European Society for Paediatric Research
Society for Pediatric Research
www.nature.com/pr

CLINICAL RESEARCH ARTICLE OPEN

Check for updates

Minute-by-minute systemic hemodynamic responses to packed red blood cell transfusion in extremely low gestational age neonates: a prospective cohort study

Aravanan Anbu Chakkarapani[1,2]✉, Asma Jamil[3], Zainab Awada[3], Phani Kiran Yajamanyam[1], Naharmal Soni[1], Sanoj Karayil Mohammad Ali[1], Kiran More[4], Venkat Kallem[5], Aisha Khalifa[3], Treesa Jilson[3] and Samir Gupta[1,6]

BACKGROUND: Packed red blood cell transfusion (PRBCT) is a common intervention for neonatal anemia, primarily guided by hemoglobin thresholds. Electrical velocimetry (EV) portable, non-invasive impedance cardiography tool, provides continuous systemic hemodynamics (SH) parameter measurements, offering valuable insights into the physiological effects of transfusions.
METHODS: This prospective, observational cohort study, conducted between May 2021 and October 2023, included 30 extremely low gestational age neonates requiring elective PRBCT during their neonatal intensive care unit stay. Using EV, 11 SH parameters were continuously recorded over 31 hours: 4 hours before, 3 hours during, and 24 hours after transfusion. The effect of transfusion on these parameters was assessed using ARIMA, paired t-tests and mixed linear models.
RESULTS: Of the 30 infants, 20 were <26 weeks gestation, and 10 were 26 + 0 to 27 + 6 weeks gestation. Index of cardiac contractility, stroke volume, and cardiac output decreased significantly post-transfusion ($p < 0.01$). Systemic vascular resistance increased significantly after transfusion compared to before transfusion ($p < 0.01$).
CONCLUSION: This pilot study detected significant hemodynamic changes in response to PRBCT, which, while notable, remained within normal physiological range. These findings underscore the need to better understand the physiological impact of PRBCT and the highlight role of non-invasive SH monitoring in optimizing neonatal care.

Pediatric Research; https://doi.org/10.1038/s41390-026-04805-y

IMPACT:

- This study is the first to apply Electrical Velocimetry (EV) for continuous, high-resolution monitoring of systemic hemodynamic (SH) parameters before, during, and after packed red blood cell transfusion (PRBCT) in extremely low-gestational-age neonates (ELGANs).
- The findings demonstrate measurable minute-by-minute fluctuations in cardiac contractility, stroke volume, cardiac output and vascular resistance temporally associated with transfusion. These fluctuations occurred even in infants who were hemodynamically stable at baseline, suggesting that EV may detect transfusion-related physiological variability not captured by routine monitoring, without implying a direct causal effect.
- Advanced monitoring technologies, such as EV, may enable more accurate and individualized neonatal care. To optimize outcomes for this vulnerable population and refine transfusion guidelines, further research including larger prospective studies and randomized controlled trials are needed.

INTRODUCTION

Globally, approximately 15 million babies are born preterm annually, accounting for one in ten births.[1] Among these, extremely low-gestational-age neonates (ELGANs), born before 28 weeks, are particularly susceptible to anemia of prematurity due to limited iron stores, reduced erythropoietin production, and cumulative phlebotomy losses during the first 4-8 weeks of life.[2,3] As a result, packed red blood cell transfusion (PRBCT) remains a common intervention (up to 90%) in this population, with international point-prevalence data highlighting substantial variation in transfusion thresholds and clinical triggers across neonatal intensive care units.[4] This variability underscores ongoing uncertainty regarding optimal transfusion practices in very immature infants.

The primary objective of PRBCT is to optimize oxygen delivery (DO_2) to tissues, improve hematocrit and Hb levels, reduce apnea

[1]Division of Neonatology, Sidra Medicine, Doha, Qatar. [2]Weill Cornell Medicine-Qatar, Doha, Qatar. [3]Research Department, Sidra Medicine, Doha, Qatar. [4]Division of Neonatology, MRR Children's Hospital, Mumbai, India. [5]Paramitha Hospital, Kompally, Hyderabad, India. [6]Durham University, Durham, UK. ✉email: aanbuchakk@sidra.org

Received: 27 April 2025 Revised: 7 January 2026 Accepted: 10 January 2026
Published online: 12 February 2026

episodes, and address potential adverse effects of anemia on cerebral oxygenation.[5–9] However, the cardiovascular effects of PRBCT remain uncertain, with some studies reporting negligible changes in cardiac function, while others suggest that transfusion may modulate the compensatory increases in cardiac output (CO) observed in anemic neonates.[10–12]

Electrical Velocimetry (EV), a non-invasive impedance cardiography technique, offers a novel approach to continuously monitor systemic hemodynamics (SH).[13,14] The ICON monitor (Osypka Medical, Berlin, Germany, and San Diego, CA) utilizes EV to analyze thoracic bioimpedance variations during the cardiac cycle, based on erythrocyte alignment during systole.[15–17] This technology provides real-time data on cardiac contractility, blood flow, vascular resistance, and fluid status.

Despite the availability of this advanced monitoring technology, evidence on minute-by-minute SH changes surrounding PRBCT in ELGANs remains scarce.[18,19] This pilot feasibility study aims to characterize minute-by-minute hemodynamic changes before, during, and after PRBCT in ELGANs using EV. The focus of this prospective, observational study is on describing high-resolution temporal associations in systemic hemodynamic parameters, rather than detecting specific abnormalities or implementing interventions. Our objective is not to infer causality, but to identify subtle hemodynamic fluctuations that may not be captured by standard bedside monitoring techniques.

METHODS

Study design

This prospective observational cohort study (Fig. 1) investigated the SH effects of PRBCT in ELGANs in a Level IV NICU. Ethical approval was obtained from the Institutional Research Ethics Board at Sidra Medicine (IRB No. 1513668), and informed written consent was provided by the parents. The study adhered to the STROBE guidelines to maintain high reporting standards.

