

Anexa nr. 2 la H.S. nr. 160/17740/26.07.2023

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# **PHD THESIS**

**A COMPARATIVE STUDY ON THE PROGNOSIS OF  
MECHANICALLY VENTILATED TERM AND PRETERM NEONATES.**

**A B S T R A C T**

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**Timișoara**

**2024**

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# **STUDY 1: EFFECT OF NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE ON RETINOPATHY OF PREMATURITY IN PRETERM NEWBORNS: A COMPARATIVE ANALYSIS WITH MECHANICAL VENTILATION AND HIGH-FLOW NASAL CANNULA THERAPY**

## **BACKGROUND**

The introduction of mechanical ventilation in the management of neonatal respiratory disorders has been a remarkable progression in the field of neonatology, significantly improving the chances of survival among newborns. However, it's essential to recognise that mechanical ventilation can potentially initiate cerebral damage through a local inflammatory process, primarily attributed to haemodynamic instability leading to neurological, pulmonary, and ophthalmological complications. These complications underline the need for careful consideration and monitoring when utilizing mechanical ventilation in neonatal care.

The risk of developing retinopathy of prematurity (ROP) is extensively documented in connection with the use of mechanical ventilation, but it has been found that nasal continuous positive airway pressure (nCPAP) can reduce this risk. However, there is limited data available on the correlation between nCPAP and ROP. Some reports indicated that there is no significant difference in the risk of ROP between nCPAP and high-flow nasal cannula (HFNC). The existing literature does not unequivocally specify which ventilation method carries the highest risk for developing ROP. Therefore, to assess the best benefit-to-risk ratio, clinicians need a clearer understanding of the risks associated with each intervention, including their impact on ROP.

This study aims to investigate the relationship between the occurrence of ROP and the management of preterm infants using mechanical ventilation, nCPAP, and HFNC. To do it, has been conducted a non-randomized controlled trial involving a no-ventilation group and three intervention groups: MV, nCPAP, and HFNC. Initially, the study performed univariate logistic regression, followed by multivariate logistic regression to consider all possible covariates in the dataset.

## **SUMMARY OF THE FINDINGS**

This study explores the incidence of retinopathy of prematurity associated with different modes of respiratory support of preterm infants. Other factors that may be associated with the etiology of retinopathy of prematurity were also studied along with mechanical ventilation,

including gender, gestational age, birth weight, APGAR score at 1 and 5 minutes, number of transfusions performed during the study period and hematologic parameters.

The study shows that at the univariate level, increased gestational age, birth weight, 1- and 5-minute Apgar scores, and day-1 hemoglobin (Hb), hematocrit (HCT), and red blood cell levels are linked to a reduced risk of retinopathy of prematurity. In contrast, male sex, transfusions, and nasal continuous positive airway pressure therapy are associated with an increased risk. In multivariate analysis, only BW remained as a protective factor and nCPAP as a risk factor, while mechanical ventilation and high-flow nasal cannula showed no significant associations with ROP.

MV, a known ROP risk factor, was not significantly associated with ROP at the univariate level, showing an odds ratio (OR) of 1.942 (95% CI, 0.948-3.978; P=0.07). The results suggest that a larger sample might reveal a significant association. HFNC, also linked to ROP in prior studies, showed no significant relationship with ROP, having an OR of 1.314 (95% CI, 0.524-3.297; P=0.560).

**Table 1. Multivariate binary logistic regression analysis results showing the associations between different interventions or various factors and ROP**

Characteristics	AOR (95% CI)	P value
Sex, male/female	2.646 (0.955–7.326)	0.061
GA	1.169 (0.874–1.564)	0.293
BW	0.998 (0.996–0.999)	<0.05
Apgar score at 1 min	0.775 (0.500–1.201)	0.254
Apgar score at 5 min	0.782 (0.398–1.537)	0.476
Hb at 1 day of life	0.764 (0.373–1.565)	0.462
HCT at 1 day of life	1.017 (0.776–1.333)	0.901
RBC count at 1 day of life	1.810 (0.354–9.264)	0.476
Transfusions, yes/no	2.413 (0.874–6.667)	0.089
nCPAP therapy, yes/no	7.264 (2.622–20.120)	<0.001

The multivariate analysis identified nCPAP, with an adjusted odds ratio (AOR) of 7.264 (95% CI, 2.622-20.120; P<0.001), as the sole risk factor, despite its low recognition in previous

studies. Some studies even suggest nCPAP reduces retinal pathologies. The high ROP risk indicated by nCPAP's 7-fold increase corresponds to a wide confidence interval, due to the relatively small sample size (table 1).

