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CRIB-II Score as an Indicator of Neonatal Morbidity among Preterm Neonates: A Prospective Observational Study

Dr. Sahana G[1], Dr. Matta Sai Kiranmai[2], Dr. Adarsh E[3]

[1]Professor, Department of Pediatrics, Dr.MGR Educational and Research Institute,Raja Rajeshwari Medical College Hospital, Bangalore

[2]Post Graduate, Department of Pediatrics, Dr.MGR Educational and Research Institute Raja Rajeshwari Medical College Hospital, Bangalore

[3]HOD, Department of Pediatrics, Dr.MGR Educational and Research Institute Raja Rajeshwari Medical College Hospital, Bangalore

Abstract: ***Advancements in the Neonatal Intensive Care with scoring systems like Clinical Risk Index for Babies-II(CRIB_II) to stratify sick new-born have decreased both morbidity and mortality. This study assessed the ability of CRIB-II score to predict neonatal morbidity and survival. A prospective observational study was conducted among 42 (21 male and 21 female) preterm neonates admitted within 12 hours of birth in a tertiary care hospital. Antenatal, perinatal variables, respiratory support, CRIB-II score and neonatal morbidity of the neonates were recorded. Association tests and Receiver operating characteristics curve analysis were performed. The mean birth weight and gestational age were 1226±229grams and 30.12±1.4weeks respectively. All had ocular complication, while 31%, 12%, 9.5% and 4.8% had neurological morbidity, sepsis, cardiac abnormality and pulmonary manifestations respectively. Mean CRIB-II score was 6.60±6.739. AUC in predicting the neonatal morbidity for CRIB-II score was 0.777 (p- 0.004) at cut-off value of ≥ 9 significant with 89.7% specificity. The cut-off value for predicting both the neonatal mortality and neurological morbidity was ≥ 9 with specificities of 92% and 87% respectively. This study concluded that CRIB-II had better discriminating ability in predicting any neonatal morbidities and better diagnostic acumen in predicting cardiac and neurological morbidities.***

Keywords: Neonatal risk scoring system, Prenatal morbidity, Prenatal mortality, Preterm neonates

1. Introduction

Worldwide, more than fifteen million neonates are born prematurely in a year and prematurity has been found to be the reason for the deaths of more than one million newborns annually [(1)]. Around sixty percentage of the preterm births are accounted by Africa and South Asia. Neonatal deaths contribute to two-thirds of all infant deaths [(2)]. While neonatal mortality is a still public health concern in India, the nation is in the right track to meet the Sustainable Development Goals (SDG) of Neonatal Mortality Rate (NMR) of 12 per 1000 live births by the year of 2030 [(3,4)].

Advancements in the Neonatal Intensive Care are to be greatly accounted for the improving the survival and decreasing the morbidity and mortality among the neonates admitted in the Neonatal Intensive Care Units (NICUs) [(5)]. With the decreasing trend and better combating the neonatal mortality, the focus is gradually shifting more towards the improving the morbidity status of the neonates. Initial assessment of a neonate at the time of admission of a neonate, with preterm delivery at the Neonatal Intensive Care Units to categorize the severity of the illness enables the health care teams to recognize the increase of mortality and morbidity and to predict the survival of the new-borns[(6)].

A multitude of such scoring systems are available to predict the survival rate, neonatal mortality and morbidity among the neonates admitted in the NICU setup[(7)].Newer scoring system namely, Clinical Risk Index for Babies- II(CRIB- II) is a score more suited for more pre-term and smaller babies and includes birth weight, gestational age, body temperature, base excess and sex of the new-born and is used to assess the neonatal mortality and illness severity in the first hour of NICU admission, with score ranging between 0 and 27, and lowest score being better prognosis [(8-10)]. While their competency in predicting mortality is studied extensively, there are little to nil studies to evaluate the same in terms of the prediction of the neonatal morbidity. This background prompted the current with an objective to assess the efficiency of CRIB-II score in predicting neonatal morbidities and survival before hospital discharge in neonates with gestational age ≤32weeks.

