Predicting Postpartum Hemorrhage (PPH) during cesarean section using the Leicester PPH Predict Tool: a retrospective cohort study

Dr. Suzanna E Dunkerton[*1], Dr. Yadav Jeve[†1], Dr. Neil Walkinshaw[‡2], Dr. Eamonn Breslin[§1] and Dr. Tanu Singhal[¶1]

[1]Department of Obstetrics and Gynaecology University Hospitals of Leicester, Leicester, UK
[2]Department of Informatics, University of Leicester, University Road, Leicester, UK

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Abstract

Objective: The aim of the present study was to develop a toolkit combining various risk factors to predict the risk of developing a postpartum hemorrhage (PPH) during a cesarean section.

Study Design: A retrospective cohort study of 24,230 women who had cesarean delivery between January 2003 and December 2013 at a tertiary care teaching hospital within the United Kingdom serving a multi-ethnic population. Data was extracted from hospital databases and risk factors for PPH were identified. Hothorn et al.s Recursive Partitioning algorithm was used to infer a conditional decision tree. For each of the identified combinations of risk factors two probabilities were calculated: the probability of a patient producing 1000ml blood loss and 2000ml blood loss.

Results: The Leicester PPH Predict Score was then tested on the randomly selected remaining 25% (n=6095) of the data for internal validity. Reliability testing showed intraclass correlation of 0.98 and mean absolute error 239.8ml with the actual outcome.

Conclusion: The proposed toolkit, which is available online, enables clinicians to predict the risk of postpartum hemorrhage. As a result, preventative measures for postpartum hemorrhage could be undertaken. Further external validation of the current toolkit is required.

Index terms— Postpartum hemorrhage, score, cesarean section, risk assessment tool, machine learning, recursive partitioning

[*]slaird@doctors.org.uk
[†]drybjeve@gmail.com
[‡]nw91@le.ac.uk
[§]Eamonnjbreslin@gmail.com
[¶]tanusinghal@uhl-tr.nhs.uk

1 Introduction

Postpartum hemorrhage (PPH) was highlighted by Mothers and Babies: Reducing Risk through Audit and Confidential Enquires (MBRRACE) across the UK, as the second leading direct cause of maternal death. The rate of maternal mortality per 100,000 after PPH, has been 0.59, 0.46 and 0.55 in the 2009-11, 2010-12 and 2011-13 reports respectively [1].

Given the severe morbidity that PPH can cause, several strategies have focused on recognizing risk factors to predict those women at risk of PPH and offer enhanced management. The Royal College of Obstetricians and Gynaecologists (RCOG) recommend being aware of both antenatal and postnatal risk factors for PPH and to modify care plans accordingly, with major risk factors including placenta previa or accreta, which are known to cause extreme PPH, being automatically managed as high risk [2]. Other factors such as age, ethnicity [3, 4], emergency cesarean, obesity [5], induction of labour [6], big baby [7], sepsis [8], hypertension [9], abruption [10], fibroids [11] and multiple pregnancy [3] have been identified as moderate risk factors, but their impact in combination has not been considered. It is possible that the combination of some of the moderate risk factors could lead to high risk of PPH. It is clinically significant therefore, to estimate the collective impact of such risk factors together, to support the identification of appropriate precautionary measures in a timely manner.

Cesarean sections (CS) are associated with increased blood loss and world-wide CS rates are on the rise [12]. It is therefore important that prophylactic measures aimed at reducing the risk of PPH are incorporated into standard clinical practice. Previous prediction tools have not been validated with further data analysis [13].

2 Objective

The objective is to identify the specific combinations of risk factors that can lead to a higher blood loss during a CS, and to quantify these risks. The ability to accurately predict the risk of blood loss would enable preventative measures to be undertaken, thus reducing the frequency of PPH and the morbidity and mortality that follows. Secondly the newly developed tool-kit will be validated within our multi-ethnic population.

3 Study Design

This study was performed as a retrospective cohort study at a University hospital trust in the UK with a multi-ethnic population. Data of all CS performed at this trust between January 2003 and December 2013 was gathered from the hospital electronic database. Database searches were supplemented by case notes review. Data for all women undergoing a CS was coded to include the estimated blood loss at CS and 18 identified risk factors for PPH, shown in Table 1. Electronic text was searched independently for risk factors not otherwise identified.