Infants included in the study were those ELGANs who required elective PRBCT during their stay. Transfused PRBCs were typically fresher, with a storage age ranging from 14 to 28 days, depending on availability. However, specific storage age data and hematocrit (Hct) values were not recorded for this study. All transfusions adhered to institutional protocols, which included the use of the SAG-M (Saline, Adenine, Glucose, Mannitol) additive solution. The blood was universally irradiated to prevent Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD) and leukoreduced to reduce the risk of Transfusion-Transmitted Cytomegalovirus (CMV).

PRBCT was administered according to our institutional restrictive transfusion guidelines. Elective PRBC transfusion decisions were made by the treating attending physician based on hemoglobin (Hb) thresholds in combination with clinical indicators of anemia, such as increased oxygen requirements, recurrent apnea, tachycardia, or poor weight gain, consistent with restrictive transfusion practice. The specific transfusion thresholds used in our study are given in Supplementary Table S1A. Furosemide was not routinely administered before, during, or after transfusion, in line with our unit's conservative diuretic policy, unless clinical evidence of fluid overload was present. No infant in this study received furosemide in association with the transfusion.

Data collection

Data collection occurred between May 2021, and October 2023 including 30 preterm infants who received elective PRBCT at a standardized dose of 15 mL/kg over three hours. The study was divided into three phases: before-transfusion (4 hours), during transfusion (3 hours), and after-transfusion (24 hours).

Inclusion criteria were gestational age at birth less than 28 weeks and post-menstrual age up to 44 weeks, requiring elective PRBCT for clinical indications. Exclusion criteria included emergency blood transfusions, major congenital anomalies, and inability to tolerate adhesive skin electrodes.

Monitoring was conducted continuously for 31 hours using EV. The 31-hour monitoring period was chosen to provide a comprehensive view of the hemodynamic changes across the entire transfusion process. This duration allowed us to compare SH parameters before, during, and after transfusion, capturing both immediate hemodynamic responses and the sustained effects over time. The baseline phase of 4 hours provided enough time for stabilization before transfusion, while the 3-hour continuous monitoring during transfusion captured real-time changes. The subsequent 24-hour post-transfusion period enabled us to assess any delayed or sustained changes in SH parameters. Four neonatal electrodes (iSense, Osypka Medical) were placed on the left side of the forehead, right side of the neck, left anterior axillary line at xyphoid level, and left inner thigh respectively. Optimal EV signal sensitivity quality (SSI > 90%) was maintained by replacing or readjusting the leads throughout the study period. SH parameters were recorded in three phases: Before transfusion: 4 hours of baseline SH monitoring. During transfusion: Continuous monitoring over 3 hours. After transfusion: Monitoring continued for 24 hours to assess sustained effects. Demographic data, clinical characteristics, and SH parameters were captured throughout the study period.

Outcomes

The primary outcomes of this study focused on changes in SH, which were assessed through parameters related to cardiac contractility, blood flow, systemic vascular resistance (SVR), and fluid status.[20–22]

Cardiac contractility was evaluated using the Index of Contractility (ICON), which reflects the contractile strength of the heart. ICON is expressed as seconds^{-1} (sec^{-1}) and generally ranges from approximately 99.8 to 126.7. The pre-ejection period (PEP) represents isovolumic contraction time. PEP is measured in Milliseconds (ms) and generally ranges from approximately 45 to 75. The left ventricular ejection time (LVET) reflects the duration of systolic ejection and can serve as an indicator of cardiac function and loading conditions. LVET is measured in Milliseconds (ms) and generally ranges from approximately 125 to 185. The systolic time ratio (STR = PEP / LVET), defined as the ratio of PEP to LVET. STR generally ranges from approximately 0.30 to 0.45. The blood flow parameters included were stroke volume (SV), heart rate (HR) and CO. The SV measures the amount of blood ejected by the left ventricle per heartbeat. It is measured in mL/kg and generally ranges from approximately 1 to 2.5. The HR, reflects the number of beats per minute (bpm) and generally ranges from approximately 120 to 160. The CO is calculated as HR multiplied by SV (CO = HR×SV), representing the total blood volume ejected by the left ventricle per minute, Liters per minute (L/kg/min) and generally ranges from approximately 200 to 400. Systemic vascular resistance (SVR) (mean ± SD ~ 10,464 ± 6,615 dynes.seconds.cm^{-5}) was estimated using mean arterial pressure (MAP) and cardiac output (CO) with the formula: SVR = (MAP − CVP) × 80/CO. MAP was obtained through non-invasive blood pressure measurements via oscillometry, with an appropriately sized cuff (cuff width: arm circumference ratio = 0.50) placed on the right upper arm, or, if contraindicated (e.g., due to vascular lines or lesions), on another limb, in accordance with our routine care protocol. CVP (central venous pressure) was not directly measured in our study population. All measurements were performed on quiet babies lying supine, with the patient's position maintained throughout the measurement process.

Fluid-related parameters were also included, such as thoracic fluid content (TFC), which reflects an indicator of the amount of fluid in the thoracic cavity. TFC is measured in kilo-ohms reciprocal (kΩ^{-1}) and generally ranges from approximately 25 to 45. Stroke volume variation (SVV) is a dynamic parameter used to assess fluid responsiveness, calculated as the percentage variation in SV during the respiratory cycle. SVV measured in percentage (%) and generally ranges from approximately 10 to 27. The corrected flow time (FTC = FT/ $\sqrt{}$ RR) derived from the measured flow time (FT) and is corrected for the HR to account for variations in cardiac cycle length. FTC is measured in Milliseconds (ms) and generally ranges from approximately 250 to 450.