2. Literature Survey

The study by Ezz-Eldin et al in Egypt showed that there is progressive increase in the neonatal mortality with increasing CRIB-II score, with the prevalence of mortality being 0%, 4.8%, 68.3% and 100% among the infants with the CRIB-II levels – 1, 2, 3 and 4 respectively [(7)]. Receiver Operating Characteristic (ROC) curve analysis by Ezz-Eldin et all showed that the Area Under Curve (AUC) was highest for the CRIB-II score, suggesting its superiority to other parameters (CRIB-II score vs Gestational age vs Birth weight – 0.968, p<0.001 vs 0.900, p<0.001 vs 0.834, p<0.001), whereas the values in the Brito et al study were 0.88, 0.81 and 0.76 respectively, which was very similar[(7,10)]. The AUC was 0.9032 for the CRIB-II score for predicting mortality for the

69 babies who stayed back till discharge, it was 0.8703 when the left neonates were considered survivors and 0.8314 when those who left when considered as non-survivors in the study by Rastogi et al[11].

The cut-off value in mortality prediction by the ROC curve analysis done in the Ezz-Eldin study showed the points ≥11 for CRIB-II score, ≤ 28 for Gestational age vs ≤ 1100 grams for Birth weight [7]. The highest specificity was shown by CRIB-II score (82.4%) followed by gestational age (74.3%) and birth weight (68.9%) [7]. In the study by Brito et al the cut-off for the CRIB-II score was 4 with a sensitivity of 75.8%, specificity of 86.7%, positive predictive value of 63.3% and negative predictive value of 92.2% [10]. The CRIB-II score was found to have highest positive predictive value (74%) and highest accuracy (86.7%), and the Hosmer-Lemeshow of goodness of fit test was done to calibrate CRIB-II score and revealed that p value was 0.952. The same result was obtained in the study by Rastogi et al with p value of 0.62 [11]. The Cox regression analysis proved that the CRIB-II score can significantly predict mortality and the hazard ratio was 1.479 (p-value <0,001) in the Egypt study by Ezz-Eldin et al[7].Brito et al concluded that higher mortality was seen among infants with birth weight less than 750 grams, gestational age of less than 29 weeks and CRIB-II score of above 10. However, it was also stated that a lower cut-off of CRIB-II score of four had higher prediction of mortality than birth weight and gestational age [10].

In the study by Vardhelli et al, median CRIP-II score was higher among the non-survivors than survivors [6 vs 12, p-value=<0.0001]. The ROC curve analysis shows the AUCs for CRIB-II score for predicting the mortality was 0.79, with a p-value of 0.689. The cut-off score with the best sensitivity, specificity, positive predictive value, negative predictive value and accuracy was ≥7 for CRIB-II score (83.8%, 57.8%, 16%, 97.3% and 60% respectively) [6]. CRIB-II also had good predictive accuracy on detecting Bronchopulmonary dysplasia (BPD), an abnormal cranial ultrasound (CUS), had acceptable predictive accuracy on detecting Retinopathy of Prematurity (ROP) requiring treatment[6]. The study in Iran by Dalili et al showed that the accuracy of CRIB-II was 0.838, with cut-off point 8.5 where the sensitivity and specificity (74.4 and 78.65 respectively) were optimum [12].

Turkish study by Karaarslan et al found that the mean CRIB-II score of their study was 9.9 with statistically difference among the survivors and non-survivors (p-value <0.001). Similarly, statistical difference was appreciated among the groups with respect to the birth weight also. The study concluded with saying that CRIB-II is preferred with lesser variables making it an easier scoring system [13].

3. Materials and Methods

This was a prospective observational study conducted in the Neonatal Intensive Care Unit of a tertiary care teaching hospital in Bangalore for a duration of 18 months among 42 Preterm babies of both sexes with birthweight of ≤ 1500gms admitted to NICU within 12hours of birth. Gestational age of>32weeks of gestation. Neonates admitted with Major congenital disorders, of gestational age less than 24 weeks, birth weight less than 500 grams and admitted for a period of more than 12 hours were excluded from the study. Structured questionnaire was administered by the interviewer after informed written consent was obtained from the parents. Age, sex, date & time of birth, date of admission, mode of delivery, antenatal steroids, Gestational age, antenatal complications, requirement of surfactant, vitals examination at the time of admission, systemic examination, respiratory support like mechanical ventilation, requirement of Continuous Positive Airway Pressure (CPAP), requirement of High Flow Nasal Cannula (HFNC), details of Sepsis, post menstrual age, ROP findings, presence of intraventricular hemorrhage, significant PDA, bronchopulmonary dysplasia (BPD), period of NICU stay, day of discharge from the hospital and CRIB-II scoring.

