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Hypoxic-Ischaemic Brain Injury: Planned Delivery before intrapartum events

D Odd (Consultant Neonatologist)[1,2]*

Al Heep (Consultant Neonatologist)[1,2]

K Luyt (Senior Clinical Lecturer)[2]

T Draycott (Senior Clinical Lecturer)[2]

1. Neonatal Unit, North Bristol NHS Trust, Bristol, United Kingdom.

2. University of Bristol, Bristol, United Kingdom.

*** Corresponding author:**

Dr David E Odd

Neonatal Unit, Southmead Hospital, Bristol, United Kingdom, BS10 5NB.

Tel: 0117 9505050

Fax: 0117 9595324

david.odd@nbt.nhs.uk

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Abstract

Background: Mothers are increasingly given greater control over many of the choices around birth, although there is little robust evidence to inform these choices. After an infant is born with HIE the question of whether it was predictable, or preventable, is often raised. Intrapartum 'sentinel' events and antenatal predictors of HIE have been well described, however there is little evidence how antenatal and intrapartum factors interact. This is particularly important when elective delivery by lower segment caesarean section (LSCS) has been shown to be beneficial in high risk groups.

Aim: To develop a clinical risk score to identify women with a higher risk of having an infant with HIE**.**

Patients and Methods: This study is based on the Avon Longitudinal Study of Parents and Children (ALSPAC). This dataset was split into two halves: with each infant being randomly allocated to either cohort one or 2. The first cohort was used for the derivation of the model, while it was tested exclusively on the second. Logistic regression modelling was then performed to develop a predictive model. The final model was used to predict the outcome of infants in the second cohort and infants divided into four risk quartiles. To give some indication of possible avoidable disease, the proportion of infants with HIE, potentially avoided by earlier delivery, was estimated by assuming that medicalised delivery by elective LSCS at 37 weeks would remove intrapartum risk of HIE for those infants undelivered at this point.

Results: In the final model seven covariates remained (parity, pre-eclampsia, polyhydramnios, pre-labour rupture of membranes, gender, concerns over fetal growth and prematurity) . When applied to the second cohort, a ROC curve for the prediction of

developing HIE in the newborn period showed good evidence for association (AOC 0.68 (0.60 to 0.77)) and the risk score derived was strongly associated with the risk of HIE, resuscitation and stillbirth, and neonatal death (all $p<0.05$). Elective delivery of high risk infants at 37 weeks gestation could prevent 14% of all HIE, with a NNT of 41.

Conclusion: It is possible to combine routine antenatal findings to identify infants at higher risk of neonatal HIE, thereby recognising those infants who may benefit most from delivery by elective caesarean section. This work suggests a clinical risk score permits antenatal identification of high-risk infants whose outcome may be amenable to changes in clinical practice to potentially reduce HIE rates, and its devastating consequences.

Introduction

Perinatal asphyxia is a major cause of hypoxic-Ischaemic encephalopathy (HIE), perinatal death and long term neurodisability [1]. This can be devastating for the individual and their family; the healthcare and litigation costs notwithstanding [2].

In recent years have attempted to quantify the effect, and wider impact of intrapartum compromise [3], as well as the underlying mechanisms for it [4].

After a poor outcome related to intrapartum care parents and healthcare practitioners often strive to understand whether the event could have been predicted and/or prevented. This can be difficult to answer, at least partly related to the heterogeneous fetal response to perinatal asphyxia. While most infants tolerate the birth process well around 7% of infants require some degree of resuscitation after they are born, and a small proportion of these go on to develop immediate signs of brain damage (Hypoxic-Ischaemic Encephalopathy) [5]. Some infants appear to tolerate severe levels of asphyxia during the birth process with little impact, whilst others do not tolerate what appear to be much milder insults.

A number of reports have demonstrated an association between maternal antenatal and birth related factors and subsequent perinatal asphyxia [6,7]. However, thus far there is very little evidence about how these risk factors interact and what processes around birth may modify adverse outcomes; although early, elective delivery has been shown to improve outcome in high risk groups [8, 9]. There is a similar dearth of data identifying the causal routes through which these outcomes may occur, whether the perinatal asphyxia could be predicted, and finally, whether the asphyxia could be prevented [10]. Mothers and the maternity service are increasingly encouraged to personalise care and their choices around the birth process, however the information required to guide these choices is most often missing. This makes it

difficult for women and professionals to make an informed choice about their care, including the safest mode of birth for them and their baby.