Statistical analysis

This is a pilot study, so no sample size calculations were performed. Baseline demographics and clinical characteristics were summarized as mean (SD), median (IQR), or frequency (percentage) as appropriate. The effects of PRBCT on SH parameters were analyzed using Auto-Regressive Integrated Moving Average (ARIMA) models, complemented by paired t-tests and mixed linear models. The ARIMA model accounted for autocorrelation, irregular patterns, and seasonality, making it particularly suitable for analyzing the time series data generated in this study. Data were averaged across the 30 infants for each SH parameter and normalized using inverse normal transformation. Following the methodology

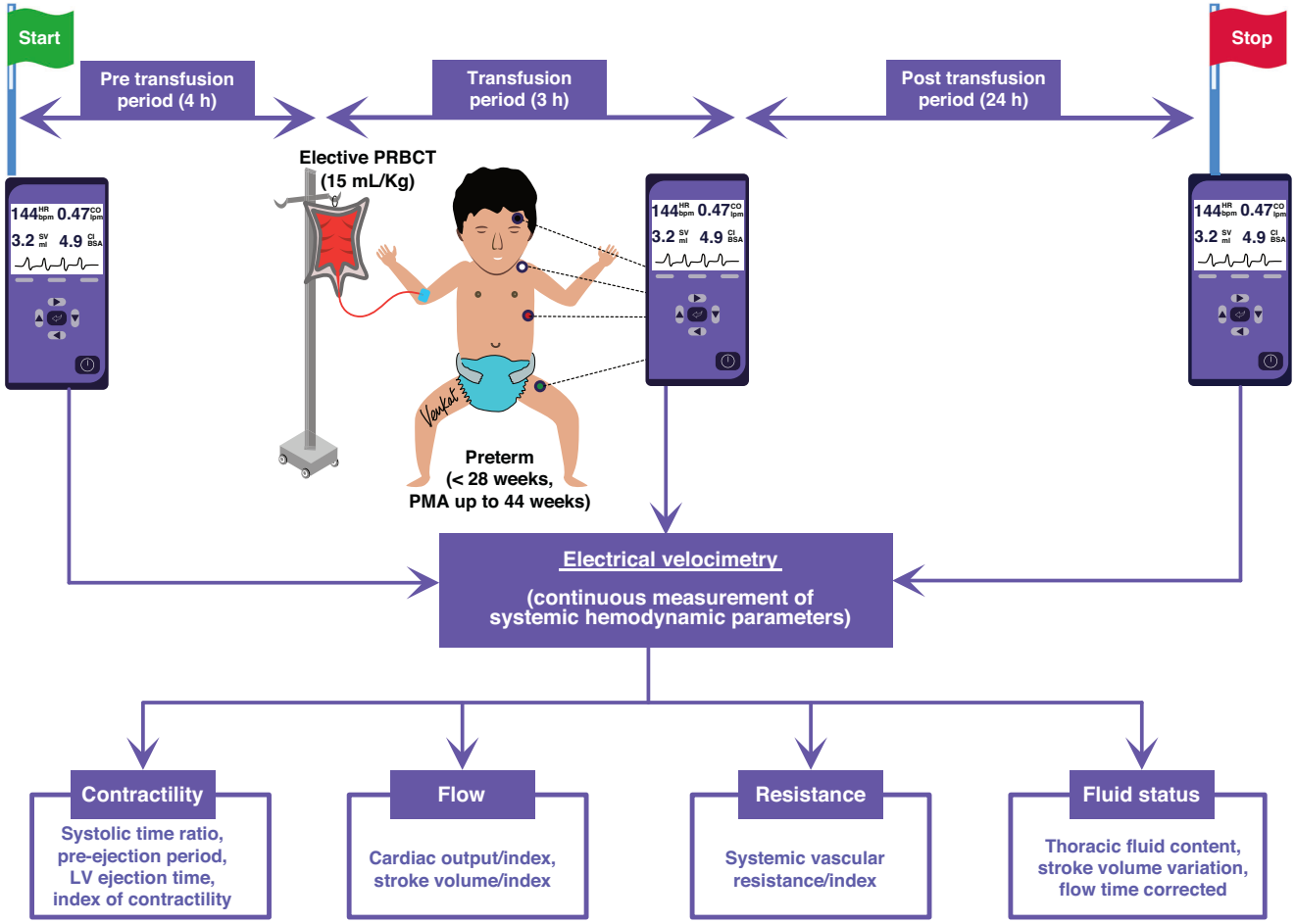

Fig. 1 Study design with systemic hemodynamic (SH) parameters. Electrical velocimetry device had four neonatal electrodes (iSense, Osypka Medical) which were placed on the left side of the forehead, right side of the neck, left anterior axillary line at xyphoid level, and left inner thigh or groin region.

described by Schaffer et al. in 2021, three transfusion-related effects were evaluated: step, pulse, and ramp. The transfusion initiation time was defined as "0," with all other time points calculated relative to this baseline. Step effects compared during and after- transfusion periods to before-transfusion period, pulse effects compared the during transfusion period to both before- and after-transfusion periods, and ramp (slope) effects assessed the change in the investigated parameter with time after transfusion.[23] Hence, all models tested for the interaction between intervention and time and evaluated the gradual change in outcome following intervention (ramp/slope). ARIMA models were optimized using the forecast package in R, with model selection based on minimizing autocorrelation in the residuals. All ARIMA models included autoregressive and moving average terms as covariates to address autocorrelation. Diagnostic evaluations of model residuals included temporal changes, autocorrelation, and distribution assessments, and the Ljung-Box test was used to evaluate autocorrelation in the residuals. The results were reported as effect coefficients with 95% confidence intervals (CI), with significance reported when the 95% CI excluded zero.

Sensitivity analysis was carried out by re-analysing the impact of intervention via paired t-tests and mixed linear models. For paired t-test, each SH parameter was averaged across the before, during, and after transfusion periods for each infant, and mean differences between before and during transfusion periods, as well as before and after transfusion periods, were tested. A Bonferroni-adjusted significance threshold of $p < 0.017$ was applied to account for the three comparisons performed for each parameter. For mixed linear models, the effect of transfusion (post *versus* pre) on systemic hemodynamic (SH) parameters was tested with adjustment of confounders, including PDA and mechanical ventilation, before and after removal of samples with inotropes and sepsis. The random effect of the sample was also included in the model.