Patients were randomly split into two groups; a training group consisting of 75% (N=18,172) of the patients, and a validation group consisting of the remaining 25% (N=6,058).

The training group was analysed by Hothorn et al.s non-parametric recursive partitioning algorithm [15]. The algorithm starts by splitting the data into two sub-groups, according to the risk factor that leads to the greatest statistically significant difference in terms of blood loss. The same process is then repeated for the sub-groups with respect to different risk factors, continuing recursively until a termination criterion is achieved (described below). The result is a decision tree [16],

Table 1: Factors that can contribute to PPH.

Factor	**References**
Previous Cesarean (CS)	[13]
Antepartum / Intrapartum Hemorrhage	[14]
Emergency Cesarean	[4]
Age $\geq$ 40	[3]
Maternal Sepsis	[3]
Suspected scar dehiscence	[2]
Second stage section	[2]
Polyhydramnios	[3]
Macrosomia	[2]
Fibroids	[11]
Preeclampsia/ Pregnancy induced hypertension (PET/PIH)	[3]
Multiple Pregnancy	[3]
Previous 3 CS	[13]
Asian Ethnicity	[4]
Grandmultip	[14]
Placenta Previa	[2, 14]
Suspected Abruption	[14]

whereby the root of the tree corresponds to a split along the lines of the most significant risk factor that spans the entire population of patients, and branches correspond to sub-groups.

The minimal threshold for this splitting procedure is specified as the minimal statistical significance that should be achieved by a given split (the maximum p-value). We selected this parameter by a process of adaptive resampling [17]. Where several p-values were attempted, the final p-value was chosen that produced the lowest Root Mean Squared Error computed by 5-folds Cross Validation. This led to the choice of a minimal threshold of 0.01. In other words, the recursive partitioning would terminate if no split could be found that produced different blood loss levels where $p < 0.01$.

For each branch in the decision tree (i.e. every distinct group and sub-group of patients contained in the tree), the blood loss data for that specific group of patients was analysed, and the probabilities of producing a blood loss $\geq$ 1000ml and $\geq$ 2000ml were calculated.

The remaining 25% unseen data was used to validate the accuracy of the probabilities computed for the various combinations of risk factors. For each of the identified combinations of risk factors, the probabilities of the likelihoods of $\geq$ 1000ml and $\geq$ 2000ml blood loss were calculated, and were compared to the corresponding probabilities for the training data. This comparison was quantified in terms of how correlated the two sets of probabilities are, and is also in terms of the mean absolute error, which was computed as: $\frac{|p_1.a_1|+...+|p_n.a_n|}{n}$, where p_i denotes the predicted value for patient i, and a_i represents the actual value for patient i.

4 Results

A total number of 24,230 CS were included in this study of which 8,736 (36.1%) were elective and 15,494 (63.9%) were emergency procedures. 2,997 women had blood loss more than 1000ml out of 24,230 (12.4%).

From the 18 risk factors in the data, the recursive partitioning algorithm highlighted nine as contributing, either individually or in combination with each other, to blood loss levels. The resulting