The study findings provide a novel perspective on the relationship between ventilation and ROP. While literature commonly associates MV and HFNC with ROP, our study highlights nCPAP as having the strongest correlation with ROP incidence, contrary to MV and HFNC. This result is unexpected given a recent systematic review where meta-analysis of three studies found no significant difference in ROP risk between nCPAP and HFNC.

## **CONCLUSIONS**

After conducting a multivariate regression analysis, it was found that only birth weight and nCPAP therapy were significantly associated with ROP. The results showed that higher birth weight was weakly protective against ROP, while nCPAP therapy was identified as a strong risk factor for ROP. Additionally, it was observed that mechanical ventilation and high flow nasal cannula were not associated with an increased risk of ROP.

## **STUDY 2. PREDICTING RETINOPATHY OF PREMATURE RISK USING PLASMA LEVELS OF INSULIN-LIKE GROWTH FACTOR 1 (IGF1), TUMOR NECROSIS FACTOR-ALPHA (TNF-ALPHA), AND NEONATAL PARAMETERS**

### **BACKGROUND**

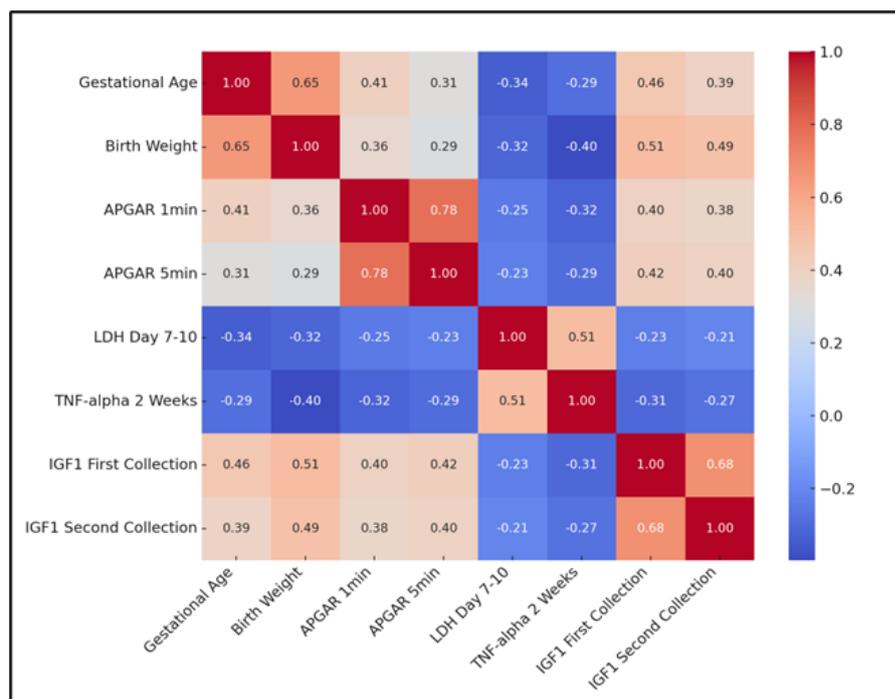
Retinopathy of Prematurity (ROP) is a major global public health issue, causing childhood blindness, especially in premature neonates. The disease is complex and involves genetic, metabolic, and environmental factors. The use of oxygen treatment and respiratory support is crucial in the development process. The rise in ROP occurrence has led to the need for early detection of predictive indicators. Insulin-like Growth Factor 1 (IGF1) and Tumor Necrosis Factor-alpha (TNF-alpha) are important indicators in ROP development due to their role in angiogenesis and inflammation. Understanding the correlation between IGF1 and TNF-alpha and ROP onset and progression could revolutionize management and treatment strategies. Other biological markers, such as Lactate Dehydrogenase (LDH), Creatine Phosphokinase (CPK), and glucose levels, also suggest metabolic disruption in premature neonates. The study aims to establish a relationship between IGF1 and TNF-alpha levels and ROP risk in preterm infants with respiratory distress syndrome that are being treated with different respiratory supports.

