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The impact of maternal characteristics on the moderately premature infant: an antenatal maternal transport clinical prediction rule

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Abstract

Background—Moderately premature infants, defined here as those born between 30 0/7 and 34 6/7 weeks gestation, comprise 3.9% of all births in the United States and 32% of all preterm births. While long-term outcomes for these infants are better than for less mature infants, morbidity and mortality are still substantially increased in comparison to infants born at term. There is an added survival benefit resulting from birth at a tertiary neonatal care center, and although many of these infants require tertiary level care, delivery at lower level hospitals and subsequent neonatal transfer are still common.

Objective—Our primary aim was to determine the impact of maternal characteristics and antenatal medical management on the early neonatal course of the moderately premature infant. The secondary aim was to create a clinical prediction rule to determine which infants require intubation and mechanical ventilation in the first 24 hours of life. Such a prediction rule could inform the decision to transfer maternal-fetal patients prior to delivery to a facility with a Level III Neonatal Intensive Care Unit (NICU), where optimal care could be provided without the requirement for a neonatal transfer.

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CONFLICT OF INTEREST

The authors have no conflict of interests to disclose

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Methods—Data for this analysis came from the cohort of infants in the Moderately Premature Infant Project (MPIP) database, a multi-center cohort study of 850 infants born at gestational age 30 0/7 to 34 6/7 weeks, who were discharged home alive. We built a logistic regression model to identify maternal characteristics associated with need for tertiary care, as measured by administration of surfactant. Using statistically significant covariates from this model, we then created a numerical decision rule to predict need for tertiary care.

Results—In multivariate modeling, 4 factors were associated with reduction in the need for tertiary care, including, surfactant administration, including non-White race (OR=0.5, [0.3, 0.7], older gestational age, female gender (OR=0.6 [0.4, 0.8]) and use of antenatal corticosteroids (OR=0.5, [0.3, 0.8]). The clinical prediction rule to discriminate between infants who received surfactant, versus those who did not, had an area under the curve of 0.77 [0.73, 0.8].

Conclusions—Four antenatal risk factors are associated with a requirement for Level III NICU care as defined by the need for surfactant administration. Future analyses will examine a broader spectrum of antenatal characteristics and revalidate the prediction rule in an independent cohort.

Keywords

infant; newborn; transport; clinical prediction rule; ROC Curve

INTRODUCTION

Beginning in the 1960s, regionalization of perinatal care has contributed substantially to improve neonatal outcomes, specifically in regards to the most appropriate location of birth of premature infants [1, 2, 3, 4, 5, 6, 7, 8, 9]. As part of this effort, the American Academy of Pediatrics (AAP) developed guidelines for the optimal place of delivery of neonatal care based on certain criteria. The AAP defines the hospital levels of newborn care that should be provided within individual nurseries. These range from Level I nursery, where basic neonatal care is provided to well infants, to Level III neonatal intensive care units (NICUs), where a full range of pediatric subspecialty services are available for treatment of premature and critically ill term neonates[10]. Level II, or intermediate neonatal care, is intended for infants greater then or equal to 32 weeks gestation and birthweight of greater then 1,500 grams [10]. The current recommendations from the AAP and American Congress of Obstetrics and Gynecology (ACOG) suggest that women presenting in labor before 32 weeks gestation are best delivered at a hospital with a Level III NICU, thus requiring antenatal referral/ transfer of the mother [11].

Currently, the aforementioned guidelines are limited by only using the gestational age cut-off when applied to the care of moderately premature infants, defined here as those between 30 0/7 and 34 6/7 weeks gestation, who comprise 3.9% of all births in the United States (US) and 32% of all preterm births [12, 13]. This group has a relatively low risk of morbidity and mortality, although substantially increased when compared to infants born at term [12, 14]. Therefore, most of these infants can be managed at a Level II facility; however, Escobar et al. demonstrated that 25% of these infants received surfactant, while 21.3% of infants <32 6/7 weeks gestation required ventilation for longer than 3 days [12]. Thus, a substantial portion

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of these infants would require neonatal transfer, with its attendant risks, if born at hospitals that are not equipped to properly manage that severity of illness.

