

Title: Association of urine output, lactate and mean arterial pressure in the transitional period with 2 years outcomes in Very Low Birth Weight Infants.

Abbreviated Title: Hemodynamics & 2-Year Outcomes in VLBW Infants

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Contributions

Junior, L.K.O.: original idea, data collection, writing.

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Carmona, F: orientation, revision.

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Abstract:

Objective: This retrospective cohort study aimed to investigate the association between hemodynamic parameters and long-term outcomes, including weight, height, and neuropsychomotor development, in very low birth weight (VLBW) infants.

Study Design: A total of 91 VLBW infants born between 2016 and 2017 were included in the analysis. Hemodynamic parameters, including urine output, lactate levels, and mean arterial pressure, were measured in the first three days of life. Weight and height were assessed at two years of age, and neuropsychomotor development was evaluated using DENVER II.

Results: The results showed that the lowest mean arterial pressure on the first day of life exhibited a moderate correlation with weight and height at two years. Similarly, the lowest mean arterial pressure on the second day of life demonstrated a weak correlation with height at two years. However, no significant correlations were found between other hemodynamic parameters, including urine output and lactate levels, and weight, height, or neuropsychomotor development at two years of age.

Conclusion: Our findings suggest that lower mean arterial pressure on the first and second days of life in VLBW infants may be associated with reduced weight and height at two years of age. However, no significant correlations were observed between other hemodynamic parameters and weight, height, or neuropsychomotor development. Further research is warranted to explore additional factors that may influence long-term outcomes in this population.

Keywords:

Infant, Very Low Birth Weight, Hemodynamics, Urine Output, Lactate, Blood Pressure, Growth, Neurodevelopment

Introduction

In recent years, there has been increasing interest in assessing the impact of hemodynamic instability on clinical outcomes in very low birth weight (VLBW) infants. Traditional clinical indicators have shown limited ability to reliably guide management and improve outcomes in this vulnerable population¹. Therefore, there is a need to identify reliable markers that can effectively support clinical decision making and improve long-term outcomes in VLBW infants.

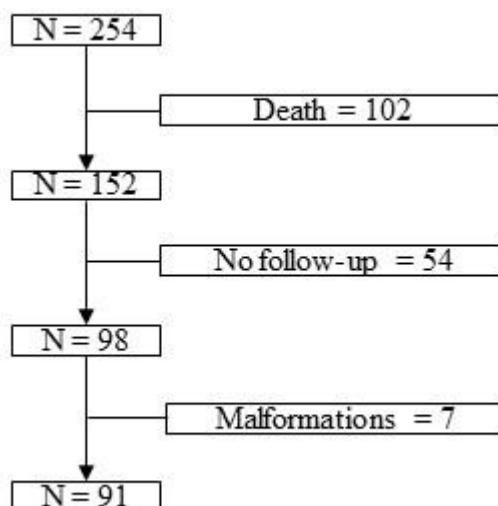
Our previous study focused on investigating the association of urinary output (UO), arterial lactate levels (LL), and lactate clearance with hemodynamic instability and mortality in VLBW infants during the transitional period². The transitional period represents a critical phase in the neonatal period when the infant undergoes significant physiological and hemodynamic changes³. Building on the findings of our previous research, the present study aims to assess the relationship between haemodynamic parameters and long-term outcomes in our previous cohort of VLBW infants. By extending our investigation beyond the transitional period, we aimed to provide a comprehensive understanding of how haemodynamic status during this critical period may influence outcomes of VLBW infants at 2 years.

The outcomes examined in this study, namely weight, height, and neuropsychomotor development at two years of age, have significant implications for the overall well-being and quality of life of VLBW infants. Understanding the relationship between these long-term outcomes and hemodynamic parameters such as UO, LL, and arterial pressure may provide valuable insight into the early identification and treatment of infants at risk for adverse outcomes.