### **SUMMARY OF THE FINDINGS**

This study identifies key laboratory parameters and biochemical markers linked to different severity levels of retinopathy of prematurity (ROP), shedding light on factors influencing its progression and risk. The findings on lactate dehydrogenase (LDH), glucose, TNF-alpha, and IGF1 levels enhance our understanding of ROP development. Notably, LDH levels, particularly between days 7-10 post-birth, were significantly higher in neonates with ROP, especially in those with Grade III ROP, suggesting LDH as a marker of cellular stress or damage. The investigation into TNF-alpha levels revealed higher levels in ROP groups, particularly on the first day of life and at two weeks, underscoring the role of inflammation in ROP pathogenesis. The analysis of IGF1 revealed consistently lower levels in neonates with retinopathy of prematurity (ROP), underscoring its protective role against the disease. This highlights the importance of IGF1 in vascular development and neonatal growth, suggesting that increasing IGF1 levels could help prevent or reduce the severity of ROP. The study emphasizes the predictive value of IGF1 and TNF-alpha levels in ROP development.

Statistical data showed significantly lower IGF1 levels in ROP cases (61.4 ng/mL for any ROP vs. 91.6 ng/mL for no ROP), consistent with literature linking low serum IGF1 to severe ROP outcomes. These findings are clinically relevant for enhancing risk assessment and early intervention strategies for preterm neonates at risk of ROP by evaluating IGF1 levels. Moreover, the strong association between TNF-alpha levels and ROP severity indicates the crucial role of inflammation, suggesting potential therapeutic interventions to reduce inflammation. Insulin-like Growth Factor 1 (IGF1) levels at two intervals were protective against ROP, with beta coefficients of 0.37 ( $p = 0.0032$ ) and 0.32 ( $p = 0.0028$ ), indicating reduced ROP risk with higher IGF1 levels. Sensitivity and specificity analyses show TNF-alpha and IGF1 as effective predictive biomarkers for ROP in premature neonates, each with an AUC (Area under the curve) of 0.616. The optimal thresholds were 24.9 pg/mL for TNF-alpha and 31.1 ng/mL for IGF1, with both markers demonstrating high sensitivity (88.2%) but lower specificity (63.7%) in identifying ROP (figure 1).

**Figure 1. Correlation matrix**



## **CONCLUSIONS**

The study found significant correlations between lower gestational age, high levels of lactate dehydrogenase (LDH), elevated TNF-alpha levels, and an increased risk of developing ROP. Conversely, high levels of IGF1 were associated with a reduced risk of ROP, while elevated TNF-alpha levels were linked to a higher risk. The study highlighted the potential of biomarkers such as IGF1 and TNF-alpha to serve as predictive indicators for ROP, providing opportunities for early intervention and improved management strategies in neonatal care.

### **STUDY 3. PREDICTIVE VALUE OF NEUTROPHIL-TO-MONOCYTE RATIO, LYMPHOCYTE-TO-MONOCYTE RATIO, C-REACTIVE PROTEIN, PROCALCITONIN, AND TUMOR NECROSIS FACTOR ALPHA FOR NEUROLOGICAL COMPLICATIONS IN MECHANICALLY VENTILATED NEONATES BORN AFTER 35 WEEKS OF GESTATION**

#### **BACKGROUND**

Mechanical ventilation is crucial in neonatology, providing essential respiratory support to newborns with insufficient pulmonary function. While necessary, this intervention is associated with potential complications due to the delicate nature of the infant respiratory system and the risks of invasive support. Although mechanical ventilation has revolutionized the treatment of critically ill neonates, it is not without challenges and risks, particularly regarding neurological complications.