Many women with threatened preterm delivery between 30 0/7 and 34 6/7 weeks could be transferred to a Level III facility emergently. However, this strategy has some substantial drawbacks. The most implicit reason is the immediate risk to the mother, neonate, or both, should delivery occur in transport. Structural limitations, such as payer or networking restrictions, may also play a role [15]. Perhaps most importantly, moderately premature infants, without other fetal anomalies, are relatively low risk compared to the very low birth weight (VLBW) population [12, 16], and thus often can be treated at a Level II facility. Therefore, clinicians might not feel compelled to transfer the maternal-fetal patient.

The optimal strategy would be to identify infants who are likely to need Level III care antenatally so that maternal-fetal transfer can take place prior to delivery. Antenatal transfer, which has been shown to be both safe and beneficial [17, 18], is essential to provide immediate optimal care for the critically ill newborn, avoid transport of a critically ill newborn, and minimize maternal-infant separation. Unfortunately, we currently do not have the ability to identify infants who would benefit from this strategy.

In this study, we sought to determine the impact of maternal characteristics and antenatal medical management on the early neonatal course of the moderately premature infant and to derive a clinical prediction rule to determine which infants require tertiary neonatal care in the first 24 hours of life and thus prompt antenatal maternal transfer.

METHODS

Study Design and Patient Population

We undertook a retrospective analysis of infants in the Moderately Premature Infant Project (MPIP) database. MPIP is a multi-center cohort that contains prospectively collected data in combination with a retrospective chart review and post-discharge telephone interviews. The patients were assembled between 2001 and 2003 from a combination of ten Level II and Level III NICUs in California and Massachusetts. MPIP includes 850 infants born at 30 0/7 to 34 6/7 weeks gestational age, who were discharged home alive from the study hospital. The cohort has been previously described in more detail [12, 19, 20, 21, 22, 23]. The original aims of MPIP were to describe the epidemiology of this low risk group of moderately premature infants and to develop a comprehensive length of stay model [12]. The data collection had been previously approved by the institutional review boards of the participating centers and the Harvard School of Public Health, and there is ongoing approval for secondary analyses from the Beth Israel Deaconess Medical Center.

Outcome Variable

The primary outcome measure was whether or not the infant received surfactant, which served as a surrogate for requirement for Level III NICU care. This was chosen as the primary outcome because most of the infants who are intubated in this age group receive surfactant, and the need for respiratory support is a key part of the definition of Level III care [10, 11]. Surfactant administration occurred either immediately after birth or after an

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infant failed non-invasive measures of respiratory support. Details on prophylactic surfactant use were not available in this database.

Predictor Variables

Predictor variables were selected if they were maternal factors that could contribute to the neonate's health status at birth, as determined either by biologic plausibility, previously known associations, or potential for an association. A total of 20 potential exposures were identified from the database. Baseline maternal demographics such as maternal age, gestational age at delivery, gravidity and parity, maternal race, education and income were included. In addition, maternal intrapartum characteristics (i.e. antenatal corticosteroids, intrapartum antibiotics, magnesium sulfate and/or other tocolytics, presence and duration of rupture of membranes) and pregnancy characteristics (i.e. infertility treatment, multiple gestation, history of illicit drug use, history of spontaneous and therapeutic abortions) were evaluated. Finally, in order to account for inter-NICU variability and regional variability, we included the level of care (i.e. II vs. III) and the state of birth (i.e. California vs. Massachusetts) as potential predictors. Excluded potential predictors were the mode of delivery and infant birthweight, since the aim of our analysis was to determine the impact of only the antenatal variables on the moderately preterm infant, and neither of the aforementioned factors could be accurately determined prior to delivery. The database did not have the detail level of maternal medical history, such as pregnancy related diseases, diabetes, or smoking history.