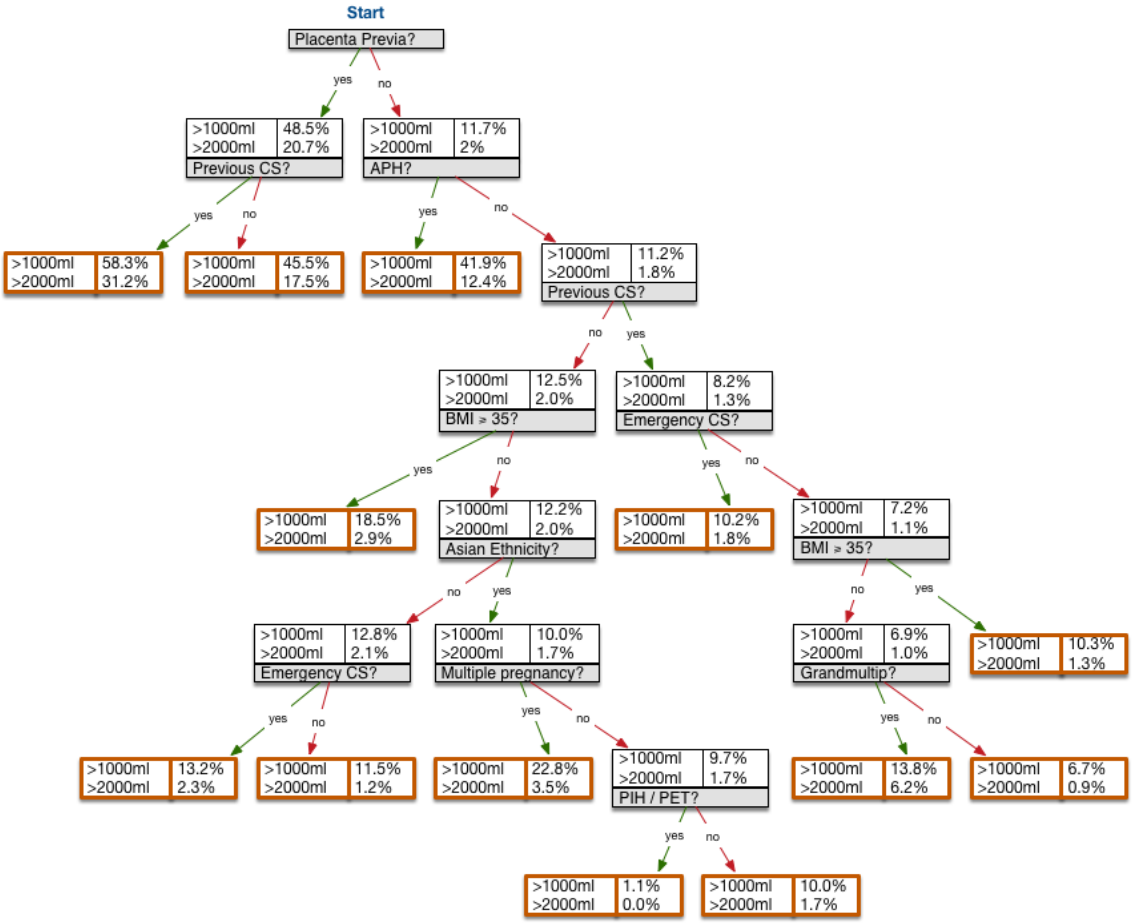

Figure 1: Decision tree produced by recursive partitioning, with added blood loss probabilities.

Table 2: Statistics comparing PPH for sub-groups of patients with and without factors identified within the decision tree.

	Patients with factor						Patients without factor						
	N	**Mean**	**SD**	**Median**	**P(>1k)**	**P(>2k)**	**N**	**Mean**	**SD**	**Median**	**P(>1k)**	**P(>2k)**	**p-value**
Placenta previa	421	1372.337	1465.192	900	0.485	0.207	17751	631.741	412.25	500	0.117	0.02	<0.001
Placenta previa & Prev. CS	96	1964.865	2046.347	1000	0.583	0.312	325	1197.314	1191.761	800	0.455	0.175	<0.001
Ante /Intrapartum Haem.	315	1086.508	877.234	800	0.419	0.124	17436	623.526	394.154	500	0.112	0.018	<0.001
Prev. CS	5632	581.017	345.399	500	0.082	0.013	11804	643.808	413.883	500	0.125	0.02	<0.001
Prev. CS and Emerg. CS	1865	613.592	421.183	500	0.102	0.018	3767	564.889	299.654	500	0.072	0.011	<0.001
Prev. CS & BMI ≥35	377	640.268	370.874	500	0.103	0.013	3390	556.506	289.514	500	0.069	0.01	<0.001
Prev. CS & Grandmultip	80	693.875	599.315	500	0.138	0.062	3310	553.186	277.132	500	0.067	0.009	<0.001
BMI≥35	712	727.949	415.875	600	0.185	0.029	11092	638.407	413.188	500	0.122	0.02	<0.001
Asian Ethn.	2478	602.494	396.593	500	0.1	0.017	8614	648.738	417.291	500	0.128	0.021	<0.001
Asian Ethn. & Mult. Pregnancy	57	802.632	718.283	600	0.228	0.035	2421	597.782	384.819	500	0.097	0.017	0.002
Asian Ethn. & PET/PIH	91	460.989	138.805	500	0.011	0	2330	603.124	390.343	500	0.1	0.017	0.01
Emerg. CS	6587	657.568	436.217	500	0.132	0.023	2027	620.041	347.318	500	0.115	0.012	0.007