The CRIB-II was assessed from the worst/poorest score in the first 12 hours of admission. The same caregiver (neonatal residents) from the participating units calculated the scores for both systems at the same time. The best obstetric estimate from the first trimester ultrasound and the last menstrual period was used to estimate gestational age, which was then verified by a new Ballard score. Electronic digital weighing scales were used to measure birth weights to the closest gram. Blood and/or cerebrospinal fluid culture positive was used to characterize sepsis. Modified Bell's classification was used to classify intraventricular hemorrhage (IVH). The guidelines of the ETROP study were followed in treating ROP. Any of the following conditions were considered serious morbidities: BPD, abnormal cranial ultrasonography (CUS: IVH grade 3 or more, periventricular leukomalacia (PVL)grade 2 or more.

The data were entered using Microsoft Office Excel 2013 and analyzed using SPSS software version 16 after data validation. Shapiro-Wilk test was used to find the normal distribution. Continuous variables which follow normal distribution like age was expressed as mean and standard deviation. Continuous variables not following normal distribution was expressed as median and Interquartile range. Description of categorical variables was expressed as frequency and proportion. Independent sample T test was used in order to compare two means. Chi square test and fishers exact test was employed to compare the distribution of qualitative variables between the groups. Mann-Whitney U test was used to compare differences between two independent groups when the dependent variable continuous, but not normally distributed. Receiver operating characteristics (ROC) curve analysis, through the comparison of area under the ROC curves was used to assess the discriminatory ability of the scores in predicting in-hospital morbidities. All tests were two tailed and results were considered statistically significant if the p-value is <0.05 at 95% confidence interval. The approval to conduct the present study was obtained from the Institutional Ethical Committee, with confidentiality and autonomy of the participants ensured throughout the study.

4. Results and Discussion

Among 42 neonates, both sexes were present in equal number. The mean gestational age of the neonates in the study is 30.12±1.4 weeks with one-third of gestational age of 31 weeks, followed by 28 weeks (19%) and14.3% below 32 weeks. The mean birthweight of the neonates is 1226±229 grams. While, all were of low birth weight (LBW), three-fourths (31/42) were Very Low Birth weight (VLBW), six were Extremely Low Birth Weight (ELBW). Less than half of the neonates (18/42, 42.9%) had an abnormal antenatal doppler (diastolic notching-4/42, uteroplacental insufficiency-12/42, utero- cum feto-placental insufficiency-2/42), less than one-fifth had Intra Uterine Growth Retardation (IUGR) (7/42, 16.7%) and around four-fifths had administration of antenatal steroids (37/42, 88.1%).

More than half of the neonates received surfactant (n=23/42, 55%), while 57.1% (24/42) needed mechanical ventilation. All except one baby (2.4%) needed Continuous Positive Airway Pressure (CPAP) ventilation and High Flow Nasal Cannula (HFNC) respiration. The mean days of mechanical ventilation for the neonates is 1.64±2.173 days while the mean days of CPAP ventilation is 7±6.674 days and for Nasal cannula high flow oxygen is 6.88±7.352 days. The duration of the hospital stay in the Neonatal Intensive Care Unit (NICU) ranged between ten and sixty days, with a mean value of 27.76±11.257 days and median of 29.50 days.

While the study observed nil mortality, the neonates had morbidities like sepsis, intraventricular hemorrhage or peri-ventricular leukomalacia, bronchopulmonary dysplasia, retinopathy of prematurity. None of the neonates had seizures. Around 40% of the neonates in the study (17/42) had probable sepsis. Of them, 12% (5/42) had culture positive sepsis, of which 7.2% (3/42) had *Staphylococcus hemolyticus* in culture and rest 4.8% (2/42) had *Klebsiella spp*. in culture. All the infants had features of Retinopathy of Prematurity, while 41 out of 42 (97.6%) had ROP features in both eyes, while one (2.4%) had ROP feature in the right eye only. More than half (23/42) of the neonates had Stage – 1,2,3 ROP (20%, 36% and 2% respectively), while the rest (18/24, 42.9%) had the precursors of ROP, namely Transient Avascular Retina (TAR). Neurological deficits are present in about one-thirds of the participants (13/42, 31%), and among them, Intraventricular hemorrhage (8/42, 19.0%) is more common than periventricular leukomalacia (5/42, 11.9%).Less than 10% of the neonates had Patent Ductus Arteriosus (PDA-4/42) and less than 5% had Bronchopulmonary dysplasia (BPD- 2/42).