Some the data elements were not available in the hospital record. Data were missing for 20% of the patients (173 out of 850) who were not captured by the follow up survey 3 months after discharge. The survey comparison between survey respondents and non-respondents has been previously described [20]; the infants were of similar gestational age and birthweight in both groups, but the mothers tended to be slightly older, to have twin or higher gestation, and were more likely to breastfeed in the respondent group [20]. However, the 20% missing data only applied to 4 of our 20 predictor variables: maternal race, maternal education, infertility treatment, and family income. Of these four variables, only one, maternal race, showed a statistically significant association with the dependent variable. For this variable we assigned the missing group to the non-White category. The results of the final logistic regression model were similar when those patients were excluded from the analysis all together. We excluded family income as a predictor variable because an additional 12.3% of patients declined to answer.

Statistical Analysis

The initial objective was to determine the impact of maternal characteristics and antenatal medical management on the early neonatal course of the moderately premature infant. A weighted analysis was used in order to account for the sampling variation at different MPIP sites [12] (actual N=850 represents a total sample of N=1250). Additionally, clustering for twins and higher order multiples performed as multiple gestation accounted for 39.1% of the cohort. Weighted regression and chi-square analyses were used as appropriate to explore the bivariate relationship between the individual exposure variables and the outcome of interest. All means and percentages reflected the weighted analyses. Twenty variables were

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identified, and those with p-value <0.2 were included in a multivariable logistic regression model. Approximately 25% of our patients had the outcome of interest. By using a general rule of 1 predictor per 10 patients with the primary outcome of interest [24], we anticipated adequate power to allow exploration of the 21 candidate variables.

In order to create a clinical prediction rule, we incorporated the significant factors from the multivariable model using a weighted point system, in which the value of each variable is derived from the regression model beta coefficients multiplied by a factor of 10. This conversion was the same methodology used to derive the SNAP-II [25] and Richardson Score [26], two clinical scores used to predict neonatal mortality and the need for prolonged mechanical ventilation, respectively. Receiver Operating Characteristic (ROC) curves were used to demonstrate the optimal cut-off value for the derived score, the Maternal Antenatal Transport Score (MATS). The c-statistic was calculated to determine the area under the curve. As a validation technique for MATS, nonparametric bootstrapping was used to derive the 95% confidence interval around the score.

Data were analyzed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The characteristics of the study populations are detailed in Tables 1 and S1. The mean gestational age of the MPIP cohort was 33 1/7 weeks, with a mean birth weight of 1,933 grams. About two thirds of the cohort was born at a Level III NICU, with an almost even contribution of births from California and Massachusetts units. Two thirds of the cohort received antenatal corticosteroids, and more than half were delivered by Cesarean section. Notably, almost all of the women received prenatal care. Nearly 30% of the pregnancies were secondary to infertility treatment, and the cohort consistent mainly of White women of higher education and family income (Tables 1 and S1).

As expected, the group that received surfactant was, on average, less mature (8 days) and smaller (180 grams) compared to the group that did not receive surfactant. Additional notable trends or differences in the surfactant group included more frequent receipt of antenatal corticosteroids and magnesium sulfate, rupture of membranes greater then 24 hours, and birth in the state of California, as well as a higher likelihood of White race and male gender. There were no differences in maternal age, maternal education or family income between the two groups (Table S1).

The resulting multivariable logistic regression model is presented in Table 2, demonstrating only the four statistically significant variables, the odds ratio, and the respective MATS points generated for each item. Lower gestational age increased the odds of requiring Level III NICU care, while female gender, non-White race, and antenatal corticosteroids decreased the odds. Of note, a higher proportion of mothers received antenatal corticosteroids in the surfactant group (70.8%) as compared to the no-surfactant group (64.9%), with a non-statistically significant trend (p=0.16). However, the multivariable model, as expected, demonstrated the use of antenatal corticosteroids to be a protective factor with an odds ratio of 0.6 [0.4, 0.9] (Table 2). The trend towards higher antenatal corticosteroid use in the

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surfactant group is most likely explained by the fact that those infants were of lower gestational age.