Neonates may experience neurological issues such as hypoxic-ischemic encephalopathy, intraventricular hemorrhage, and periventricular leukomalacia, which can significantly impact long-term neurodevelopmental outcomes. The pathophysiology of these complications involves multiple mechanisms, including oxygen toxicity, direct mechanical effects, and systemic inflammation. It is essential for healthcare professionals to identify newborns at high risk for neurological issues to develop targeted interventions that may reduce this risk. In this context, the neutrophil-to-monocyte ratio (NMR), lymphocyte-to-monocyte ratio (LMR), and inflammatory biomarkers such as C-reactive protein (CRP), procalcitonin, and tumor necrosis factor alpha are potential methods for early identification of at-risk neonates. These markers provide insights into the neonate's inflammatory state and immune response, which are closely linked to.

#### **SUMMARY OF THE FINDINGS**

This study illuminates the complex relationship between neonatal physiological responses to stress and infection and their potential to predict neurological complications in mechanically ventilated neonates. Although initial 24-hour measurements did not show statistically significant results across all parameters, there were indications of higher CRP and procalcitonin levels in neonates with neurological complications. While these trends did not reach conventional statistical significance, they suggest an underlying inflammatory response that may be more pronounced in at-risk neonates, as observed in adult patients.

By the 72-hour mark, CRP and procalcitonin levels reached statistical significance, along with increased white blood cell and neutrophil counts, indicating a more pronounced

inflammatory response. This suggests that these markers could indicate neurological complications beyond the first few hours of life, allowing for predictive intervention.

The significant findings regarding neutrophil-to-monocyte ratio (NMR) and lymphocyte-to-monocyte ratio (LMR) support their inclusion in routine neonatal screenings. Notably, an NMR above its optimal cutoff had a hazard ratio of 2.16, indicating neonates with elevated NMR values were more than twice as likely to develop neurological complications. This association had a 95% confidence interval of 1.18 to 4.09 and a p-value of 0.022, underscoring NMR as a robust predictive marker. Similarly, an elevated LMR showed a hazard ratio of 1.94, indicating nearly double the risk of neurological complications for neonates with high LMR values (p-value = 0.008).

TNF-alpha emerged as a reliable indicator of neurological complications in the early neonatal period. After all the analysis were finished, TNF-alpha exhibited the most substantial hazard ratio of 3.32, indicating that neonates with TNF-alpha levels above the optimal cutoff were over three times more likely to develop neurological complications, with a 95% confidence interval of 2.06 to 6.39 and a highly significant p-value of less than 0.001 (table 2).

These biomarkers could be used in real-time to guide clinical decisions for monitoring and managing neonates at risk of neurological complications. The goal is to improve outcomes for mechanically ventilated neonates.

**Table 2. Regression analysis for neurological complications development**

Factors above the best cutoff	Hazard Ratio	95% CI	P-value
CRP	1.41	1.06–4.81	0.030
Procalcitonin	1.30	0.94–3.17	0.093
NMR	2.16	1.18–4.09	0.022
LMR	1.94	1.32–4.26	0.008
TNF-alpha	3.32	2.06–6.39	<0.001

## CONCLUSIONS

This study indicates that TNF-alpha and the neutrophil-to-monocyte ratio (NMR) can effectively predict neurological complications in newborns undergoing mechanical ventilation. When assessed within the first 72 hours after birth, these markers are crucial for early identification of high-risk infants. Their common use and accessibility in clinical settings make them practical for widespread application.

Incorporating these biomarkers into regular assessments can enhance intervention strategies, potentially preventing or mitigating neurological complications. This proactive approach reflects a shift towards personalized medicine in neonatal care, where tailored interventions based on individual biomarker profiles can improve neurodevelopmental outcomes. The findings underscore the need for advanced biomarker monitoring in standard neonatal care protocols, promoting more detailed and preemptive management strategies for newborns in critical care.