decision tree model is shown in Figure 1. To interpret this, one starts from the top node, which starts from the most significant decision, and works down through the subsequent factors until a leaf-node is reached, where the probability of blood loss being $\geq$ 1000ml and $\geq$ 2000ml is given. The tree-structure imparts a hierarchy on the risk factors that are of particular concern for blood loss. Faced with a patient with a multitude of potential risk factors, the tree-structure makes it clear that the questions of placenta previa and previous CS take precedence over all others. Additionally, the question of multiple pregnancies only appears to be a significant factor for Asian patients and is overridden by the question of a large BMI index in any case.

Placenta previa is the main risk factor, leading to a 45.5% chance of 1000ml and a 17.5% chance of $\geq$ 2000ml estimated blood loss (EBL) respectively. However, this is hugely exacerbated when combined with a previous CS, where the probabilities rise to 58.3% and 31.2% respectively. Independently, APH is associated with a 41.9% and 12.4% chance of an EBL $\geq$ 1000ml and $\geq$ 2000ml respectively.

There are many different paths through the decision tree; the following are a few examples. Let us consider a patient with no placenta previa or APH but there has been a previous CS, if the subsequent CS is an emergency the patient has a 1 in 10 chance of PPH $\geq$ 1000ml. If it is not an emergency but their BMI is greater than 35 the patient again has a PPH risk of 10.3%. Then, if you do not have a raised BMI, whether you are a grandmultip becomes important and you have a risk of 13.8% of EBL $\geq$ 1000ml.

If no history of previa, APH or previous CS, BMI is again an important risk factor and the risk of $\geq$ 1000ml is 18.5%. If BMI was less than 35, the patient was of Asian ethnicity and it was a multiple pregnancy, the associated EBL would be $\geq$ 1000ml in 22.8%. PET/PIH and being of Asian origin was associated with low EBL of 1.1% of blood loss $\geq$ 1000ml.

Validation of the predictions for blood loss of $\geq$ 1000ml and $\geq$ 2000ml against the cohort of patients who were not used for model inference indicates that the predictions are accurate. A comparison of the probabilities predicted from the training data and the corresponding probabilities within the validation data is shown in Figures 2 and 3. The mean absolute error is 239.8ml, which is reasonably accurate, and the interclass correlation between the predicted mean EBL and actual mean EBL 0.98. The correlation between percentage predicted $\geq$ 1000ml and actual blood-loss $\geq$ 1000ml is 0.97, shown in Figure 2. For $\geq$ 2000ml the correlation is 0.96, shown in Figure 3.

It is noteworthy that, contrary to previous results [11], the inferred model does not highlight fibroids as influencing blood loss. This should not be interpreted as meaning that fibroids are not a factor. However, our data set only contained 37 patients with fibroids (and the 75% sample used for training the model contained only 28). Furthermore, many of these patients also exhibited other factors that did feature in the model (only nine patients with fibroids did not have other characteristics that also feature in the model). Nevertheless, looking at the statistics for those patients with fibroids, the mean blood loss is 809.459ml, the probabilities of $\geq$ 1000ml and $\geq$ 2000ml are 32.4% and 5.4% respectively, so the data (albeit with few data points) still corroborates that the presence fibroids is a potentially significant factor.