The statistically significant factors from the multivariable model were included in the MATS. The possible scores range from 0 (i.e. 34 weeks, female gender, received antenatal corticosteroids, and non-white race) to 48 (i.e. 30 weeks, male gender, no antenatal corticosteroids, and white race). The mean score for the overall cohort was 16 (SD=10.7), with a score of 24.9 (SD=10.8) for the surfactant group and 14.2 (SD=9.3) for the no-surfactant group ($p<0.0001$) (Table 3). Figure 1 shows the true positive and false positive rates for various score cut-offs in a Receiver Operating Curve, which has an Area Under the Curve of 0.77 [0.73, 0.8] (Hosmer and Lemenshow Goodness of Fit Test p-value=0.76).

Table 4 demonstrates the comparison of two MATS cut-off values with the AAP/ACOG referral/antenatal transfer threshold of less then 32 weeks gestation. The MATS cut off value represents the mean MATS in the two groups, surfactant (24.9) and no surfactant (14.2). The application of MATS improves the sensitivity of antenatal identification of infants who require tertiary care. However the specificity is decreased as compared to the current gestational age cut off, thus resulting in higher number of maternal transports of infants who will not require tertiary care (i.e. higher false positives) (Table 4). When the rule is applied to the MPIP cohort, the gestational age cut off would result in the fewest antenatal transports, but would miss the largest number of infants requiring tertiary care and thus a postnatal transport.

DISCUSSION

We have developed a simple score that uses clinical parameters to help predict the requirement for tertiary level neonatal care in the first 24 hours of life prior to the delivery of a moderately premature infant. The MATS includes four simple and readily-available parameters: fetal sex, gestational age, administration of antenatal corticosteroids and maternal race.

Several clinical prediction scores in the field of neonatology have helped to build the framework for our antenatal risk assessment score. These include the Score for Neonatal Acute Physiology (SNAP) [25, 27], Clinical Risk Index for Babies (CRIB) [28, 29, 30], Richardson Score [26], and the Mortality Index for Neonatal Transportation (MINT) Score [31]. As does MATS, all of these rules incorporate either physiology alone or a combination of physiologic parameters and readily available neonatal clinical factors that are associated with severity of illness. In contrast to MATS, however, all focus on postnatal prediction of clinical events, ranging from mortality to prolonged ventilation. To our knowledge, only one previous study attempted to identify exclusively intrapartum factors to predict the severity of illness of the neonate [16], but the analysis was in a different health care delivery setting in France, only included infants up to 32 weeks gestation and did not derive a clinical prediction score. In addition, the Alberta Perinatal Health Plan uses an Antepartum Risk Score for all pregnant women to help identify the high risk pregnancies for that region to help guide the obstetric providers throughout the pregnancy [32]. However, this risk score is

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intended to be used throughout the antenatal period to assess maternal risk, and does not explicitly focus only on the high risk infants [32].

The discriminatory performance of MATS, with a c-statistic of 0.77 [0.73, 0.8], is in the moderate range and is similar to other recently published models for survival without disability in extremely premature infants [33], prediction of discharge time in infants under 27 weeks gestation [34], and transport risk assessment for prediction of 7-day and total NICU mortality [35]. In addition, a model matching the current AAP/ACOG[11] guidelines (i.e., transfer if < 32 weeks) had a c statistic of 0.65. In contrast, the MATS offers a 15% improvement in the area under the curve, thus leading to improved ability to antenatally discriminate the need for tertiary neonatal care.

Since this was a secondary data analysis, we must acknowledge certain limitations in our work. First, not all variables that might signal a need for tertiary care were available in our prospective cohort (e.g. hypoglycemia requiring central access, hypotension requiring pharmacologic support, etc). We used a surrogate outcome for the requirement of tertiary neonatal care - the administration of surfactant - as surfactant appeared a reasonable marker for moderately preterm infants who require intubation. While this assumption seems reasonable, it may not account for some intermediate neonatal-care programs which provide care to infants who require central lines or pressor support without the need for mechanical ventilation. We may have also missed a portion of infants who required intubation without the need for surfactant, such as in the case of perinatal depression or respiratory distress secondary to pneumonia. Furthermore, the cohort only included those infants who were discharged home alive from the study hospital. Their severity of illness likely would have qualified them as Level III infants. Although this is a potential source of bias, it is unlikely to be significant given the low mortality of this gestational age group as compared to their VLBW counterparts[12, 14].