The mean CRIB-II score was 6.60±6.739 among the study participants and the median was 6. About two-thirds (28/42) had abnormal base excess which was a component of CRIB-II score. The Receiver Operator Characteristic (ROC) Curve analysis depicted above (figure – 1) shows that the area under curve (AUC) for the CRIB-II score in predicting the neurological manifestations like intraventricular hemorrhage and periventricular leukomalacia was 0.777 (p value- 0.004, 95% CI – 0.629 and 0.926). The cut-off value of ≥ 9 for CRIB-II score with specificity of 89.7% and sensitivity of 84.6% was diagnostic of IVH/PVL.

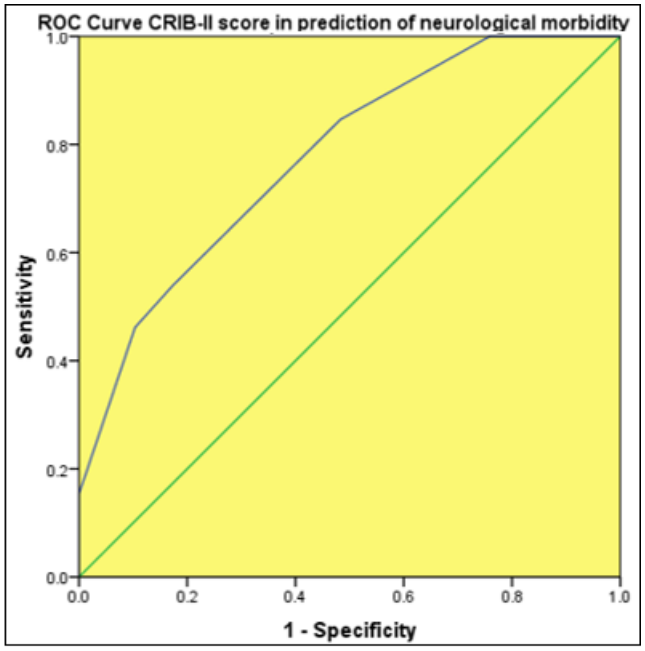

Figure 1: CRIB-II score predicting neurological problems

CRIB-II score was also significant in predicting the PDA in a low birthweight neonate, as depicted in the Figure – 2 below with an AUC of 0.875 (p value- 0.015, 95% CI – 0.770 and 0.980. The specificity of CRIB-II score in predicting PDA was found to be 94.7% for the cut-off value of ≥ 16 and 84.2% for a cut-off value of ≥ 9.

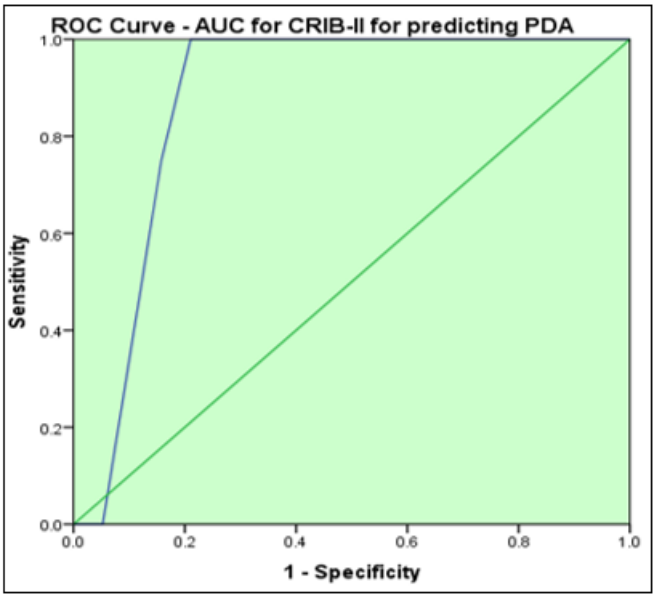

Figure 2: CRIB-II score predicting Patent Ductus Arteriosus

ROC Curve below shows that CRIB-II was not significantly good in predicting the BPD with AUC of 0.888 (p value-0.067, 95% CI – 0.782 and 0.993) as shown in the figure – 3

below. Similarly, the score was not useful in predicting the neonatal sepsis as the AUC was 0.486 (p value- 0.923, 95% CI – 0.197 and 0.776) as shown in figure-4.

