**INTRODUCTION**

Recent research trends in healthcare applications of machine learning focus on the interpretability of the models. While in some healthcare applications accuracy of the model s much more important than its interpretability, there are many cases where interpretability is preferred despite loss of accuracy. The ideal scenario where the model has both high accuracy and high interpretability can be achieved either by starting with a simple model such as a generalized additive model (GAM) and then making it more complex (thus more accurate), such as GA2M (GAM with pairwise interactions), or by starting with a complex model, such as XGBoost, and try to interpret it locally with methods like LIME. During NeurIPS (Neural Information Processing Systems) 2017, one of the leading conferences in the world on machine learning, a debate session was arranged between Yann Lecun (head of AI research at Facebook) and Rich Caruana (lead machine learning researcher at Microsoft on healthcare applications). This session at the end of the “Interpretable ML Symposium” highlighted the need for further case studies on accuracy vs. interpretability trade-off in machine learning for healthcare.

In this paper, we will investigate a case study around Severe Retinopathy of Prematurity (Severe RoP) that leads to full or limited blindness in newborns if not treated. Stevie Wonders is a well-known musician who suffered from severe RoP. Back in the 1950’s, doctors were recently realizing that oxygen could be used to save premature babies. However, it took them additional years to figure out that excess dosage of oxygen would cause vessels in the eye grow irregularly. Premature babies with this condition and excess oxygen treatment would suffer from lifelong blindness.

World Health Organization (WHO) estimates that, out of the 130 million babies born annually, around 15 million babies are born prematurely, before 37 completed weeks of gestation. Approximately 1 million children die each year due to complications of preterm birth. Many of the survivors face a lifetime disability, both visual and hearing problems, as well as learning disabilities. Among these issues, retinopathy of prematurity (RoP) is a leading and serious cause of disability. Retinopathy of Prematurity (RoP) was first reported by Terry [11] in 1942 as a developmental, vascular, and proliferative retinal disorder occurring in the premature newborns’ retinas that have not completed vascularization. Along with cortical blindness, RoP is among the most common causes of childhood blindness in the world. The seriousness of RoP intensifies with lower birth weight and lower gestational week, and various risk factors are reported relating to the development of RoP. If severe RoP is untreated, it causes bliness with retinal detachment. Thus, it is very important to diagnose early and use appropriate treatment to prevent the progression of the disease International Classification for Retinopathy of Prematurity (ICROP) is used to classify the progression and seriousness of the disease. Classification starts with 1st level as the lightest diagnosis of RoP and ends with 5th level, retinal detachment, as the heaviest outcome of RoP.

The clinical data for our analysis was collected by the Newborn Clinic of Zeynep Kamil Woman and Child Diseases Hospital in Istanbul between 2011 and 2014. Every year in Turkey, around 150 000 babies are born with birthweights below 1500g. These newborns have a higher tendency to be diagnosed with severe RoP. We will investigate the risk factors that are thought to cause or to be correlated with severe RoP. As we improve our model of prediction, we will observe how the accuracy of our interpretable model increases as we combine numerical and categorical values and add further interaction terms.

ROP is a serious morbidity of prematurity, whose incidence and severity increase with decreasing GA and BW. Studies conducted in high-income countries have shown that infants born at ≥32 weeks are not at risk for developing ROP and most infants born at >28 weeks who develop ROP have a mild disease that spontaneously regressed without treatment.9 The findings of the TR-ROP study were comparable to those from other developing countries and showed that more mature and heavier babies were at risk for severe ROP.10

There were no differences in any ROP and severe ROP development between VLBW infants of refugees and citizens in our study. The Ministry of Health of Turkey has been involved in direct healthcare services in the refugee camps and through the referral of refugees to Turkish hospitals. The 2015 report of the Turkish Neonatology Society reported a mortality rate of 26% for babies with a BW<1500 g, according to data obtained from 59 NICUs.11 However, there were insufficient data on the neonatal mortality of refugees in this report.

GA, BW and oxygen therapy are well-known major risk factors in the development of ROP.12 In this study, a lower BW, shorter GA and total days on oxygen were found as independent risk factors for severe ROP in infants with a BW≤1500 g and for any ROP in infants with a BW>1500 g.