The aim of this work is to develop a clinical score that would alert obstetric services and women at higher risk of an infant with perinatal asphyxia and hypoxic-ischemic encephalopathy (HIE), thereby facilitating interventions to prevent this.

Methods

This study is based on the Avon Longitudinal Study of Parents and Children (ALSPAC), an on-going longitudinal study containing data for more than 14,000 infants [11]. The cohort includes children born in the Bristol area, England from April 1991 to December 1992. Data on cohort members and their families have been collected using self-completed questionnaires, at half-day research clinics and/or retrieved from routine medical or educational records. Further information about the study can be found on the ALSPAC website: www.alspac.bristol.ac.uk. Initially the dataset in this work contained details on 13522 infants born between 36 weeks and 44 completed weeks of gestation.

Infants were defined with hypoxic-ischaemic encephalopathy if they developed seizures, jitteriness, high pitched cry, hypo- or hypertonia or hyper-reflexia during the neonatal period following the need for resuscitation [5]. Potential predictors were defined a-priori and categorized into three groups:

- Booking Factors (maternal age, smoking, primiparity, previous lower segment caesarean section (LSCS), multiple births)
- Antenatal Factors (pre-eclampsia, gestational diabetes, pre-labour abruption, placenta previa, oligohydramnios, polyhydramnios, threatened preterm labour, gender, concerns of IUGR infant)

- Labour factors (induction of labour, pre-labour rupture of membranes, planned LSCS, gestation at birth, presentation, prelabour breech, breech delivery, duration of ruptured membranes)

Most covariates were extracted from patients notes, routine data collection or as part of a routine clinical database. Some covariates (pre-labour abruption, placenta previa, oligohydramnios, polyhydramnios, threatened Preterm Labour, induction of labour, pre-labour rupture of membranes, prelabour breech) were available on a sub-set of the cohort, either due to a process of random extraction (n=2,671) or as part of a targeted extraction for a particular disease, clinical process or study (n=7,988) (Appendix 1). In total 7,988 (59.1%) patients had data extracted on these additional nine co-variates. Details are shown in Appendix 1. Multiple imputation was used to impute the data of all missing covariates [12]. Included in this model was the reason for possible extraction, and so assumptions for missing at random in this group are felt likely to be fulfilled. For practical reasons only one in three infants without HIE were selected and used in the analysis (with all analyses weighted to represent the initial cohort).

The dataset was divided into two halves: with each infant being randomly allocated to either cohort one or two by computer derived random number allocation. There were no differences in the risk of HIE (p=0.465), resuscitation (p=0.700), still-birth, death or resuscitation (p=0.989) or special educational needs (p=0.675) between the two cohorts. 1) In step one (development of the model), the first cohort of infants (n=6712) was used for the derivation of the model. Logistic regression modelling was performed to develop three models. Initially, the associations between the proposed risk factors and HIE were analysed, both in the initial dataset and in the imputed one. A logistic regression model was developed using all the *a-priori* defined variables (the "saturated" model). A step-wise removal of covariates was deemed unlikely to improve the model's fit (Wald test p>0.10) then took place until only

those with a Wald test p value of less than or equal of 0.10 remained. A simplified model was developed where all variables were re-entered in the model one-by-one to check that they did not improve the fit, and retained if there was evidence ($p<0.10$) that they did ("final" model).
2) In the second step (application of derived model), the derived model was used to predict the outcomes in infants in the second dataset (cohort 2; n=6688). This final model was used to predict the outcome of infants in the second cohort. Receiver Operator Characteristic (ROC) curves were derived, and the population divided into four antenatal risk quartiles and their absolute risk for HIE derived for both the saturated and the final model. The association between an increasing antenatal risk score and the chance of common neonatal and childhood adverse outcomes (HIE, need for neonatal resuscitation, stillbirth or neonatal death, cerebral palsy, developing special educational needs or an IQ of less than 70 at the age of 8) was estimated.
Finally, in step three (potential avoidance of events) to give some indication of possible avoidable disease, the proportion of infants with HIE, potentially avoidable by earlier delivery was estimated by assuming that elective delivery would remove intrapartum risk of HIE for those infants undelivered at this point. This was calculated for the whole cohort and for each antenatal risk strata at each gestational age between 36 and 40 weeks. The *a-priori* clinical cut-off used was "clinical intervention" (e.g. elective LSCS) at 39 weeks [8].
All analyses were conducted with Stata 10 software (Stata Corp, TX, USA). All data are presented as odds ratio (OR) (95% confidence interval (CI)), mean (SD), mean difference (95% CI), median (interquartile range (IQR)), or number (percent (%)). Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee.