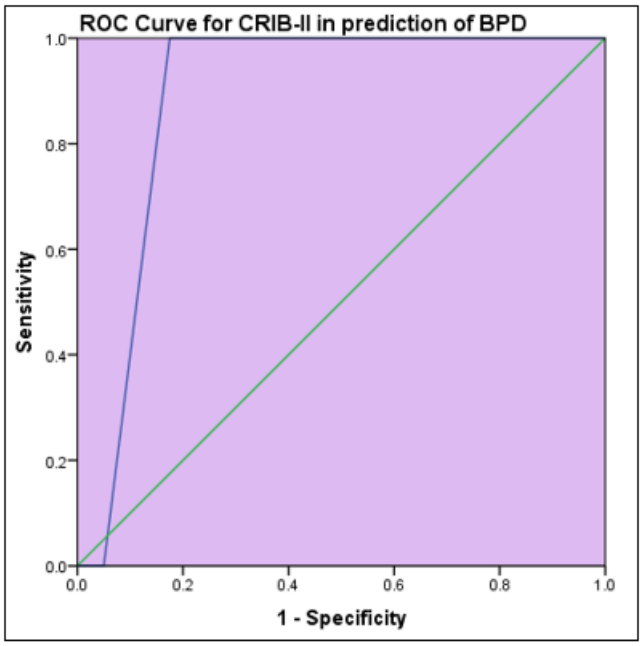

Figure 3: CRIB-II score predicting Broncho-Pulmonary Dysplasia

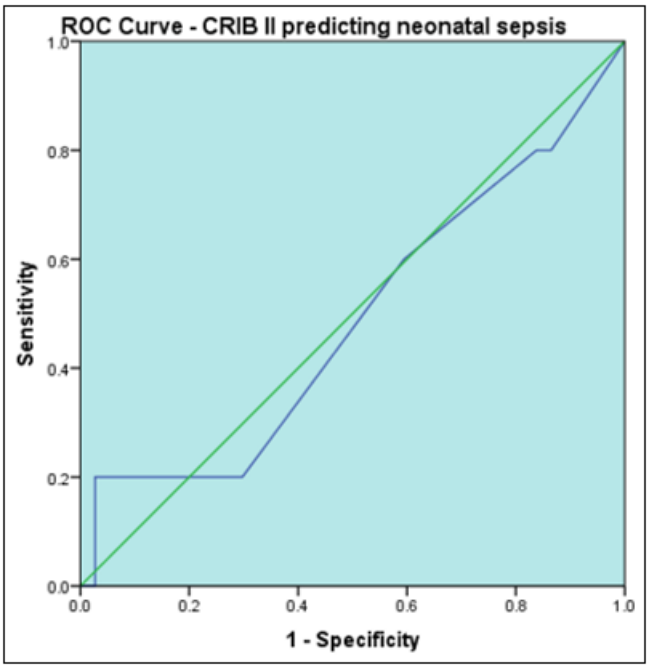

Figure 4: CRIB-II score predicting culture positive sepsis

To assess the score's ability in predicting morbidity, morbidities included are neurological (IVH & PVL), cardiac (PDA), pulmonary (BPD) manifestations and culture positive neonatal sepsis. Retinopathy of Prematurity was not included as all the neonates in the study had a stage in the spectrum of the disease and the regression of the condition was not studied as no follow-up was done. AUC for CRIB-II score in predicting the morbidity in low birth weight infants is 0.751 (p value- 0.007, 95% CI – 0.5957 and 0.907), as depicted in the figure – 5 below. The cut-off value for CRIB-II score in predicting the morbidity is ≥ 9 with a specificity of 92.3% while the sensitivity was high (81.3%) for the cut-off value of ≥ 5.