RESULTS

Baseline demographics are presented in Table 1, and the clinical characteristics are presented in Supplementary Table S1,B. Time series analysis of 11 SH parameters over 31 hours is shown in Fig. 2, with individual changes in Supplementary Fig. S1.

The statistical analyses were performed for all parameters using ARIMA and paired t-tests (Table 2). The quality control metrics of the ARIMA model are mentioned in the Supplementary Figs. S2-S12. The data for these 11 SH parameters ranged from −452 and 2038 minutes and had no missing values, except for SVR, which had 0.3% missingness. Hb levels increased from 89.3 ± 10.1 g/L before transfusion to 120.5 ± 9.4 g/L after transfusion. The increase was statistically significant ($p < 0.01$). The SH parameters results are shown below.

Transfusion resulted in significant reductions in several contractility and flow parameters. ICON demonstrated a negative step change of −1.1 (95% CI: −1.7, −0.4), and paired t-tests confirmed significant decreases during and after transfusion compared with before ($p < 0.01$). SV showed a step change of −0.9 (95% CI: −1.4, −0.3) with a significant reduction post-transfusion ($p < 0.01$). CO decreased with a step change of −0.8 (95% CI: −1.2, −0.3), also showing a significant post-transfusion decline ($p < 0.01$). In contrast, PEP, LVET, STR, HR, TFC, SVV, and FTC showed no significant step, pulse, or slope changes, consistent with the nonsignificant paired analysis comparisons. SVR was the only parameter to increase significantly, with a step change of 1.2 (95% CI: 0.8, 1.6), supported by significant increases during and after transfusion ($p < 0.01$). The findings of mixed linear model are

Table 1. Baseline Demographics at the time of birth and at the study transfusion.

Baseline Demographics at birth	Overall		Group 1 (< 26 weeks GA)		Group 2 (26 to < 28 week)	
	Total ($n = 30$)	Percentage/mean ± SD/ median (Q3-Q1)	Total ($n = 20$)	Percentage/mean ± SD/ median (Q3-Q1)	Total ($n = 10$)	Percentage/mean ± SD/ median (Q3-Q1)
Female	11	36.7	8	40	3	30
Male	19	63.3	12	60	7	70
Gestational Age at birth (weeks)	30	24.9 ± 1.4	20	24 ± 0.8	10	26.6 ± 0.5
Birth Weight (grams)	30	796.9 ± 142.1	20	695 (825-645)	10	908 ± 144.3
Vaginal	14	46.7	10	50	4	40
C section	16	53.3	10	50	6	60
Singleton	21	70	14	70	7	70
Dichorionic Diamniotic Twins	9	100	6	100	3	100
Antenatal Corticosteroid x 1 dose given	14	46.7	8	40	6	60
Antenatal Corticosteroid x 2 dose given	16	53.3	12	60	4	40
Magnesium Sulphate given Yes	13	43.3	11	55	2	20
APGAR at 1 minute	29	4.8 ± 2.5	20	4.9 ± 2.3	9	4.7 ± 3.0
APGAR at 5 minutes	29	8 (8–7)	20	8 (8–7)	9	8 (8–5)
IUGR (Yes)	1	3.3	0	0	1	10
Chorioamnionitis (Yes)	5	16.7	5	25	0	0
Gestational Hypertension (Yes)	1	3.5	1	5.3	0	0
Gestational Diabetes (Yes)	5	17.2	3	15.8	2	20
At the time of transfusion						
Postnatal Age at the time of transfusion (days)	30	41.0 ± 22.7	20	38.4 ± 20.8	10	46.3 ± 26.7
Corrected Gestational Age at the time of transfusion (weeks)	30	30.7 ± 3.7	20	29.4 ± 3.2	10	33.4 ± 3.6
Weight at the time of transfusion (grams)	30	1281.8 ± 432.4	20	1158.7 ± 347.2	10	1528 ± 496.8
Any previous transfusion in NICU (Yes) prior to study transfusion	27	90	19	95	8	80
On Iron (Yes) prior study transfusion	6	20	5	25	1	10
Duration of transfusion in hours	30	3 (3.3–3)	20	3.1 (3.5–3)	10	3 (3.2–3)
Volume (ml/kg) of transfusion	30	15 (20–15)	20	15 (17.5–15)	10	16.5 ± 2.4