5 Discussion

Risk models have been successfully used in medicine and surgery to prepare clinicians with safety tools. These models help patients to understand their individualized risk, which is much closer to reality than the background population risk. Such risk prediction helps patients to make an informed decision and consider alternatives to proposed treatment. In surgery, Parsonnet et al created an additive model to predict chance of mortality within 30 days after cardiac surgery for

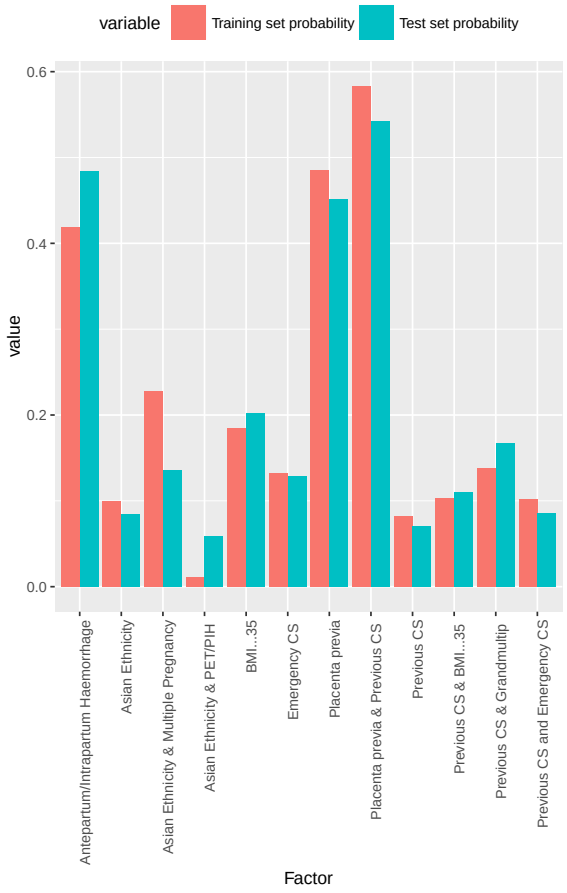

Figure 2: Comparison of predicted probabilities for EBL of $\geq$ 1000ml.

adult acquired heart disease [18]. It was then tested prospectively and shown to have excellent correlation between anticipated and observed mortality. Like our current model, Parsonnets model was based on the data from one unit. When applied to other units there was a slight variance in predicted mortality, but it inspired Nashef et al to create the EuroScore using multicenter data which is now a highly regarded and well used risk model [19]. The current model to predict PPH could similarly form the foundation for a multi-centre study.

Risk factors for PPH have been described in other studies. Multiple pregnancy [2] causes extra uterine distention compared to a singleton, making it less effective at returning to its contracted state and susceptible to bleeding. Previa is associated with a high incidence of PPH in some studies, which would be in agreement with our results [2, 14]. APH [14] and raised BMI [5] have been previously associated with complications including PPH. The novel result of this study was the ability to quantify and individualize the risk for women undergoing CS.

The proposed tool has many advantages over the traditionally used qualitative risk assessment approach. In addition to improving patient safety and care, these models provide a base for standardized comparison of incidence of this complication across different units. Comparison of PPH

