Assessing the prognostic impact of KDIGO criteria on acute kidney injury in very low birth weight infants: a critical insight

Laís Fagundes Pasini[1] (ID), Léia de Lima Kuchart[2] (ID), Sarah Assoni Bilibio[1] (ID), Roberta Florian Santa Catarina[2] (ID), Breno Fauth de Araújo[2] (ID), Luciano da Silva Selistre[1,2] (ID), Vandréa C. de Souza[1,2] (ID)

[1]Programa de Pós Graduação em Ciências da Saúde, Universidade de Caxias do Sul, Caxias do Sul, Brazil
[2]Neonatal Intensive Care Unit, Hospital Geral de Caxias do Sul, Caxias do Sul, Brazil

Purpose: We aimed to evaluate the incidence and identify risk factors for acute kidney injury (AKI) within the first 15 days of life in very low birth weight (VLBW) infants in a neonatal intensive care unit. Additionally, we examined whether AKI correlates with increased mortality rate in this population.

Methods: A prospective analysis was conducted on VLBW infants admitted to the neonatal intensive care unit from March 2017 to July 2021, diagnosing AKI based on the neonatal modified Kidney Disease: Improving Global Outcomes criteria. Neonates who died before obtaining consent, had complex malformation, or only one serum creatinine measurement were excluded.

Results: Out of 121 admitted VLBW infants, 97 were analyzed, with 20 (20.6%; 95% confidence interval, 12.6–28.7) diagnosed with AKI. Among these, 50% had creatinine abnormalities, 30% had urinary output changes, and 20% had both. Severe AKI (stage 2 or 3) was observed in 30% of cases, none required dialysis. AKI was associated with higher SNAPPE-II (Score for Neonatal Acute Physiology with Perinatal Extension-II) scores, more frequent severe intraventricular hemorrhage, and an increased mortality rate (35%). Multivariate analysis identified AKI as an independent risk factor for mortality, with a 9.72-fold increased risk (95% confidence interval, 2.53–37.4; *P*<0.01), and a shorter time to death.

Conclusions: Our findings underscore a significant incidence of AKI among VLBW infants, along with its strong association with increased mortality. These results highlight the critical need for thorough assessment of both serum creatinine and urinary output when diagnosing AKI in this vulnerable population.

Keywords: Acute kidney injury; Infant mortality; Infant, premature; Intensive care, neonatal

Introduction

Acute kidney injury (AKI) is a frequent complication in neonatal intensive care unit (NICU), characterized by its multifactorial nature and associated with increased morbidity and mortality [1-4]. Historically, the variability in definitions and classifications of AKI within the pediatric population has hindered the ability to compare therapeutic strategies and patient outcomes effectively. The Kidney Disease: Improving Global Outcomes (KDIGO) has provided a currently accepted definition for AKI,

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based on the rise in serum creatinine (SCr) and changes in urinary output, which facilitates a more standardized approach to diagnosis and management [5-7].

Accurate diagnosis of AKI in premature infants is crucial, due to their ongoing nephrogenesis and the heightened risks presented by the challenging NICU environment. Understanding the epidemiology of AKI in this vulnerable group is essential for evaluating healthcare processes and identifying gaps between evidence and practice [8,9].

Although the epidemiology of AKI is well-documented in critically ill neonates and children from high-income countries, significant data gaps exist regarding its occurrence in low- to middle-income countries [8,10]. Addressing these gaps is vital for gaining a comprehensive understanding of AKI in various socioeconomic settings and ensuring the implementation of effective healthcare strategies globally. This study aimed to evaluate the incidence and risk factors for AKI in very low birth weight (VLBW) infants in a NICU situated in a medium-income region. Additionally, this study evaluated whether AKI was associated with an increased mortality rate in this population.

Methods

Study design and participants
This study encompassed all VLBW infants admitted to the NICU from March 2017 to July 2021. Exclusion criteria were complex malformations, only one SCr sample, lethal chromosomal anomalies, and death within the first 48 hours of life.