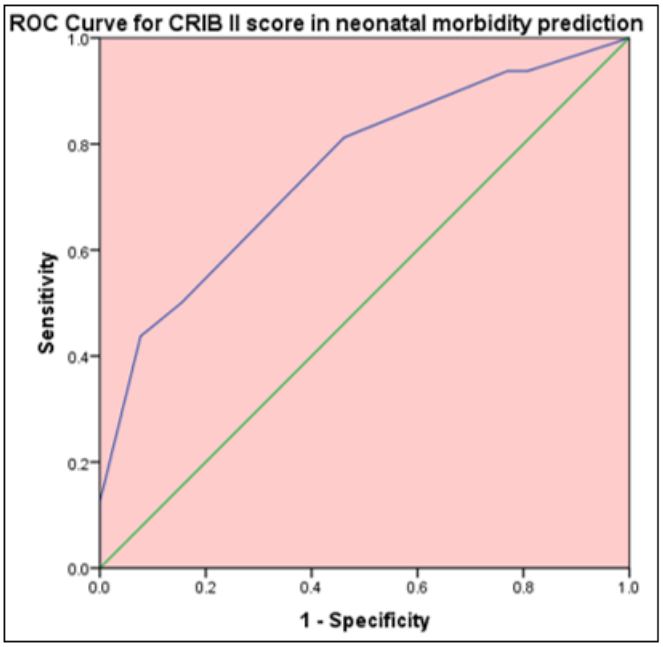

Figure 5: CRIB-II score predicting morbidity

5. Discussion

The current study was done as a prospective observational study among 42 preterm neonates who were low birth weight and had equal distribution of both the sexes. The study followed up the neonates from the time of admission in the neonatal intensive care unit (NICU) after birth till the time of discharge from NICU. The study done presently included infants of birth weight ranging from 750 to 1600 grams having representation of LBW, VLBW and ELBW with majority in the middle group, whereas Ezz-Eldin et al, Vardhelli et al, Rastogi et al and Gagliardi et al included the newborns with very low birth weight only in their studies[6,7,11,14]. The mean birth weight in the present study was 1226 grams, which was similar as that of the study by EzzEldin et al, Vardhelli et al, Rastogi et al, but it was less in the study by Gagliardi et al [6,7,11,14].

The equal distribution of male and female sexes in the present study was similar to that of the study done in Italy by Gagliardi et al, but the study by Vardhelli et al had higher proportion of males[6,14].The average hospital stay duration in the current study was around four weeks, which was closer in number to that scenario in the studies by EzzEldin et al and by Karaarslan et al, studying the ability of CRIB-II score[7,13]. The mechanical ventilation was needed in 57.1% of the neonates in the present study which was very similar to that in the study by Gagliardi et al(58.5%), but lesser in the study by Vardhelli et al (35%)[6,14]. The current study, in addition studied the

average days of mechanical ventilation, CPAP ventilation and HFNC ventilation and the day of initiation of all three types. CPAP was given for the highest duration and mechanical ventilation, the lowest duration.

While none of the neonates in the present study expired, i.e., the mortality was 0% and the study mainly focused on the morbidity predicting ability of the scores. While the mortality was higher in the other studies by Mia et al (35%), EzzEldin (34.5%), Brito et al (34.8%),Dalili et al (26.4%), Gagliardi et al (16.7%), Vardhelli et al (8.8%) and highest in the study by Karaarslan et al (50.7%)[5-7,10, 12-14].While the studies by Gagliardi et al and Dalili et al concentrated only on the neonatal mortality especially in-hospital mortality, while the current study concentrated on the morbidity prediction of the score[12,14]. The studies done in India by Vardhelli et al and in Turkey by Karaarslan et al included morbidity in addition to mortality, and considered the Bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage, periventricular leukomalacia, neonatal sepsis and necrotizing enterocolitis [6,13]. The current study considered all the morbidities except the Necrotizing Enterocolitis, in addition presence of patent ductus arteriosus was also included in the mortality.

The current study also included them as one of the risk predictor variables, and found that both the need for antenatal steroids (Fisher exact test statistic – 0.788, p value – 0.633) and an abnormal antenatal doppler (Fisher exact test statistic – 6.932, p value – 0.050) was not associated with the neonatal morbidity (Fisher exact test statistics –6.932, p value – 0.50). In addition, it was also found that surfactant administration in the immediate post-natal period was not statistically associated with neonatal morbidity and not a reliable morbidity predictor (Chi square test statistic – 0.625, p value – 0.429). While both the presence of Intra Uterine Growth Retardation (Fisher exact test statistic – 0.323, p value – 0.690) and the Small for Gestational Age of the neonate (Fisher exact test statistic – 0.342, p value – 0.720) were also found not associated with predicting morbidity in the current study, the multiple logistic regression in the study by Gagliardi showed that being appropriate for their gestational age (non-SGA) is associated statistically with the survival of the infant [14]. Also, the study by Karaarslan et al showed that one-fifth of the participants were of Small for Gestational Age (SGA) [13].