Methods

This retrospective cohort study included a total of 254 very low birth weight (VLBW) infants born between 2016 and 2017. Of these, 102 infants had documented mortality, 54 infants were lost to follow-up and 7 infants had congenital malformations. The final sample size for analysis consisted of 91 VLBW infants who were assessed for long-term outcomes (Figure 1)

Urine was measured by weighing diapers or urinary catheter (as indicated by the attending physician) on a high-precision scale (SHIMADZU model



BL320H). Blood pressure was measured non-invasively. Lactate was measured in a Coda 221 Roche as indicated by the attending physician, with blood drawn in syringes coated with lithium heparin.

Outcomes of interest included weight and height, which were measured between 1 year and 11 months and 2 years and 6 months. Neuropsychomotor development was assessed using the Denver Developmental Screening Test II (DENVER II). The DENVER II evaluation was conducted by a trained psychologist and the assessment was done at or as close to 2 years of age as possible.

Statistical analyses were performed to determine correlations between haemodynamic parameters and long-term outcomes. Pearson correlation coefficient was calculated for variables with symmetrical distribution, Spearman correlation coefficient for variables with asymmetrical distribution and logistic regression was used for categorical independent variables. The significance level was set at $p < 0.05$. The software used was RStudio 2023.03.0 Build 386. Results

The study included a cohort of very low birth weight (VLBW) infants with a mean gestational age of 29.6 weeks (SD +/- 2.67) and a birth weight of 1091.6 g (SD +/- 258.2). Mean urine output was 3.46 ml/kg/hour on day one (SD +/- 1.64), 3.94 ml/kg/hour on day two (SD +/- 1.29) and 3.54 ml/kg/hour on day three (SD +/- 1.04). The mean lactate level was 4.8 (SD +/- 3.4) on the first day, 3.33 (SD +/- 2.1) on the second day and 2.69 (SD +/- 1.32) on the third day. The mean lowest blood pressure was 30.6 (SD +/- 7.41) on the first day, 32.89 (SD +/- 6.68) on the second day, and 36.43 (SD +/- 9.33) on the third day.

At two years of age, the mean weight was 10.56 kilogrammes (SD +/- 1.58) and the mean height was 82.48 centimetres (SD +/- 4.55). The mean age at which weight and height were measured was 2.03 years (SD +/- 0.14). Of the 91 infants, 29 showed some delay in neurological development as determined by DENVER II.

Correlation analysis showed that the lowest mean arterial pressure on the first day of life had a moderate correlation with weight and height at two years of age. Similarly, the lowest mean arterial pressure on the second day of life showed a weak correlation with height at two years of age. However, no significant correlations were found between other haemodynamic parameters, including urine output and lactate levels, and weight, height or neuropsychomotor development at two years of age (Table 1)

diurese1	peso	-0.01640702	0.8773
diurese1	comprimeto	0.09656923	0.3675
diurese2	peso	-0.03254364	0.7594
diurese2	comprimeto	0.09656923	0.1934
diurese3	peso	0.08388969	0.08388969
diurese3	comprimeto	0.08388969	0.4041
lactato1	peso	-0.1752028	0.1354
lactato1	comprimeto	-0.1267998	0.2817
lactato2	peso	0.02619341	0.8439
lactato2	comprimeto	0.1569819	0.2351

lactato3	peso	-0.1312866	0.3738
lactato3	comprimento	-	0.9778
PA1	peso	0.2900297	0.0116*
PA1	comprimento	0.0116	0.04201*
PA2	peso	0.2291279	0.06018
PA2	comprimento	0.2512774	0.03874*
PA3	peso	0.08102547	0.4987
PA3	comprimento	0.0676689	0.5722
diurese1	ADNPM		0,736
diurese2	ADNPM		0,758
diurese3	ADNPM		0,889
lactato1	ADNPM		0,51
lactato2	ADNPM		0,627
lactato3	ADNPM		0,22
PA1	ADNPM		0,777
PA2	ADNPM		0,251
PA3	ADNPM		0,548

Table 1

Discussion

In the present study, we investigated the relationship between haemodynamic parameters and long-term outcomes such as weight, height and neuropsychomotor development in very low birth weight (VLBW) infants at two years of age. The results showed a moderate correlation between lowest mean arterial pressure on the first day of life and weight and height at two years of age, but no significant correlation was found between other haemodynamic parameters (such as urine output and lactate levels) and the outcomes studied.