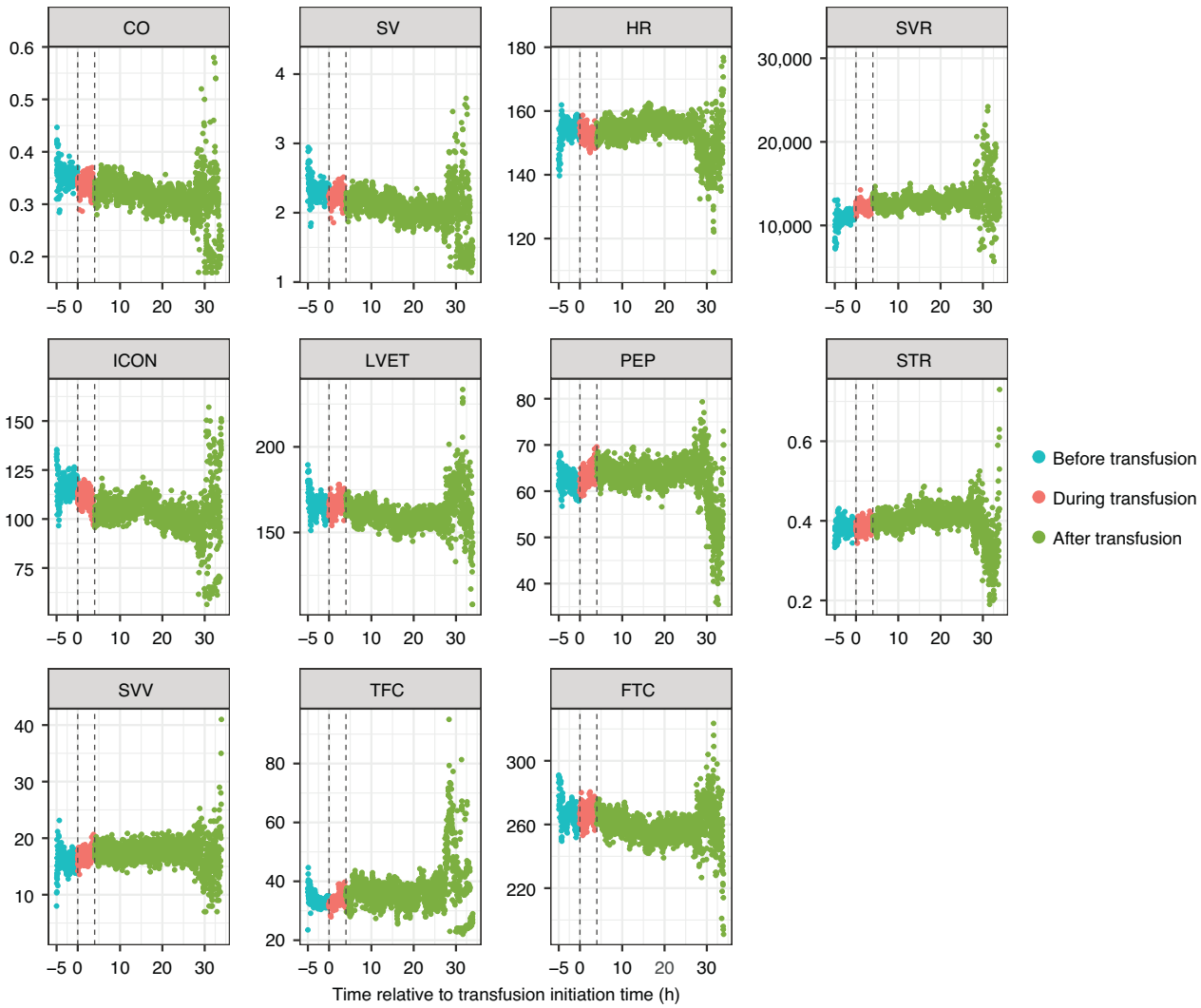

Fig. 2 Time series data for 11 SH parameters were averaged across 30 babies and plotted over study period (Auto-Regressive Integrated Moving Average (ARIMA) model). Time was calculated relative to the transfusion initiation time, and the dashed lines show the transfusion period between t = 0 (transfusion start time) and t = 4 h. (transfusion end time). The regression lines were derived from the regression model: Y = time + after transfusion time + transfusion status; whereby after-transfusion time is "0" before transfusion and is "time + 1" during and after transfusion.

shown in Supplementary Tables S2A and S2B, where ICON, SV, CO, and SVR were also found to be significant. The average values across time for 11 SH parameters before, during, and after PRBCT in each of the 30 samples analyzed by Auto-Regressive Integrated Moving Average (ARIMA) model complemented by paired t-tests is shown in Fig. 3.

DISCUSSION

PRBCT remains a cornerstone in the management of anemia of prematurity, particularly in ELGANs. This study introduces a novel application of EV for continuous, minute-by-minute monitoring of SH before, during, and after-transfusion phases. By evaluating SH across four domains, cardiac contractility, blood flow, vascular resistance, and fluid status, this work offers a comprehensive understanding of the physiological impacts of PRBCT in this vulnerable population.

Arterial oxygen delivery (DO_2), calculated as $DO_2 = CO \times CaO_2$, is a critical determinant of tissue oxygenation and depends on both CO and arterial oxygen content (CaO_2). CO is influenced by HR, SV, and factors such as preload, contractility, and afterload. In the context of PRBCT, optimizing DO_2 is essential to counteract the adverse effects of anemia and to meet the elevated metabolic demands of preterm infants. Although a substantial rise in Hb and a modest decrease in CO were observed, the overall impact on DO_2 is influenced by the combined effect of these competing factors. The increase in Hb would likely enhance CaO_2, thereby supporting oxygen delivery. However, the decrease in CO may reduce overall oxygen delivery despite the increase in Hb. These opposing effects underscore the need for precise hemodynamic monitoring to assess the net impact on oxygen delivery during transfusions. While the DO_2 equation provides a theoretical framework, we did not calculate or quantify DO_2 directly in this study due to the complex interplay of variables involved and the limitations of our observational design.

EV is a novel tool that has been validated for use in the NICU. A pilot study by Hsu et al. established hemodynamic reference data for neonates of varying ages and weights using EC.[20] Boet et al. further validated EV as a reliable tool for measuring SV and CO, showing strong correlations with echocardiography.[21] Additionally, a recent expert consensus by van Wyk et al. that while TEBT (Thoracic Electrical Bioimpedance Technology) is not

Table 2. Paired t-test analysis of systemic hemodynamic (SH) parameters.