Outcome measure
AKI was defined following the neonatal modified Kidney Disease: Improving Global Outcomes (nKDIGO) criteria as either an increase in SCr of 0.3 mg/dL or more from the baseline, or a urinary output of less than 1 mL/kg/hr during the initial 14 postnatal days. AKI was further classified into three stages of severity (Table 1) [11]. Stage 1 AKI involves a 1.5- to 1.9-fold increase in SCr from baseline or an increase of 0.3 mg/dL within 48 hours. Stage 2 was defined as a 2.0- to 2.9-fold increase from baseline, and stage 3 was a more than 3-fold increase in baseline SCr or a SCr level exceeding 2.5 mg/dL. Two SCr samples were collected: the first from the third day of life to avoid maternal creatinine influence, and the second within the subsequent week. Urine output was monitored over 2 weeks through diaper weight, employing a precision electronic scale (Fanem PN-91TS), and quantified in milliliters per kilogram per hour.

Data collection
Data collected included maternal and perinatal factors: maternal age, parity, gestational diabetes mellitus, preeclampsia, gestational age at birth, birth weight, resuscitation details, length of stay, and complications (including the duration and mode of invasive and non-invasive ventilation, vasopressor support duration, intraventricular hemorrhage [IVH], necrotizing enterocolitis, bronchopulmonary dysplasia, exposure to nephrotoxic medication) (Table 2). All patients who underwent mechanical ventilation (MV) started therapy within the first 24 hours of life. The Score for Neonatal Acute Physiology with Perinatal Extension-II (SNAPPE-II) was employed to assess severity within the first 12 hours of NICU admission [12]. The SNAPPE-II is a widely used scoring system that assesses illness severity and predicts mortality risk in neonates. This score includes variables such as birth weight, gestational age, blood pressure, body temperature, urine output, and blood gas measurements. Each variable is assigned a specific number of points, and the total score ranges from 0 to 162, with higher scores indicating greater illness severity and higher mortality risk.

Laboratory assessments
All SCr measurements adhered to methods traceable to the National Institute of Standards and Technology creatinine standard reference, calibrated by isotope dilution mass spectrometry.

Sample size
With an anticipated AKI occurrence of 30% within the VLBW cohort, a sample size of 81 participants was calculated to estimate the expected proportion with a 10% absolute precision and 95% confidence interval (CI) level.

Table 1. Classification of acute kidney injury according to KDIGO criteria[a)]

Stage	Increase in serum creatinine	Urine output over 24 hr
0	No change or <0.3 mg/dL	>1 mL/kg/hr
1	≥0.3 mg/dL within 48 hr or ≥×1.5–1.9 from baseline	>0.5 to 1 mL/kg/hr
2	≥×2–2.9 from baseline	>0.3 to 0.5 mL/kg/hr
3	≥×3 from baseline or ≥2.5 mg/dL or dialysis	≤0.3 mL/kg/hr

KDIGO, Kidney Disease: Improving Global Outcomes.
[a)]Based on the neonatal modified version from Jetton et al. Front Pediatr 2016;4:68 [4].

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Table 2. Characteristics of neonatal cohort

Variable	AKI (n=20)	No AKI (n=77)	P-value
Maternal characteristics			
Age (yr)	23.5 (20.7–29.2)	27.0 (21.0–32.0)	0.24
Disease			
Diabetes (DM+GDM)	2 (10.0)	10 (13.0)	0.74
Hypertensive disorder	8 (40.0)	22 (28.6)	0.47
Neonate characteristics			
Male sex	13 (65.0)	39 (50.6)	0.37
Gestational age (wk)	28.5 (27.0–31.0)	30.0 (28.3–32.0)	0.11
<28	7 (35.0)	14 (18.2)	0.18
28–32	10 (50.0)	43 (55.8)	0.82
>32	3 (15.0)	20 (26.0)	0.46
Birth weight (g)	1,110 (831–1,296)	1,170 (1,000–1,295)	0.34
<1,000	8 (40.0)	20 (26.0)	0.33
Apgar score at 5 min	6 (3–7)	7 (5–8)	0.20
Resuscitation in the delivery room	15 (75.0)	58 (75.3)	0.97
SNAPPE-II score	18 (0–42)	13 (5–27)	0.43
SNAPPE-II ≥40	8 (45.0)	8 (10.4)	<0.01
Drug exposure			
Surfactant	15 (75.0)	41 (53.2)	0.13
Ibuprofen	2 (10.0)	3 (3.90)	0.27
Vasoactive drugs	9 (45.0)	24 (31.0)	0.36
Aminoglycosides	16 (80.0)	62 (80.5)	0.77
Prenatal corticosteroid	16 (80.0)	58 (75.3)	0.27
Vancomycin	14 (70.0)	41 (53.2)	0.27
Umbilical artery catheter	15 (75.0)	50 (65.0)	0.43
Diagnosis			
Necrotizing enterocolitis	6 (30.0)	13 (16.9)	0.31
Small for gestational age	10 (50.0)	36 (46.8)	0.99
Early-onset sepsis	12 (60.0)	38 (49.3)	0.14
Late-onset sepsis	14 (70.0)	41 (53.2)	0.27
Bronchopulmonary dysplasia	6 (30.0)	38 (49.4)	0.19
Patent ductus arteriosus	2 (10.0)	5 (6.49)	0.98
IVH grade 3 or 4	3 (15.0)	4 (5.19)	0.03
Mechanical ventilation (day)	2 (0–12)	0 (0–5)	0.16
Length of stay (day)	60 (40–74)	45 (38–66)	0.37
Death	7 (35.0)	4 (5.19)	<0.01