A study conducted by Kim S et al (2023)⁴ analysed the growth patterns of preterm infants over two years based on birth weight and length percentiles. While this study provided insights into the growth patterns of preterm infants and emphasised the importance of growth monitoring, it did not examine the relationship between haemodynamic parameters and these growth outcomes. This highlights the unique contribution of our study in assessing the impact of haemodynamic parameters on weight and height.

It is also important to consider neuropsychomotor development. The study by Agarwal et al. (2023)⁵ examined neuropsychomotor outcomes in very preterm, very low birth weight infants at 2 years of age and identified risk factors associated with significant developmental delay or neurodevelopmental impairment (NDI). Importantly, this study identified hypotension requiring inotropes as a risk factor for delayed cognitive skills. However, Agarwal et al. focused on neurodevelopmental outcomes and did not analyse the effects on weight and height. This highlights the relevance of our study, which offers insights into the possible influence of haemodynamic parameters, including arterial pressure, on physical growth outcomes.

In addition, a study by Osborn et al (2007)⁶ sheds light on the relationship between low systemic blood flow and neurodevelopmental outcomes in preterm infants. The study found that early low superior vena cava flow in preterm infants was associated with increased mortality, morbidity and developmental impairment at 1 and 3 years of age. In particular, the study highlights the role of systemic blood flow and its management through inotropic support in influencing neurodevelopmental outcomes. This is particularly relevant to our findings as it emphasizes the importance of early haemodynamic management in preterm infants in ensuring better long-term neurodevelopmental outcomes.

However, it is important to acknowledge the limitations of this study. First, the retrospective nature of the study design limits the ability to establish causality between haemodynamic parameters and long-term outcomes. Furthermore, the high rate of loss to follow-up could introduce bias and affect the generalisability of the results. Furthermore, the relatively small sample size (N) could limit the statistical power to detect significant associations between variables. Future prospective studies with larger samples and a more comprehensive approach to reducing loss to follow-up are warranted to validate and build on the findings of this study.

Conclusion

In conclusion, understanding the interplay between haemodynamic parameters and long-term physical and neuropsychomotor outcomes in very low birth weight infants is critical for early intervention and optimised care. The findings underscore the importance of monitoring and managing blood pressure and other haemodynamic parameters from the early stages of life to promote not only physical growth but also neurological development.

1. Osborn DA. Clinical detection of low upper body blood flow in very premature infants using blood pressure, capillary refill time, and central-peripheral temperature difference. *Arch Dis Child Fetal Neonatal Ed.* 2004;89(2):168F - 173. doi:10.1136/adc.2002.023796
2. Junior LKO, Carmona F, Aragon DC, Gonçalves-Ferri WA. Evaluation of urine output, lactate levels and lactate clearance in the transitional period in very low birth weight preterm infants. *Eur J Pediatr.* 2021;180(1):91-97. doi:10.1007/s00431-020-03717-1
3. Wu TW, Azhibekov T, Seri I. Transitional Hemodynamics in Preterm Neonates: Clinical Relevance. *Pediatr Neonatol.* 2016;57(1):7-18. doi:10.1016/j.pedneo.2015.07.002
4. Kim S, Choi Y, Lee S, et al. Growth patterns over 2 years after birth according to birth weight and length percentiles in children born preterm. *Ann Pediatr Endocrinol Metab.* 2020;25(3):163-168. doi:10.6065/apem.1938180.090
5. Agarwal PK, Shi L, Rajadurai VS, et al. Factors affecting neurodevelopmental outcome at 2 years in very preterm infants below 1250 grams: a prospective study. *J Perinatol.* 2018;38(8):1093-1100. doi:10.1038/s41372-018-0138-3

6. Osborn DA, Evans N, Kluckow M, Bowen JR, Rieger I. Low Superior Vena Cava Flow and Effect of Inotropes on Neurodevelopment to 3 Years in Preterm Infants. *Pediatrics*. 2007;120(2):372-380. doi:10.1542/peds.2006-3398