SH Parameters	Before transfusion mean ± SD/ median (Q3-Q1)	During transfusion mean ± SD/ median (Q3-Q1)	After transfusion mean ± SD/ median (Q3-Q1)	p1	p2	p3
Cardiac Contractility						
ICON (sec^{-1})	107 ± 41.7	103.1 ± 41.4	98.1 ± 37.3	**<0.01**	0.3	**<0.01**
PEP (ms)	61 (58–66)	63 (59–69)	63 (60–71)	0.1	0.3	0.1
LVET (ms)	169.3 (152.5–177)	170.5 (145–182)	161.5 (148–173)	0.5	0.1	0.2
STR	0.4 (0.3–0.4)	0.4 (0.4–0.4)	0.4 (0.4–0.4)	0.6	0.3	<0.05
Blood Flow						
SV (mL/kg)	2.3 ± 0.9	2.3 ± 1	1.8 (1.6–2.8)	0.2	0.2	**<0.01**
HR (bpm)	154 ± 10	152.1 ± 9.8	153.4 ± 9.6	0.3	0.3	0.8
CO (L/kg/min)	0.4 ± 0.1	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.1	0.3	**<0.01**
Vascular Resistance						
SVR (dynes.seconds.cm^{-5})	10739 ± 4698	11677 ± 467	11971 ± 4461	**<0.01**	0.3	**<0.01**
Fluid Status						
TFC ($k\Omega^{-1}$)	29 (23–41)	28 (23–40)	27 (23–47)	0.5	0.2	0.2
SVV (%)	17 (13–19)	17 (14–20)	18 (15–20)	0.1	0.5	<0.05
FTC (ms)	271 (259.5–283)	278 (240–290)	263 (240–277)	0.7	<0.05	0.1

A) **Cardiac Contractility** measured through (i) ICON: Index of Contractility (sec^{-1}), (ii) STR: Systolic Time Ratio, (iii) PEP: Pre-Ejection Period (ms), (iv) LVET: Left Ventricular Ejection Time (ms),
B) **Blood Flow** measured through (v) SV: Stroke Volume (mL/kg), (vi) HR: Heart rate (bpm), (vii) CO: Cardiac Output (L/kg/min),
C) **Vascular Resistance** measured through (viii) SVR: Systemic Vascular Resistance **(dynes.seconds.cm^{-5})**.
D) **Fluid Status** measured through (ix) TFC: Thoracic Fluid Content ($k\Omega^{-1}$) (x) SVV: Stroke Volume Variation (%) (xi) FTC: Flow Time Corrected (ms).
p1 (during transfusion vs before transfusion), p2 (during transfusion vs after transfusion), p3 (after transfusion vs before transfusion). Presented as mean ± SD. Since two tests were performed for each health variable, an adjusted $p < 0.017$ (0.05/3) was considered significant. Significant p values are shown in asterisks.

recommended as an accurate determinant of absolute cardiac output, its value lies in tracking longitudinal hemodynamic changes in individual patients. This highlights the specific utility of EV in our study: to monitor dynamic, real-time responses to clinical intervention.[13]

Hemodynamic findings in context

Cardiac Contractility: This study found a transient decrease in ICON after transfusion, indicating a brief decline in myocardial performance, though ICON stayed within the normal physiological range. Other parameters remained stable, highlighting that ICON changes were isolated. These results align with Alkalay et al., who found no significant cardiac function change after PRBCT in premature infants.[24]

Blood Flow Dynamics: SV decreased significantly after transfusion, reducing CO despite a stable HR. These changes, though within normal physiological ranges, may reflect compensation for improved oxygen-carrying capacity. Similar trends were noted by Mansfield et al., with SV variability across devices.[25]

Vascular Resistance: The increase in SVR after transfusion likely compensates for elevated blood viscosity, maintaining perfusion pressure despite reduced SV and CO. Bisceglie et al.'s nomograms for preterm infants, with an average (mean ± standard deviation) SVR of approximately 10,464 ± 6,615 dyn.s.cm^{-5}, provides a useful reference point. Our observed post-transfusion SVR (~ 11,970 dyn.s.cm^{-5}) remains within this expected range, supporting the physiological plausibility of the observed changes in SVR in our study population.[22]

Fluid Status: Despite concerns about fluid overload, TFC and SVV remained stable during transfusion. Additionally, FTC did not show significant changes. These findings are consistent with recommendations from van Wyk et al., who emphasized the value of EV-derived fluid status parameters for longitudinal monitoring in neonatal care.[13]

Clinical Utility and Application: Based on current evidence, EV is most valuable not as a replacement for echocardiography but as a continuous surveillance tool for high-risk patients, such as the ELGANs in our cohort. Its ability to provide beat-to-beat data during each transfusion event allows for an individualized assessment of physiological tolerance, which is impossible with intermittent monitoring. The significant changes we observed in ICON, SV, and SVR post-transfusion underscore the potential for this technology to help clinicians tailor transfusion volumes and rates to an infant's specific hemodynamic response, rather than relying solely on hemoglobin thresholds. Furthermore, the non-invasive nature of EV means it can be operated by bedside nurses without requiring additional personnel, integrating smoothly into the existing clinical workflow once the initial sensor placement and setup are complete. A critical consideration in interpreting these results is the clinical complexity of the ELGAN population, where factors such as mechanical ventilation and PDA can independently influence hemodynamics. To address this, we performed a rigorous sensitivity analysis using linear mixed models to adjust for these potential confounders. Importantly, the significant post-transfusion decreases in ICON, SV, and CO, alongside the increase in SVR, remained statistically robust even after this adjustment and after excluding the few patients with sepsis or on inotropes (Supplementary Tables S2A and S2B). This strengthens our conclusion that the findings demonstrate measurable minute-by-minute fluctuations in cardiac contractility, stroke volume, cardiac output and vascular resistance temporally associated with transfusion. These fluctuations occurred even in infants who were hemodynamically stable at baseline, suggesting that EV may detect transfusion-related physiological variability not captured by routine monitoring, without implying a direct causal effect.