It must also be acknowledged that significant practice variation exists among NICUs [36, 37] and that this may alter the patient outcomes, such as intubation and receipt of surfactant. Specifically, the case report forms did not collect information on whether surfactant was given as a prophylactic or rescue strategy. In order to account for some of such variation, we adjusted for both the state of birth (MA vs. CA) and the level of care (II vs. III) received by the neonate, but neither factor was a statistically significant predictor of surfactant administration in our multivariable logistic regression model. Since variation of perinatal care, including the types of services offered at the designated levels of neonatal care, will vary by regions and states beyond the units represented in this analysis [38], the application of a clinical prediction rule such as the MATS will need to be considered in the context of each individual area to help provide the most optimal outcomes. One approach that might be undertaken by a region is to determine if it is best for them to optimize the sensitivity or specificity of MATS. The optimal cut-off thresholds would have to be evaluated in the context of optimal resource availability and utilization, including that of maternal-fetal and neonatal transport.

Thirdly, our dataset provided a limited number of maternal conditions (e.g. gestational diabetes, hypertension, etc.) as candidate independent risk factors for neonatal morbidities,

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especially in late-preterm infants [39]. With only four factors used to predict the outcome, the MATS is both parsimonious and has strong face validity, but its predictive validity might be strengthened if other intrapartum and antepartum risk factors were available for analysis. We also did not have the power to split the cohort to derive the MATS on one half and validate it on the other, and therefore addressed this limitation using nonparametric bootstrapping (Table 3). This issue will be addressed further by validation of MATS on an external cohort.

Finally, we must address the issue of generalizability of our cohort, which was a relatively advantaged group, most of whom had received prenatal care, were highly educated and with adequate family income. Given the evidence that preterm birth disproportionately affects people of lower socioeconomic status, it will be important to validate this rule in other populations prior to clinical use. Similarly, we did not attempt to validate the score on late-preterm infants of gestational ages 35-0/7 to 36-6/7 weeks, who are also known to be at increased risk for morbidities requiring tertiary level neonatal care are [39]. Plans for such extension to more diverse maternal and neonatal populations are underway.

In summary, the MATS provides reasonable discriminatory power to identify which infants may require tertiary level care prior to delivery and thus prompt a maternal-fetal transport. We hope that the provision of a best-care setting for at-risk infants would improve infant outcomes at the population level and optimize resource utilization in regions where there are barriers to neonatal transport.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ACOG	American Congress of Obstetrics and Gynecology
MATS	Maternal antenatal transport score
ROC	Receiver operating characteristic curve
MPIP	Moderately Premature Infant Project
NICU	Neonatal intensive care unit
VLBW	Very low birth weight

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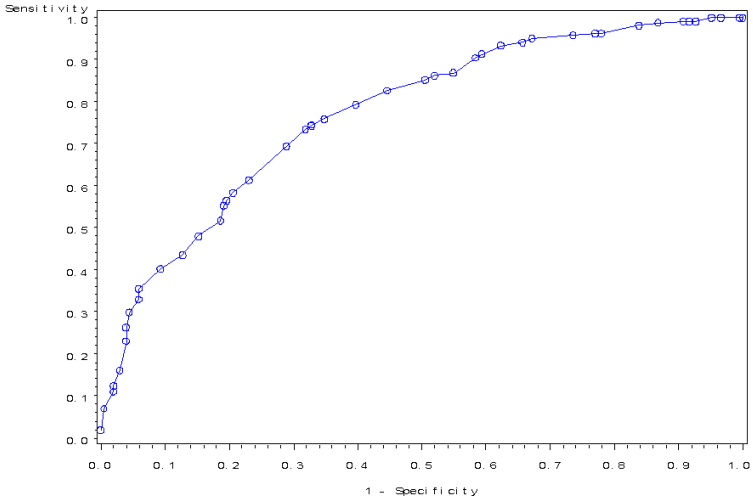

Figure 1.