Results

In the first cohort, infants with HIE differed from those without HIE for the categories: parity, pre-eclampsia, gender, induction of labour, pre-labour rupture of membranes and concerns over fetal growth (all $p<0.05$) (Table 1). In the saturated model, all *a-priori* variables were included in the regression analysis (Table 2). The final model development (as discussed above) left seven covariates (parity, pre-eclampsia, polyhydramnios, pre-labour rupture of membranes, gender, concerns over fetal growth and early term delivery) that all appeared to strengthen the antenatal prediction of HIE.

In step two (application of derived model); applying the derived model to predict risk in the second cohort demonstrated good evidence for additional prediction of HIE (Area under the curve of (0.62 (95% CI 0.52-0.72)) (Figure 1). When the infants were categorised into risk quartiles the infants' absolute risk of HIE ranged from being 0.5% (0.2%-0.7%) in lowest quartile of the final model, up to 2.0% (1.2%-2.9%) in the highest risk quartile (Table 3). This final model strongly predicted HIE, resuscitation and stillbirth, neonatal death or HIE in the second cohort (all associations $p<0.001$) (Table 4). In addition there was some evidence of an association between these risk factors and special educational needs at school age ($p<0.001$), but not a low IQ score at seven years ($p=0.959$). In a post-hoc analysis, HIE was strongly associated with SEN ($p=0.015$), with 21% of the HIE infants having SEN (vs 23% in non-HIE infants).

In step three (potential avoidance of events) the estimation of avoidable HIE, by elective LSCS prior to fetal compromise was calculated. The number of elective LSCSs required in each antenatal risk group, by each gestational cut off, is shown figure two with further details in Appendix 2. At 39 weeks gestation, the number of elective LSCSs required to prevent one case of HIE ranged from 200 in the lowest risk quartile to 46 in the highest.

Discussion

Development of a risk score in clinical perinatal practice appears feasible and by informing perinatal management may reduce the number of infants born with perinatal asphyxia. Whilst the risk factors identified in this work are consistent with those previously identified [6,7]; this work suggests that integrating them into a single risk-profile is possible and many (e.g. maternal age) may simply represent confounders for other, causal factors. While the models developed in this work do not fully predict HIE in infants, they did provide additional value over the baseline risk, and above those elective LSCSs already performed for clinical indications and risk factors by obstetricians. It is interesting that the high risk group identified here had a 2% chance of substantial neurological damage in their infants, predictable before labour, and the risk profile was associated with a pragmatic and important measure of special educational needs at school. This suggests a substantial number of infants could have the risk of perinatal asphyxia attenuated or removed given timely obstetric intervention. While this is provisional work, we suggest that a sizable proportion of HIE may be predictable and potentially avoidable. Elective caesarean section at 39 weeks gestation would remove the risk of intrapartum HIE as well as reduce *in utero* death and may be worth considering.

Around 0.6% of the infants died prior to birth but due to limited data on when this occurred could not be include in this analysis. Hence any reduction in perinatal asphyxia may also reduce term stillbirth rates.

This is provisional work and was designed to investigate whether a clinical risk score may help personalise care by both targeting clinical interventions to those women and infants that would be most likely to benefit from them, whilst reassuring those at lower risk. Research into the timing of elective caesarean section has previously focussed on transient neonatal respiratory disease rather than the avoidance intrapartum asphyxia[8]. However targeted caesarean section has been associated with improved neonatal outcomes in high risk populations [13]. Indeed some have suggested that both intrapartum asphyxia (the biggest

preventable cause of HIE) and late fetal death could be significantly reduced by routine elective caesarean section at 39 weeks gestation [8, 9].