Values are presented as median (interquartile range) or number (%).
AKI, acute kidney injury; DM, diabetes mellitus before gestation; GDM, gestational diabetes mellitus; SNAPPE-II, Score for Neonatal Acute Physiology Perinatal Extension; IVH, intraventricular hemorrhage.

Statistical analysis

The primary endpoint was the incidence of AKI among VLBW infants in the first 2 weeks of life. Continuous variables were presented as median and interquartile range (IQR). Group comparisons utilized the Student t-test or the Mann-Whitney U test, as dictated by data distribution. Categorical variables were shown as relative and absolute frequencies and compared using the Fisher exact test. The SNAPPE-II variable was evaluated as a continuous variable and also categorized as <40 or ≥40,

according to the findings of Muktan et al. [13]. Variables were evaluated for an association with AKI using multivariate logistic regression analysis after controlling for potential confounders. Odds ratios and their corresponding 95% CI were calculated. The variance inflation factor (VIF) was used to measure the extent of multicollinearity in the multivariable regression model. VIF values above 10 typically indicate significant multicollinearity, suggesting that the predictors are highly correlated. Differences in baseline variables were examined for their impact on

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mortality rates using a Cox proportional hazards model. Patient survival rates were estimated by the Kaplan-Meier curves and compared using the log-rank test. The 95% CI for all estimates was derived using the adjusted bootstrap percentile method. A *P*-value of <0.05 was deemed statistically significant. All analyses were performed using R for Windows version 4.3.1 (R Foundation for Statistical Computing).

Results

Clinical characteristics of the cohort
Among the 121 VLBW infants admitted to the NICU from March 2017 to July 2021, 97 neonates were included in the analysis. Of these, 20 neonates (20.6%, 95% CI, 12.6–28.7) were diagnosed with AKI. Exclusions were as follows: 10 due to death within 48 hours of birth, nine due to a single SCr measurement, four due to complex malformations, and one due to family refusal (Fig. 1). The cohort comprised 53.6% males, with a median gestational age of 30.0 weeks (IQR, 28.0–31.5 weeks) and a median birth weight of 1,160 g (IQR, 915–1,295 g).
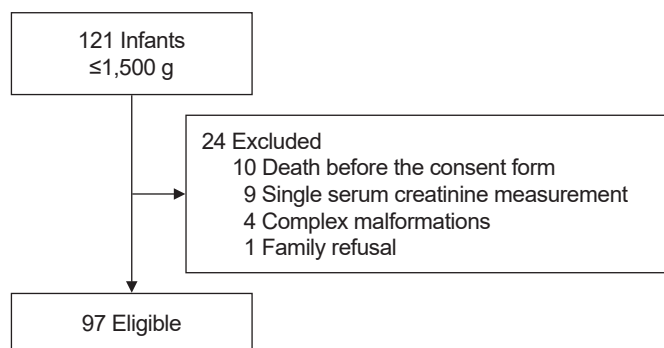

Fig. 1. Study flow diagram.

AKI characteristics
Of the neonates with AKI, 50% (n=10) exhibited isolated creatinine abnormalities, 30% (n=6) had exclusive alterations in urinary output, and 20% (n=4) showed abnormalities in both creatinine levels and urinary output. Severe AKI (stage 2 or 3) was identified in 30% (n=6) of the cases with no patients requiring dialysis.