Receiver Operating Characteristic Curve

ROC curve for the MATS for the entire MPIP cohort. The area under the curve is 0.77 [0.73, 0.80]. The optimal cut off value for MATS depends on the perinatal regionalization network that exists for a particular region and the associated trade-off from optimizing sensitivity versus specificity.

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Table 1

MPIP study baseline population characteristics[†]

Parameter	MPIP Cohort N=850	Surfactant *n = 204*	No Surfactant *n= 646*	p-value *
Infant Characteristics:				
Gestational age – weeks	33 1/7 (0.06)	32 2/7 (0.1)	33 3/7 (0.06)	<0.0001
Birth weight – grams	1,933 (17)	1,797 (32)	1,977 (19)	<0.0001
Gender – % male	50.3 %	58.8 %	47.6%	0.013
Birth by Caesarean Section – %	59.0 %	71.4 %	54.9 %	0.0002
Maternal Characteristics:				
Rupture of Membranes ≥ 24 hrs – %	17.7 %	12.3 %	19.4 %	0.03
Maternal Race:				0.03
White – %	45.7 %	54.9 %	42.7 %	
Black – %	10.2 %	10.1 %	10.2 %	
Hispanic – %	8.0 %	9.1 %	7.6 %	
Other – %	14.6 %	8.9 %	16.5 %	
Missing – %	21.5 %	17.0 %	23.0%	

[†]Mean (Standard Error) unless otherwise indicated. The means and percentages are based on a weighted analysis in order to adjust for sampling, with a total N representing the sample of 1250.

[*]Comparison is between the “Surfactant” and “No-Surfactant” Groups; Chi square or T-test ere used as indicated

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Table 2

Logistic Regression Model and Maternal Antenatal Transport Score (MATS)

Parameter	Beta (SE)	Odds Ratio [95% CI]	p-value	MATS Points
Gestational age (week)				
30 vs. 34	3.01 (0.35)	22.1 [11.0, 44.4]	<0.0001	31
31 vs. 34	2.00 (0.32)	7.4 [4.0, 13.8]	<0.0001	20
32 vs. 34	1.83 (0.30)	6.3 [3.5, 11.2]	<0.0001	18
33 vs. 34	0.45 (0.30)	1.6 [0.9, 2.8]	0.13	5
34 reference	reference	--	--	0
Female Gender	−0.41 (0.23)	0.7 [0.4, 0.99]	0.04	0
Male	reference	--	--	4
Antenatal Corticosteroids	−0.52 (0.23)	0.6 [0.4, 0.9]	0.02	0
No Antenatal Corticosteroids	reference	--	--	5
Non-White Race	−0.77 (0.21)	0.5 [0.3, 0.7]	0.0002	0
White	reference	--	--	8

SE=Standard Error

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Table 3

MATS between the 2 groups

Group	N	Mean (SD)	Min-Max Range	Bootstrapped 95% CI	p-value
Overall Cohort	850	16 (10.7)	0 – 48	[16.03, 17.45]	--
Surfactant Group	204	24.9 (10.8)	0 – 48	[23.13, 26.08]	<0.0001*
No Surfactant Group	646	14.2 (9.3)	0 – 43	[13.49, 14.92]	--

*p-value represents the weighted regression comparison between the MATS in the surfactant and no-surfactant groups

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Table 4

Threshold Cut Off for Transfer

Transfer Threshold	Sn	Sp	PPV	NPV
MATS>/= 25 points	52%	85%	53%	85%
MATS>/= 14 points	79%	56%	36%	89%
Gestational Age< 32 weeks	43%	86%	50%	83%

MATS=Maternal antenatal transport score; Sn=Sensitivity; Sp=Specificity; PPV=Positive Predictive Value; NPV=Negative Predictive Value. The positive and negative predicative values were calculated for the MPIP database, in which the incidence of the outcome of interest was 24%.