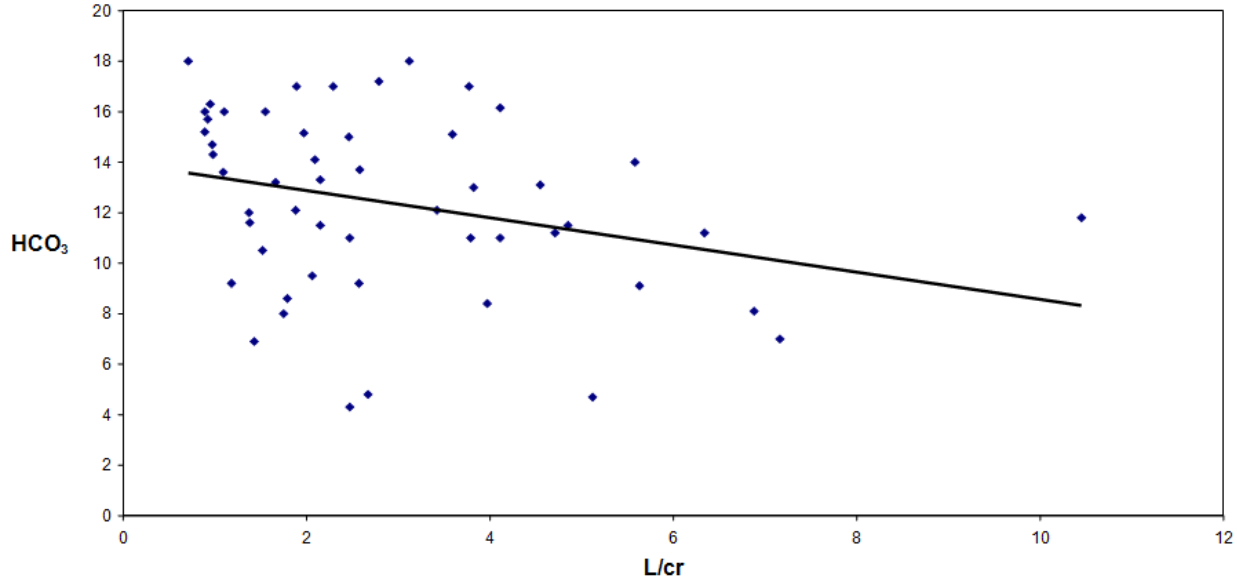

Figure 4: Correlation coeffecient btween HCO 3 and lactate creatinine ratio among the studied groups