Some previous studies have reported that the prevalence of ROP was higher in SGA infants compared with appropriate for GA preterms, while SGA was not found to be a risk factor for ROP in other reports.13 14 Factors that are considered an increased risk for severe ROP in SGA babies include chronic uterine hypoxia, abnormal growth factor levels, nutrient restriction and antioxidant deficiency.15 However, in our study, SGA was surprisingly associated with a decreased incidence of severe ROP in VLBW infants when using a multivariate logistic regression model.

There was a relationship between poor postnatal weight gain and an increased risk for ROP.16 Poor postnatal weight gain was also found as an independent risk factor for severe ROP in infants with a BW≤1500 g in our study. Using univariate analyses, several risk factors including RDS, respiratory support, sepsis, NEC, PDA, intracranial haemorrhage and BPD were significantly associated with severe ROP in VLBW infants in our cohort. These perinatal morbidities may have decreased postnatal weight gains.

This study showed that RBC transfusions had strong effects on the development of ROP. Transfusions may increase oxygen delivery to the retina because of the lower oxygen affinity of adult haemoglobin in packed red cells. Repeated transfusions may also cause free iron accumulation, which may result in increased production of free hydroxyl radicals as assessed by the Fenton reaction, resulting in damage to the retina.17 Although the role of blood transfusions as a risk factor for ROP was suggested by numerous reports,18 19 several studies have reported that a transfusion limitation policy did not reduce the prevalence of ROP.20 Our data suggested that limiting blood transfusion in regards to threshold haemoglobin values in guidelines could contribute to reducing the prevalence of ROP.

Multiple studies have reported the role of neonatal sepsis in the development of ROP.21 22 In this study, late onset sepsis was an independent risk factor for severe ROP in VLBW infants. Sepsis may act through cytokines and endotoxins, which directly affect retinal angiogenesis. This process is frequently accompanied by hypotension, which can cause tissue perfusion impairment and retinal ischaemia.23

Treatment was performed in 6.7% of the infants screened for ROP in the current study. In nearly half of the infants with severe ROP, the treatment modality involved laser photocoagulation and IVB was performed in the other half as the first choice. A nationwide population-based study from the UK reported that diode laser photocoagulation was performed in 90.5% of infants requiring treatment.1 The higher usage of IVB in our study may be due to ease of administration (typically at the bedside). In addition, paediatric anaesthesia for performing laser photocoagulation was not available in some NICUs in our study.

Notably, 66 (16%) of 414 infants were treated earlier than type 1 ROP and did not fulfil the ETROP requirements for treatment in our study. Twenty-six of these 66 infants were treated with IVB. The popularity of anti-VEGF agents is increasing in Turkey; however, the long-term safety and efficacy of these agents are still not definitively known. The risk of progression to retinal detachment in type 1 ROP is around 15%, but is much lower with less severe disease.8 Evidence-based data are not available to confirm a favourable risk–benefit ratio of IVB usage in cases earlier than type 1 ROP.

In our study, the incidence of severe ROP varied between the three types of NICU which reflects the differences in neonatal care. The rates of severe ROP were lower in university hospital NICUs, where practices for newborn care are likely to be better than non-university NICUs. Based on the results of present study, the screening criteria for ROP need to be wider in state and private hospitals than applied in the university hospitals. ROP programmes in Turkey should adopt the criteria of <1700 g or ≤34 weeks to capture all babies requiring treatment.

The strength of the TR-ROP study was that it was a large multicentre cohort study that allowed us to prospectively obtain data via a special network. However, the neonatologists did not go through any training in order to standardise definitions of potential risk factors before the study started. Similarly, the participating ophthalmologists also did not undergo any processes to standardise how they graded ROP. These situations are the limitations of the study.

In conclusion, screening criteria for ROP in Turkey needs to be wider than developed countries. The high incidence of infants with ROP in our study emphasised the need for aggressive measures for prevention and control of the disease. The safe implementation of oxygen therapy with appropriate monitoring, better antenatal and neonatal care, meticulous attention to hygienic procedures and control of sepsis may reduce the prevalence of ROP. Therefore, monitoring standards of neonatal care and conducting quality improvement projects across the country are essential for improving neonatal outcomes in Turkish NICUs.