The two substantial limitations of this work are the time the data was collected (in the 1990's), and the amount of missing data. Infants born twenty years ago may not represent those born today and obstetric care has also evolved in that time. However rates of HIE have remained similar [10] and using this cohort has also allowed us to look at longer term impacts. Neonatal care has also improved over this time, however HIE is still a devastating outcome to a pregnancy and reducing incidence a current priority. Despite limitations of power we found some evidence that the profile of risk before birth remained associated with school performance in these infants. The missing data for some obstetric measures is also an important limitation and while missing data techniques were used to impute the missing data (and hence use all the data that was collected), these data should be interpreted with caution. Given we know the reasons for the missingness (no routine extraction), and the reason for data collection, the assumption of Missing At Random (MAR) appears to be appropriate. In addition only two selectively extracted measures (polyhydramnios and pre-labour rupture of membranes) were used in the final model. However this work is likely to under-represent the proportion of infants that may benefit from the score because it is likely that clinicians had risk assessed and intervened pre-emptively for high risk women.

To identify a relatively important population impact after these interventions is interesting and supports further work in this area. This is timely because current models of maternity care are population based, whereas women and providers want to personalise their care and choices using the best possible information.

However while we can quantify the number of interventions needed to reduce one case of neonatal disease, the threshold at which this becomes reasonable is unclear, and further work looking at the level of risk that is acceptable to the mother, and the service. Indeed the recent

Montgomery decision suggests that the service should accommodate different thresholds for different women after adequate information has been provided [14].

We are not aware of other studies that have tried to predict the outcome of pregnancies using only antenatal derived variables i.e. information available to women and their carers to make choices prior to birth. Previous work has investigated risk factors for HIE or CP and found similar results to ours, but not combined them into a predictive model [6, 7]. Restricting the score to antenatal factors in this work supports the premise that better prediction of infants at high risk of perinatal asphyxia is possible. It is worth noting that we were unable to demonstrate an association with cognition, perhaps due to the known specific impacts of perinatal asphyxia on motor rather than cognitive function [15].

This work is based on a retrospective cohort and further data are required to establish validity. However we have demonstrated that it is possible to identify both high risk and low risk women from antenatal pregnancy factors, over and above standard obstetric care. Prediction of infants at higher risk of neurological damage or death around term is possible and may well have clinical utility.

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Table 1. Characteristics of study population (cohort 1: n=6712)

Measure	Number with data	Term Infants (n=6,582)	HIE Infants (n=130)	P	P*
Booking Factors					
Maternal age	6712	28.1 (4.9)	27.2 (5.2)	0.212	0.165
Smoking	6278	3170 (50.8%)	22 (52.4%)	0.842	0.789
Primiparous	6219	2683 (43.4%)	27 (65.9%)	0.004	0.012
Previous LSCS	6048	382 (6.4%)	2 (5.0%)	0.726	0.632
Multiple Births	6712	128 (1.9%)	2 (4.4%)	0.234	0.242
Antenatal Factors					
Pre-eclampsia	6712	547 (8.2%)	10 (21.7%)	0.001	0.001
Gestational Diabetes	6604	46 (0.7%)	1 (2.2%)	0.226	0.201
1st trimester Placenta Previa	3963	18 (0.5%)	1 (2.3%)	0.078	0.278
Oligohydramnios	3963	35 (0.9%)	2(4.7%)	0.011	0.054
Polyhydramnios	3963	47 (1.2%)	2 (4.7%)	0.042	0.123
Threatened Preterm Labour	3963	148 (3.8%)	4 (9.3%)	0.061	0.335
Male	6712	3430 (51.5%)	32 (69.6%)	0.014	0.021
IUGR concerns	3920	111 (2.8%)	7 (16.3%)	<0.001	0.001
Labour Factors					
Induction of labour	3900	782 (20.3%)	17 (39.5%)	0.002	0.004
Pre-labour Rupture of Membranes	3866	1380 (36.1%)	23 (54.8%)	0.012	0.031
Gestation at birth (weeks)	6712	39.6 (1.4)	39.3 (1.9)	0.082	0.079
Prelabour Breech	3977	1430 (36.4%)	21 (48.8%)	0.091	0.088
Duration of ruptured membranes (hours)	5789	2 (0-7)	4 (1-9)	0.957	0.959

Standard deviations are given for means of normally distributed continuous variables, median (IQR) for non-normal distributions and percentages for proportions.
* Derived from imputed dataset. n=6712 for all measures

