COMPLICATIONS OF PREMATURITY AS RISK FACTORS FOR OUTCOME

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Abstract. The increased rate of prematurity has been accompanied by high rates of neonatal complications and neurodevelopment sequels. Objective: The study was design to evaluate whether identifying certain complications of prematurity may be useful in predicting neurodevelopment outcome.
Observational longitudinal study, over six years, of a cohort of premature infants. The risk factors quantified were: gestational age, birth weight, birth asphyxia, necessity of mechanical ventilation , specific pathology (respiratory distress syndrome, intraventricular hemorrhage, periventricular leukomalacia) ,results of Amiel –Tison, neurologic exam at discharge, total numbers of evaluations, final results of evaluations, acording to Bayley Scales of Infant Development, 2nd Edition at two years corrected age. The data were analyzed using SPSS Statistics version 18.0. From January 1, 2005 to December 31, 2011 the incidence of prematurity in our maternity was 13.65%. 33.03% (n=2182) were prematures and from these, 1845 were enrolled in this study. Complications of prematurity, developped by included patients were : respiratory distress syndrome (70.51%), apneea of prematurity (40.76%), perinatal asphyxia (22.82%), intraventricular hemorrhage (17.01%), periventricular leukomalacia (5.42%). Birth weight less than 1500g, type of mechanical ventilation , intraventricular hemorrhage, results of Amiel-Tison evaluations and adherence of patients to program are predictive factors for results of final evaluation. Gestational age remains the leading factor in including premature infants in a specific group of risk ($F=69.65$, $p<<0.01$, 95%CI). We speculate that early identification of the degree of risk may facilitate early interventions with the potential to improve the neurological outcome of these patients.

INTRODUCTION

Advances in antenatal medicine and neonatal intensive care, have resulted in improved survival rates of preterm infants (Fanaroff AA et al, 2003; Hintz SR et al, 2005). Prematurity is defined as a birth that occurs before 37 completed weeks (259 days or less) of gestation (AAP, 2004; AAP and ACOG 2002; Berg AT, 1991). Internationally, the rate of preterm birth ranges from 5% to 18% of babies born, with a dramatic survival gap for prematures, depending on where they are born (Howson CP et al, 2012; Beck S et al, 2010). In Romania the rate of preterm birth varies from 8- 12.5%. For our maternity, preterm delivery increases from 6.19% in 2000, to 12.90% in 2013, due to advances technologies in this field. Similar to mortality, neonatal morbidity is inversely related to gestational age. The most immature infants commonly suffer from multiple and interacting medical conditions, which may lead to permanent impairments.Because among the generation of survivors of preterm birth, cognitive, behavioral, neurological sequels are not uncommon (Laroque B et al, 2008; Hack M, 2009; Bhutta AT et al, 2002), were organized neonatal follow-up services with an important role in early identification of neuro-developmental problems (Hack M, 2012). The purpose of present study is to evaluate degree of risk for neurologic sequels in a cohort of premature infants included in follow-up program.

MATERIALS AND METHODS

Observational longitudinal study conducted from January 1, 2005 to December 31, 2011 at Neonatal Intensive Care Unit, Cuza-Voda Maternity Hospital, Iasi. Inclusion criteria were in accordance with our national guide for follow-up of high-risk neonates (Mâtu E, 2010). Infants with major congenital anomalies and infants needing major surgery were excluded. Perinatal data were collected prospectively during admission, stored in the NICU database, and retrospectively retrieved for data analysis. Parental informed consent was obtained for participation in the follow-up program. The neonatal neurological examination was performed at discharge, as described by Amiel-Tison (Amiel-Tison C, 2001) and the Bayley Scales of Infant Development, 2nd Edition (BSID II) (Bayley N, 1993; Bayley N, 2006) during regular evaluations. The BSID II includes 2 subscales: a motor scale and a mental scale, with 11-13 items based on age level. The total number of items failed, places the infant in a category of low, moderate or severe risk for developmental delay.
In order to examine correlation between risk factors /complications presented by premature, frequency of evaluations and degree of neurodevelopmental risk, we selected next parameters:

- gestational age (GA) who plays the most important rol in development of complications of prematurity (Wood NS et al, 2003; Wilson-Costello D et al, 2007); birth weight (BW) (Vohr BR et al, 2004); sex, as risk factor for severity of hyaline membrane disease (HMD) (Greenough A et al, 2005; West JB, 2008; Gomella TL, 2009); Apgar score; birth

asphyxia; necessity of mechanical ventilation (Cools F et al, 2009; Greenough A et al, 2008; Göpel W et al, 2011); specific prematurity pathology (respiratory distress syndrome, intraventricular hemorrhage, periventricular leukomalacia) (Volpe JJ, 2008; de Vries LS et al 2009; Greisen G et al, 2001; Khashu M et al, 2009); Amiel –Tison neurologic exam at discharge (Amiel-Tison C, 2001); results of neurologic examinations during follow-up program; total numbers of evaluations; final results of evaluations, at two years corrected age.(Barrington KJ et al, 2006; Kirkegaard I et al, 2006; Petrini J et al, 2009).

The data were analyzed using the SPSS version 18.0. Correlations between variables were investigated using the Pearson product moment correlation coefficient (r), contingency coefficient, or by Spearman Rank correlation coefficient, as appropriate. The mean value differences were analyzed with Kruskal Wallis Test and the qualitative differences of variables were tested with Chi-2 test with nominal significance defined as $p<0.05$.

RESULTS AND DISCUSSION

Over the 6-year period of study, 45887 infants were admitted in our hospital. 13, 65% (n=6278) were premature and 29, 39% (n=1845) were introduced in the follow-up program and so were enrolled in this study. GA, varied between 23 weeks of gestation (wg) to 36 wg with mean GA of 30wg (Fig. 1).

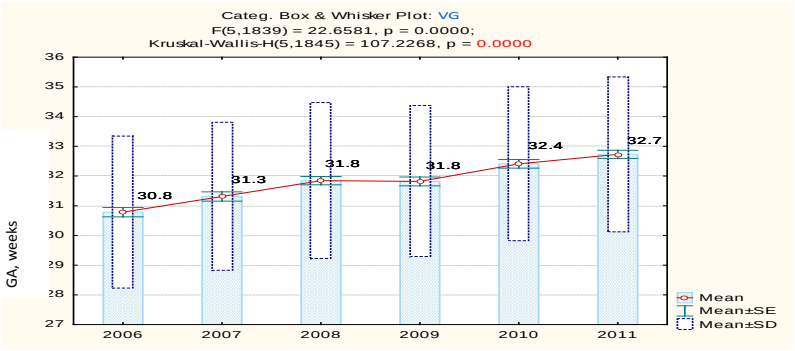


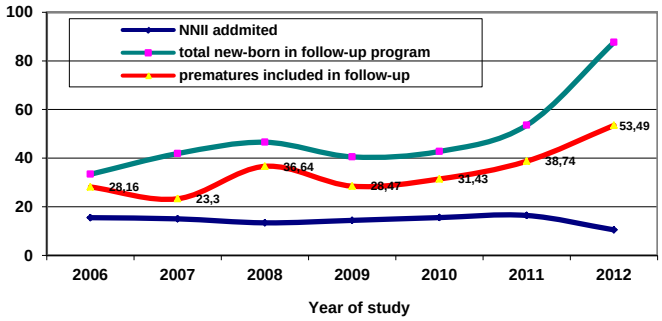
Fig. 1 Statistical analysis of gestational age

We noticed a constant predominance of male sex, over the studied period.

The mean birth weight was 1350 g (birth weight varies from 550g to 4550g). The mean Apgar score at one minute was 5 and 6 and at 5 minutes 6 and 7.

Complications of prematurity, developped by included patients and quantified as risk factors for outcome were : respiratory distress syndrome (70.51%), apneea of prematurity (40.76%), perinatal asphyxia(22.82%), intraventricular hemorrhage (17.01%), periventricular leukomalacia (5.42%), retinophaty of prematurity (25.47%).