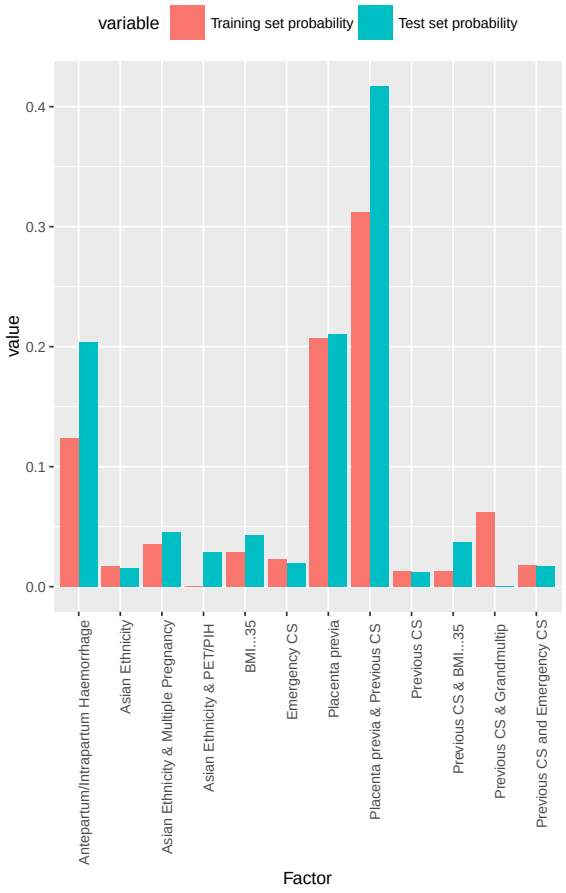

Figure 3: Comparison of predicted probabilities for EBL of $\geq$ 2000ml.

rates alone without accounting for the complexity of patient risk factors and demographics could be biased.

A paper risk assessment tool has been used to help prevent obstetric venous thromboembolism (VTE) which is widely used and forms part of the RCOG green top for prevention of VTE [20]. The Leicester PPH Predict tool could form a part of the pre-theatre checklist and these tools are increasingly being implemented as mobile apps in other specialities. Nogueira et al have created an app to use prehospital to triage patients using simple yes/no answers to help direct them to the appropriate hospital for their care [21]. Our tool has been developed into a free online website[1]. This allows the user to click yes or no to each patient characteristic question, producing as output a probability of blood loss $\geq$ 1000ml and $\geq$ 2000ml. This online tool is available to be used by other units globally for clinical and research purposes, please note information inputted will be stored anonymously on the website but not used for any purpose. This could also provide an opportunity for external validity of this tool.

Medical data has increased in quantity over the last few decades and machine learning techniques,

[1] `http://bit.ly/2eEtSn0`

such as we have used in our statistical analysis, allow far more complex relationships to be revealed compared to standard methods of data processing. The decision tree is especially useful because it is sensitive to the more subtle interrelationships between factors. So, for example in our model, the question of whether you have had a previous CS is particularly important if you also had a placenta previa. Scheer et al created a computer based preoperative predictive model for an orthopaedic complication using a similar split of trained and untrained data. It was shown to have 86% accuracy at predicting the complication [22]. Jurarut et al developed a simple score system using traditional multivariate analysis for predicting PPH in Thailand at CS using retrospective data on 2,405 patients with an overall prevalence of PPH of 10.1% [13]. Similarly, they found previa, emergency CS, multiparity to increase risk of PPH.

Having a risk assessment tool allows consideration of what might be required to prevent or deal with the PPH. Those at lower risk would have the routine 5 units IV syntocinon. If stratified as medium risk then administration of prophylactic 40 units or carbetocin and other oxytocics/ balloons could be available if required. Then those at higher risk could be delivered in a unit with access to cell salvage, gynecological theatre equipment, crossed matched blood, embolization, senior support in theatre and vascular surgeon availability [23, 24, 25]. Preparations such as this are likely to be routine when known extreme risk factors such as placenta previa are present, but this risk assessment tool also takes into account when multiple minor risk factors add up and can lead to previously less predictable high blood losses that would not normally trigger the same level of preventative care.

A limitation of this study is that it was performed at single center. However, this provides the additional advantage of having uniform clinical protocols, practice and documentation for all patients. Another limitation could be the use of estimated blood losses as documented in the notes by trained staff rather than measured blood loss. This is due to the retrospective nature of this study design. Yearly mandatory staff training includes correctly estimating blood loss with pictorial reference cards and has improved estimations of blood loss over recent years. It is noteworthy that, contrary to previous results [10], the inferred model does not highlight fibroids as major risk factor for blood loss. However, this finding should be interpreted with caution as the current data set had limited number of fibroid cases.

6 Conclusion

The Leicester Predict PPH tool predicts the risk of significant PPH following CS using preoperative characteristics of the patient. This risk assessment tool showed reliable results when tested for internal validity. The use of this tool in clinical practice will help to plan and execute the strategies to minimise the blood loss in high risk patients. Such an approach of quantified individualized risk will improve CS surgery safety and will also enable patients to make informed choices. Further research using a prospective multi-center trial design to externally validate this toolkit is recommended.

Disclosure of conflict of Interest:

None

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