Table 2. Full and simplified logistic regression models (cohort 1: n=6712)

Measure	Saturated Model	Final Model
	OR (95% CI)	**OR (95% CI)**
Booking Factors		
Maternal age	0.98 (0.92-1.05)	-
Smoking	1.00 (0.52-1.90)	-
Primiparous	2.20 (1.04-4.66)	2.08 (1.08-3.99)
Previous LSCS	0.95 (0.20-4.58)	-
Multiple Births	0.92 (0.19-4.57)	-
Antenatal Factors		
Pre-eclampsia	4.48 (1.58-12.71)	6.56 (2.60-16.60)
Gestational Diabetes	1.34 (0.14-12.92)	-
Placenta Previa	3.53 (0.35-35.16)	-
Oligohydramnios	2.42 (0.42-14.00)	-
Polyhydramnios	5.70 (0.88-36.86)	5.74 (0.96-34.22)
Threatened Preterm Labour	1.26 (0.38-4.17)	-
Male	2.19 (1.15-4.20)	2.16 (1.14-4.08)
Labour Factors		
Induction of labour	1.67 (0.79-3.51)	-
Pre-labour Rupture of Membranes	1.89 (0.89-4.04)	1.66 (0.85-3.22)
IUGR concerns	4.30 (1.50-12.35)	5.65 (2.15-14.82)
Gestation at birth		
Early term (36-37 weeks)	2.01 (0.90-4.53)	2.13 (0.99-4.58)
Late term (41-44 weeks)	1.37 (0.46-4.09)	-
Prelabour Breech	1.37 (0.71-2.66)	-
Duration of ruptured membranes (hours)	0.98 (0.94-1.02)	-

Table 3. Overall risks in four quartiles (cohort 2: n=6688)

Risk Quartile	**Saturated Model**	**Final Model**
	Absolute risk (CI)	Absolute risk (CI)
1	0.6% (0.2%-1.1%)	0.5% (0.2-0.7%)
2	0.4% (0.3%-0.7%)	0.5% (0.1%-0.9%)
3	0.7% (0.3%-1.2%)	0.6% (0.2%-1.0%)
4	1.4% (0.8%-2.0%)	2.0% (1.2%-2.9%)

Table 4. Association between final model and infant outcome. (covariates; parity, pre-eclampsia, polyhydramnios, pre-labour ROM, gender, poor growth, and early term (36-37 weeks) delivery)

Infant Outcome	**Increasing Risk Quartile**	**p_{trend}**
	OR (95% CI)	
Neonatal Outcomes		
Hypoxic-Ischaemic Encephalopathy	1.69 (1.29-2.20)	<0.001
Resuscitation	1.22 (1.13-1.32)	<0.001
Stillbirth, neonatal death or Hypoxic-Ischaemic Encephalopathy	1.55 (1.24-1.94)	<0.001
Childhood Outcomes		
Educational Special Needs	1.51 (1.21-1.88)	<0.001
Low IQ (<70)	1.00 (0.79-1.28)	0.959

Appendix 1. Details of Imputation

Variables available in non-random sample

Placenta Previa
Oligohydramnios
Polyhydramnios
Pre-labour Rupture of Membranes
Induction of labour
Threatened Preterm Labour
IUGR concerns
Prelabour Breech

Samples retrieved with numbers

Reason for Extraction	**Number extracted**
The random Sample	2,671
Sample of teenage pregnancies	610
Sample of depressed mums	1,393
Sample with caesarean section	1,338
Sample with instrumental delivery	1,509
Sample that attended any of the CIF clinics	1,355
Sample of possible preterm deliveries	554
Sample with possible PLIKS	847
Child had cerebral palsy	15
In missing twin study	179
In Rutter/Thorpe study	251
Out of Avon hospital deliveries	336
Sample of miscellaneous deliveries	30
Total with additional data extraction	**7,988**

Data is from eligible cohort (n=13,552)

Appendix 2. Impact of LSCS, at increasing gestational age, split by risk quartile.