Over the 6 year period of study, 6606 newborn were addmited in neonatal intensive care unit (NICU) and 47.26% (n=3122) were enrolled in the follow-up program. Among these, 33,03% (n=2182) were prematures with risk and from these, 1845 were enrolled in this study. We notice a constant increase in number of high risk prematures, included in follow-up, as shown in figure 2.



. **Fig. 2 Anual incidence of prematures included in follow-up program**

All infants were evaluated by the Amiel-Tison neurologic evaluation at discharge from hospital and 23.6% were found with low risk, 60.1% moderate risk and 16.3% severe risk, as presented in Table I.

Table I. Distribution of risk categories based on discharge evaluation

Discharge evaluation Risk category	**n**	**%**
Low risk	435	23.58%
Moderate risk	1109	60.11%
Severe risk	301	16.31%
	1845	

Infants included in low risk category had GA of 33 wg and over and birth weight 1800 g and over; medium risk had 32 wg or less and a medium birth weight 1600g and severe risk, 30 wg or less and birth weight 1260 g and less. Severe risk was inversely proportional with gerstational age, demonstrate by GA analysis and discharge evaluation , ($F=69.65$, $p<<0.01$, 95%CI) and with birth weight ($F=50.94$, $p<<0.01$, 95%CI).

Patients with Apgar score less than 5 at one minute and 6 at 5 minutes was in a larger percent categorized in severe risk group.

19.71% from infants with neonatal asphyxia were included at discharge in severe risk group and 50.59% in medium risk, aspect which emphises the corelation between asphyxia and degree of risk of newborn ($\chi^2=56.22$, $p<<0.01$, $r=0.65$, $p<<0.01$, 95%CI).

Newborns ventilated by intermittent positive pressure ventilation (IPPV) associate severe risk in a percent of 33.3% versus 12.98% ventilated by continous positive pressure ventilation (CPAP).There is a significant corelation between type of mechanical ventilation and Amiel Tison exam at discharge ($\chi^2=249.03$, $p<<0.01$, $r=0.28$, $p<<0.01$, 95%CI).

From infants with apneea of prematurity, 60.64% were included in medium risk group and 22.56% in severe risk.

All newborns with intraventricular hemorrhage (IVH) stage III, presented severe risk according to Amiel-Tison exam and moderate risk in 72% of cases. 73% of cases with periventricular leukomalacia (PVL) were categorized in severe risk (Fig. 3 and Fig. 4).