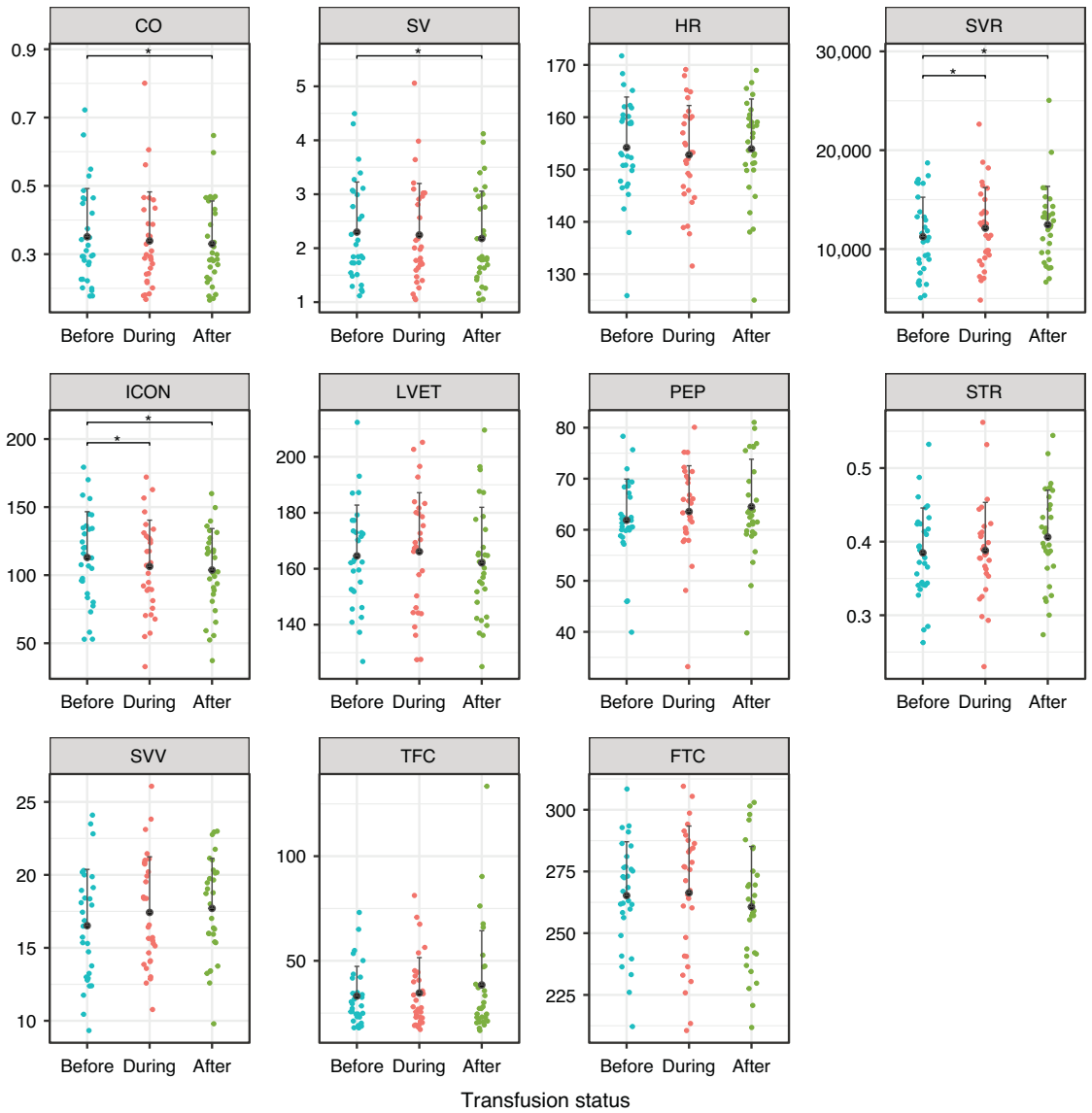

Fig. 3 The average values across time for 11 SH parameters before, during, and after PRBCT in each of the 30 samples analyzed by Auto-Regressive Integrated Moving Average (ARIMA) model) complemented by paired t-tests. Grey bars indicate mean + SD among the 30 samples. Significance of the difference in means between before and during transfusion and between before and after transfusion was evaluated by two-tailed paired t-tests. Since two tests were performed for each health variable, an adjusted $p < 0.017$ (0.05/3) was considered significant. Significant p values are shown in asterisks.

Limitations and Future Directions. This study's strengths include its focus on ELGANs, with continuous, high-resolution monitoring of 11 SH parameters. However, limitations include the small sample size, single-center design, and potential selection bias. While a formal cost-effectiveness analysis was beyond the scope of this pilot study, it is a critical consideration. Although no extreme preterm neonatal data exist, studies in adult and term neonatal populations suggest that continuous hemodynamic monitoring to guide therapy can be cost-effective.[13]

Most importantly, we strongly agree with the need for larger, more definitive trials. This observational study demonstrates the feasibility of using EV to capture critical hemodynamic data and provides the necessary foundation for a future randomized controlled trial (RCT). Such an RCT would be essential to determine if an EV-guided transfusion strategy improves clinical outcomes compared to the current standard of care. Integrating EV with other advanced monitoring tools, such as NIRS, could also offer deeper insight into the physiological effects of transfusions and help refine evidence-based clinical guidelines.