During the current study conducted during the hospital (NICU) stay all the neonates were found to have one or other stage of Retinopathy of prematurity (ROP – 100%), 58% had various stages of the ROP, but the other 42% had precursor stages of the ROP. As the study participants were not followed up for the duration required for spontaneous regression of the features of ROP. Hence, the final diagnosis retinopathy of prematurity was not made and was not included as a morbidity in the analysis to evaluate the ability of CRIB-II score in the prediction of neonatal morbidity.

The most common present morbidity in the present study was the neurological manifestations (31%) with 19% having interventricular hemorrhage and 12% had periventricular leukomalacia. The other morbidities namely, Patent Ductus Arteriosus (PDA) was seen among 9.5% of the neonates and bronchopulmonary dysplasia among 4.75% of the neonates included in the study. Probable Sepsis was present in 40% of the participants, and 12% of the neonates had culture positive sepsis. In the study by Karaarslan et al in Turkey, ROP was seen in 43% followed by ICH (15.1%), BPD (2.2%) and necrotizing enterocolitis was seen in 2% of the neonates [13]. The hemorrhage in the cranial cavity was higher in the current study than in the study by Karaarslan et al, whereas the proportion of BPD was similar in both the studies[13]. The study by Vardhelli et al showed that NEC stage was seen in 7% of the neonates but not seen in the current study among any neonate and the culture positive sepsis was seen in 20% of the participants, but the proportion was lesser in the current study [6].

The mean value of the CRIB-II score in the current study was 6.60 and median was 6.00. The score was averaged at 9.9 in the study by EzzEldin et al, 3.8 in the Brito et al study [7,10]. In the study by Dalili et al, the CRIB-II score was 6.12 in the survivors and 10.28 in the dead neonates [12].The current concluded that the CRIB-II [AUC – 0.751 (p value- 0.007)] was better in predicting the morbidity in the preterm neonates than the traditionally used birth weight [AUC – 0.216 (p value- 0.002)] and gestational age [AUC – 0.135 (p value<0.001)].CRIB-II was found to be more reliable in predicting the neonatal morbidity in the preterm neonates with better prediction ability (75%). Similarly, EzzEldin et al in Egypt showed that the CRIB-II score was superior to gestational age and birthweight in predicting neonatal mortality[7]. The study by Brito et al also showed an AUC of 0.9032 for CRIB-II predicting the mortality[10]. EzzEldin and Brito mentioned that the cut-off values for CRIB-II in predicting the mortality are ≥ 11 and 10 respectively [7,10].

To predict the neonatal risk of developing neurological manifestations like IVH and PVL, the present study detected the cut-off value of ≥ 9 for CRIB-II score with specificity of 89.7% The CRIB-II cut-off value for detecting PDA was ≥ 9 with a specificity of 84.2%. However, the predicting ability of CRIB-II for BPD and culture positive sepsis was insignificant. The cut-off value for CRIB-II score in predicting any morbidity was ≥ 9 with a specificity of 92.3% while the sensitivity was high (81.3%) for the cut-off value of ≥ 5. Likewise, the study by Vardhelli et al showed cut-off value of ≥7 was found to have good diagnostic accuracy [6]. Similarly, Daliliet al also showed the cut-off value of CRIB-IIas 8.5, which was again similar to the current study [12]. The study done in Turkey while presenting a similar cut-off value for CRIB-II, when compared to the current study [13]. While the current study included many of the neonatal morbidity to assess the predictive ability of the CRIB-II score, the study limited number of participants. Larger study with more neonates and longitudinal design would assist in better understanding of the scores diagnostic accuracy of predicting neonatal morbidity including ROP and rare and late morbidities.

6. Conclusion

The study concludes that in preterm neonates that the CRIB-II score were found to have better discriminating ability in predicting various neonatal morbidities, when compared to the birth weight, gestational age, certain antenatal intra-natal and postnatal markers. CRIB-II score was found to be having better diagnostic acumen in many of the neonatal morbidity like IVH/ PVL, ROP, PDA, BPD and sepsis.

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