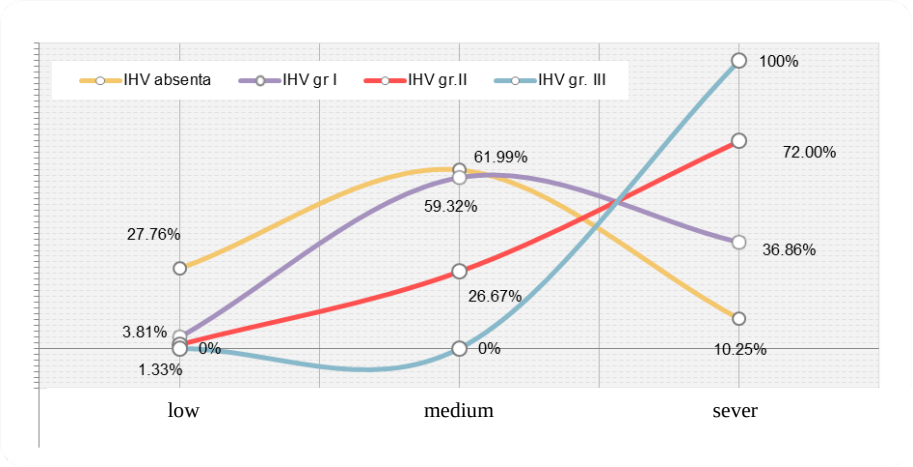


Fig. 3 Amiel Tison at discharge- risk category vs IVH

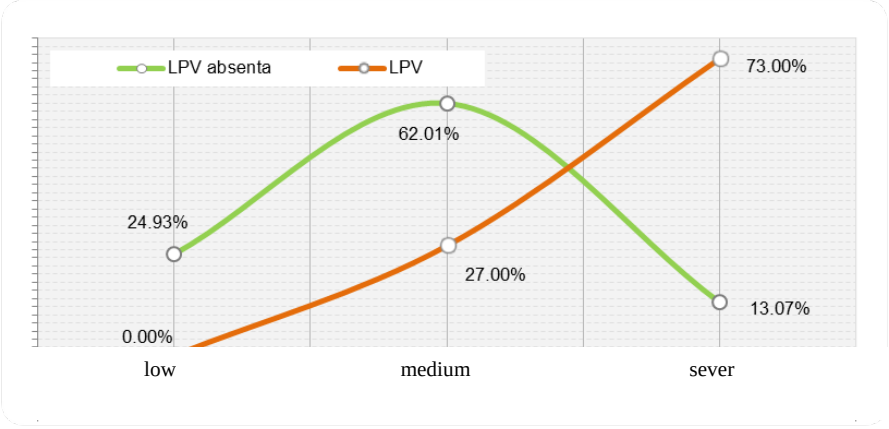


Fig. 4 Amiel Tison at discharge- risk category vs LPV

Mothers were informed about the significance and importance of the follow-up program and were asked to return for periodic evaluations according to a personalized schedule.

Statistic correlation from this study, demonstrate that infants who benefit of regular evaluations, reaches the highest percent with low risk, compare with those with only one evaluation.

According to the BSID II evaluation, at the end of the follow-up program, 11.03% were included in the severe risk group, 47.75% in the medium-risk group and 41.42% were considered to have a low risk of developing subsequent neurologic disabilities.

The results at two years corrected age were summarized into three domains: cognitive development, neuromotor development and both, cognitive and motor, according to main affected domain.

Motor deficit was predominant in 16.04% of cases, cognitive development was impaired in 12.68% of cases and mixt deficit was in 12.68% of cases. In 58.54% of cases there were no significant disabilities.

The results of evaluation at discharge were significant associated with final evaluation at the end of follow-up program (χ^2=1553.1, p<<0.01, r=0.65, p<<0.01, 95%CI).

This study reveal the presence of a significant correlation between Amiel-Tison examination at discharge and the results of dynamic neurologic evaluations, meaning that newborns with severe risk at discharge evaluates to medium risk through six month corrected age, meanwhile number of cases with severe risk, decrease in dynamic. The incidence of infants with low risk increase over the studied period and those with moderate risk slightly decrease, as shown below.

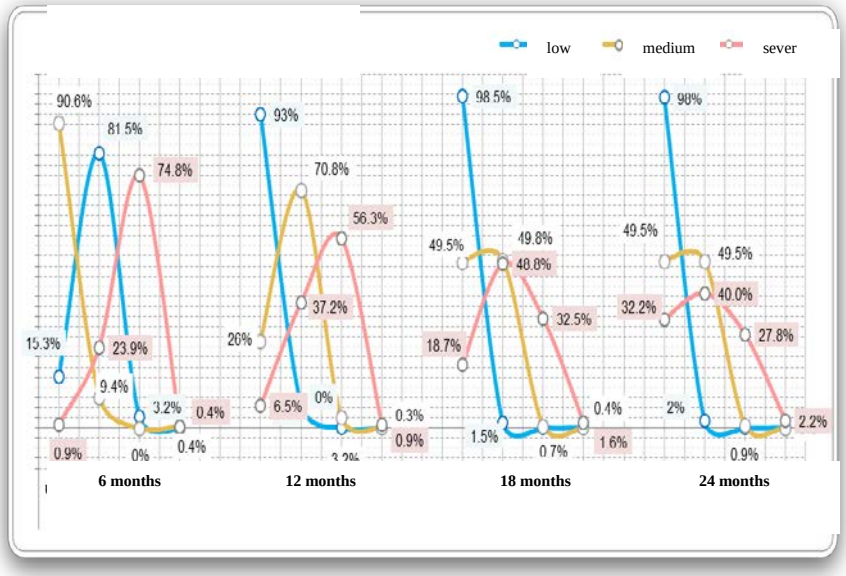


Fig. 5 Risk evaluation over follow-up period

From risk factors and complications of prematurity, we selected the following parameters in order to establish power of prediction: GA, Apgar score at one and five minutes, birth weight < 1500g, birth asphyxia, type of mechanical ventilation, apnea of prematurity, IVH, LPV, results of Amiel-Tison evaluation and number of total evaluations (Table II, Fig. 6).