Measure	Risk Quartile	Age at intervention									
		36	37	38	39	40	41	42	43	44	No intervention
Number of LSCS	1	2516	2516	2516	2284	1771	978	390	390	167	164
	2	1281	1266	1237	1122	824	423	145	145	23	23
	3	1825	1795	1751	1560	1246	774	403	403	262	262
	4	1255	1135	909	770	573	348	236	236	197	194
	All	6877	6713	6413	5738	4413	2522	1174	1174	649	643
Number of infants with HIE	1	0	0	0	1	3	5	10	11	12	12
	2	0	1	1	1	3	6	6	6	6	6
	3	0	0	0	3	4	7	9	10	10	10
	4	0	2	8	13	16	24	25	25	25	25
	All	0	3	9	18	26	42	51	53	54	54
Number of additional LSCS needed to reduce one case of HIE	1	202	202	202	200	186	123	113	226	-	-
	2	194	227	222	202	232	843	-	-	-	-
	3	150	147	142	175	164	164	141	-	-	-
	4	42	40	41	46	38	87	-	-	-	-
	All	115	119	128	142	135	157	177	531	-	-

Table shows the number of elective LSCS, cases of HIE, and number of additional LSCS to reduce one case of HIE, by gestational age at intervention.

Figure 1. ROC of final logistic regression model: prediction of Hypoxic-ischaemic encephalopathy by clinical risk score in cohort 2

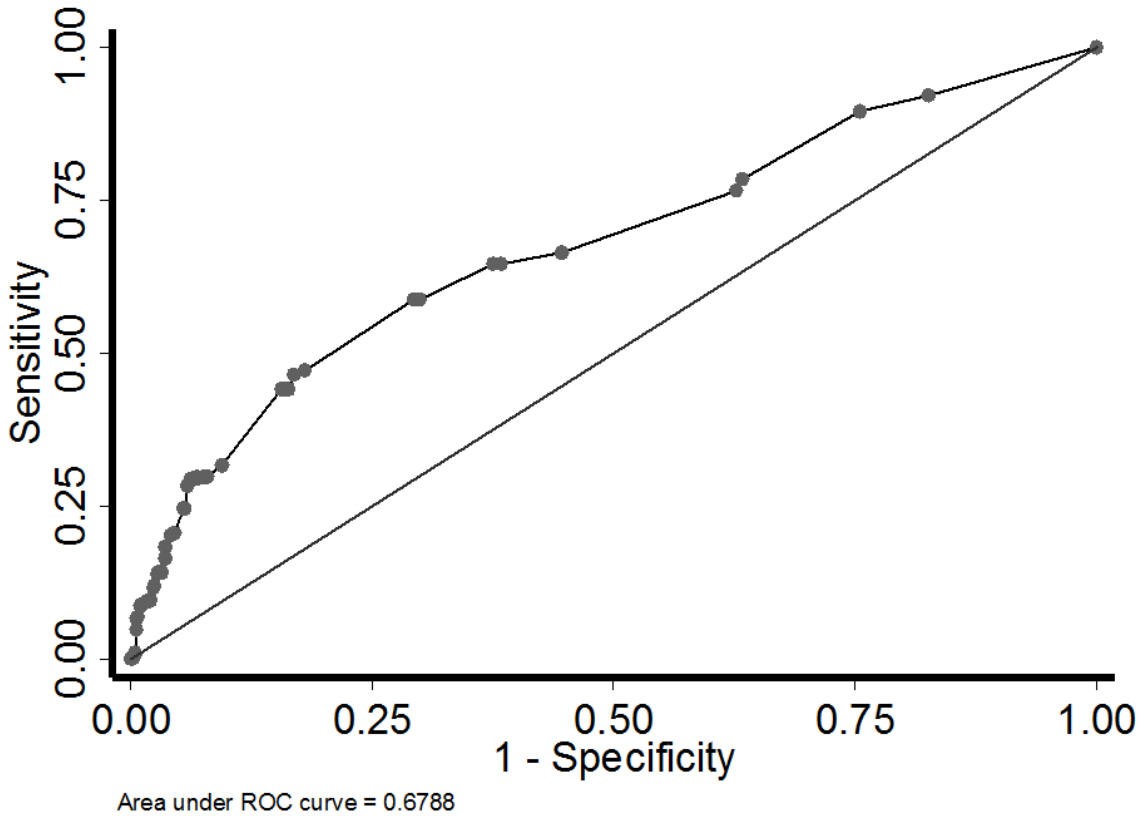

Figure 2. Number of additional elective LSCSs needed to prevent one case of HIE split by predicted risk quartile (Quartile 1: low risk to Quartile 4: high risk)