CONCLUSION

This pilot study suggests that significant hemodynamic changes in cardiac contractility (ICON), stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR) occur in ELGANs after PRBCT. While these changes are notable, they remain within the normal physiological range, emphasizing the need for individualized transfusion strategies beyond hemoglobin thresholds. Advanced non-invasive monitoring, such as EV, offers real-time, high-resolution data, potentially enabling more tailored neonatal care. Further research, particularly randomized controlled trials, is needed to validate these findings, establish EV-derived therapeutic thresholds, and ultimately improve outcomes for this vulnerable population.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Bellach, L. et al. Packed red blood cell transfusion in preterm infants. *Lancet Haematol* **9**, e615–e626 (2022).
2. Strauss, R. G. Anaemia of prematurity: pathophysiology and treatment. *Blood Rev* **24**, 221–225, https://doi.org/10.1016/j.blre.2010.08.001 (2010).
3. Villeneuve, A., Arsenault, V., Lacroix, J. & Tucci, M. Neonatal red blood cell transfusion. *Vox Sang*. **116**, 366–378 (2021).
4. Houben, N. A. M. et al. Red Blood Cell Transfusion in European Neonatal Intensive Care Units, 2022 to 2023. *JAMA Netw Open* **7**, e2434077 (2024).
5. Valieva, O. A., Strandjord, T. P., Mayock, D. E. & Juul, S. E. Effects of transfusions in extremely low birth weight infants: a retrospective study. *J Pediatr* **155**, 331–37 e1 (2009).
6. Westkamp, E. et al. Blood transfusion in anemic infants with apnea of prematurity. *Biol Neonate*. **82**, 228–232 (2002).
7. Franz, A. R. et al. Effects of Liberal vs Restrictive Transfusion Thresholds on Survival and Neurocognitive Outcomes in Extremely Low-Birth-Weight Infants: The ETTNO Randomized Clinical Trial. *JAMA*. **324**, 560–570 (2020).
8. Holzapfel, L. F., Rysavy, M. A. & Bell, E. F. Red Blood Cell Transfusion Thresholds for Anemia of Prematurity. *Neoreviews* **24**, e370–e376 (2023).
9. Kirpalani, H. et al. Higher or Lower Hemoglobin Transfusion Thresholds for Preterm Infants. *N Engl J Med*. **383**, 2639–2651 (2020).
10. Bifano, E. M., Smith, F. & Borer, J. Relationship between determinants of oxygen delivery and respiratory abnormalities in preterm infants with anemia. *J Pediatr* **120**, 292–296 (1992).
11. Fredrickson, L. K. et al. Acute physiological effects of packed red blood cell transfusion in preterm infants with different degrees of anaemia. *Arch Dis Child Fetal Neonatal Ed* **96**, F249–F253 (2011).
12. Ibonia, K. T. et al. Blood transfusions in preterm infants: changes on perfusion index and intermittent hypoxemia. *Transfusion* **58**, 2538–2544 (2018).
13. Van Wyk, L. et al. A recommendation for the use of electrical biosensing technology in neonatology. *Pediatr Res*, (2024).
14. Van Wyk, L., Gupta, S., Lawrenson, J. & de Boode, W. P. Accuracy and Trending Ability of Electrical Biosensing Technology for Non-invasive Cardiac Output Monitoring in Neonates: A Systematic Qualitative Review. *Front Pediatr* **10**, 851850 (2022).
15. Raaijmakers, E., Faes, T. J., Scholten, R. J., Goovaerts, H. G. & Heethaar, R. M. A meta-analysis of three decades of validating thoracic impedance cardiography. *Crit Care Med* **27**, 1203–1213 (1999).
16. Summers, R. L., Shoemaker, W. C., Peacock, W. F., Ander, D. S. & Coleman, T. G. Bench to bedside: electrophysiologic and clinical principles of noninvasive hemodynamic monitoring using impedance cardiography. *Acad Emerg Med* **10**, 669–680 (2003).
17. Van De Water, J. M., Miller, T. W., Vogel, R. L., Mount, B. E. & Dalton, M. L. Impedance cardiography: the next vital sign technology? *Chest* **123**, 2028–2033 (2003).
18. O'Neill, R., Dempsey, E. M., Garvey, A. A. & Schwarz, C. E. Non-invasive Cardiac Output Monitoring in Neonates. *Front Pediatr* **8**, 614585 (2020).
19. Weaver, B. et al. Hemodynamics and Perfusion in Premature Infants During Transfusion. *AACN Adv Crit Care* **29**, 126–137 (2018).
20. Hsu, K. H. et al. Hemodynamic reference for neonates of different age and weight: a pilot study with electrical cardiometry. *J Perinatol* **36**, 481–485 (2016).
21. Boet, A., Jourdain, G., Demontoux, S. & De Luca, D. Stroke volume and cardiac output evaluation by electrical cardiometry: accuracy and reference nomograms in hemodynamically stable preterm neonates. *J Perinatol* **36**, 748–752 (2016).
22. Bisceglie, V. et al. Neonatal reference values and nomograms of systemic vascular resistances estimated with electrical cardiometry. J Perinatol. 2024.
23. Schaffer, A. L., Dobbins, T. A. & Pearson, S. A. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. *BMC Med Res Methodol* **21**, 58 (2021).
24. Alkalay, A. L., Galvis, S., Ferry, D. A. & Sola, A. Packed Red Blood Cell Transfusions Do Not Modify Cardiac Function of Premature Infants with "Very Low Hematocrits. *Pediatric Research* **45**, 261 (1999).
25. Mansfield, R. C. et al. Cardiac Output Measurement in Neonates and Children Using Noninvasive Electrical Bioimpedance Compared With Standard Methods: A Systematic Review and Meta-Analysis. *Crit Care Med* **50**, 126–137 (2022).

AUTHOR CONTRIBUTIONS

A.C. led conceptualization, data verification, analysis, funding, methodology, project administration, resources, software, supervision, validation, visualization, and manuscript writing and editing. A.J. handled data curation, analysis, verification, and manuscript editing. Z.A. performed statistical analysis (ARIMA, regression, t-tests and mixed linear models), interpretation, and manuscript review. P.Y., N.S., S.A., K.M. participated in investigation and manuscript review. VK created illustrations and reviewed the manuscript. A.K. and T.J. managed project administration, data collection, and manuscript review. S.G. contributed to conceptualization, investigation, and manuscript review. All authors contributed to design, drafting, and approval of the content.

FUNDING

This study was funded by Sidra Institutional Research Fund (IRF) 2019 - SDR200075. The funder did not influence the results/outcomes of the study despite author affiliations with the funder. Open Access funding provided by the Qatar National Library.

COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

Informed written consent was provided by the parents for their children to be part of this study.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-026-04805-y.

Correspondence and requests for materials should be addressed to Aravanan Anbu Chakkarapani.