Table II. Multiple correlations of predictive factors for final evaluation (BSID II)

Multiple correlations	Estimate values
r	0.45622
R^2	0.20813
F	0.20291
p	39.84229
Std.Err. of Estimate	0.00000

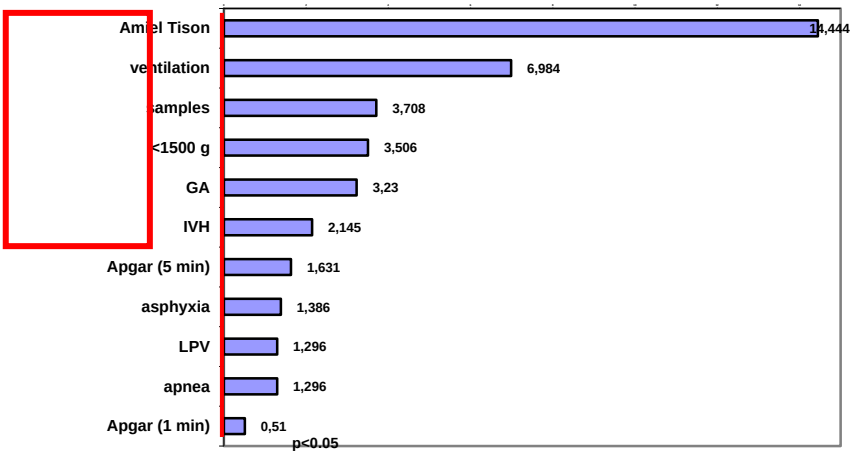


Fig. 6 Predictors in evaluation of BSID II

We found that birth weight less than 1500g, type of mechanical ventilation, intraventricular hemorrhage, results of Amiel-Tison evaluations and number of evaluations (adherence of patients to program) are predictive factors for results of final evaluation and for infant's outcome.
A reliable follow-up program depends on maintaining a high rate of participation which is strength conditioned by educational and socio-economic parental status.
As it reveals by many literature data (Aarnoudse-Moens CSH, et al, 2009; Johnson YR, 20111), we found a strong correlation between low gestational age and severe risk for neurologic sequels ($F=69.65$, $p<<0.01$, 95%CI)
Because high vulnerability (Volpe JJ, 2008; Volpe JJ, 2009) of premature brain, intraventricular hemorrhage is one of decisive complications of prematurity in increase the risk for adverse neurologic outcome ($p<0.05$).
Patients with LPV were initial categorized in high risk group because LPV is an ischemic white matter injury , frequently bilateral (Volpe JJ, 2008; Weindling M, 2010).
From both category of patients with IVH and LPV, those who benefit of early kinesiotherapy performed by a specialist, but also by instructed mothers, passes from severe to moderate risk.
The highest proportion of severe and moderate risk was reach at discharge and at three month corrected age mostly explained by the interest and orientation of mothers to "basic needs": feed and sleep. After infants' growth, parents seem to realize the importance of neurologic acquisitions and became more involved in stimulate motor and cognitive evolution of their infants.

CONCLUSIONS

Gestational age remains the leading factor in including premature infants in a specific group of risk ($F=69.65$, $p<<0.01$, 95%CI)
Birth weight under 1500g, type of mechanical ventilation, Amiel-Tison evaluation, intraventricular hemorrhage, number of evaluations (adherence to follow-up program) are predictive factors for the results of final evaluation.
Unfortunately, the cognitive and behavioral outcomes remain unpredictable, so all possible measures must be implemented so that premature infants can benefit from high-quality medical and family assistance.

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