Predictors of AKI
Significant differences were observed in the AKI group, including a higher frequency of a SNAPPE-II score exceeding 40 (45.0% vs. 10.4%, *P*<0.01), severe IVH (15.0% vs. 5.2%, *P*=0.03) and mortality (35.0% vs. 5.2%, *P*<0.01) (Table 2). No statistical differences were found in other neonate and maternal characteristics between the AKI and non-AKI groups (Table 2).

In the AKI group, there was a higher frequency of extreme prematurity (35.0% vs. 18.2%), extremely low birth weight (40.0% vs. 26.0%), maternal hypertensive disorders (40.0% vs. 28.6%), and both early-onset (60.0% vs. 49.3%) and late-onset sepsis (70.0% vs. 53.2%). Although there was no statistically significant difference in the distribution of these characteristics, these factors could still predispose infants to AKI. In the studied population, 21 neonates (21.6%) were less than 28 weeks gestational age, with a 33.3% incidence of AKI (n=7). Among the 76 neonates older than 28 weeks, the AKI incidence was lower at 18.4% (n=14). However, there was no statistically significant difference between the two groups. The same trend was observed among neonates with extremely low birth weight. Of the 28 neonates weighing less than 1,000 g, eight developed AKI (28.6%). This proportion was higher compared to the 17.3% incidence (n=12) among the 69 neonates with higher birth weights. However, this difference was not statistically significant.

In the univariate logistic regression model, the SNAPPE-II score and severe IVH were associated with AKI (Table 3). In the

Table 3. Effects of neonatal characteristics on the probability of acute kidney injury

Variable	Univariable model		Multivariable model		
	OR (95% CI)	*P*-value	aOR (95% CI)	*P*-value	VIF
Gestational age <28 wk	2.42 (0.78–7.12)	0.11	1.36 (0.22–7.90)	0.73	1.83
Birth weight <1,000 g	1.90 (0.66–5.29)	0.22	0.32 (0.03–1.87)	0.26	1.91
Severe intraventricular hemorrhage[a]	6.17 (1.24–34.0)	0.02	6.07 (0.99–43.9)	0.05	1.09
SNAPPE-II >40	5.75 (1.80–18.7)	<0.01	10.2 (1.82–86.1)	0.01	1.59
Early-onset sepsis	1.46 (0.54–4.11)	0.45	0.82 (0.22–2.85)	0.76	1.28

OR, odds ratio; 95% CI, confidence interval; aOR, adjusted OR; VIF, variance inflation factor; SNAPPE-II, Score for Neonatal Acute Physiology with Perinatal Extension-II.
[a]Intraventricular hemorrhage stage 3 or 4.

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multivariable analysis (Table 3), the SNAPPE-II score demonstrated a 10-fold increase in the risk of AKI when the score was 40 or higher. Severe IVH (grade 3 or 4) was also associated with AKI, though this association was at the threshold of statistical significance (P=0.05) after adjustment. The VIF indicated no multicollinearity among the model variables.

Mortality

The overall mortality rate was 11.3%, with a higher incidence observed in the AKI group (35%) compared to the non-AKI group (5%). A multivariate Cox proportional hazards model identified AKI as an independent risk factor for mortality, with an adjusted hazard ratio of 9.72 (95% CI, 2.53–37.4, P<0.01) for the AKI group compared to the non-AKI group (Table 4). All stages of AKI were associated with increased mortality, with hazard ratios of 9.89 (95% CI, 2.63–37.2) for stage 1 AKI and 7.60 (95%

CI, 1.38–41.8) for severe AKI (stage 2 or 3). The time to death was notably shorter in the AKI group (Fig. 2).

Discussion

This study explored the incidence and implications of AKI in a cohort of 97 VLBW infants, uncovering an AKI incidence of 20.6%, a notable association between higher SNAPPE-II scores and AKI, and a significantly elevated mortality rate in the AKI group.

The AKI incidence aligns closely with findings from Burg-maier et al. [14], Daga et al. [15], and Srinivasan et al. [16], despite variations in diagnostic criteria across studies, emphasizing the importance of standardized diagnostic frameworks for AKI in neonatal populations. Burgmaier et al. [14] screened 128 VLBW infants for AKI utilizing the nKDIGO criteria. Daga et
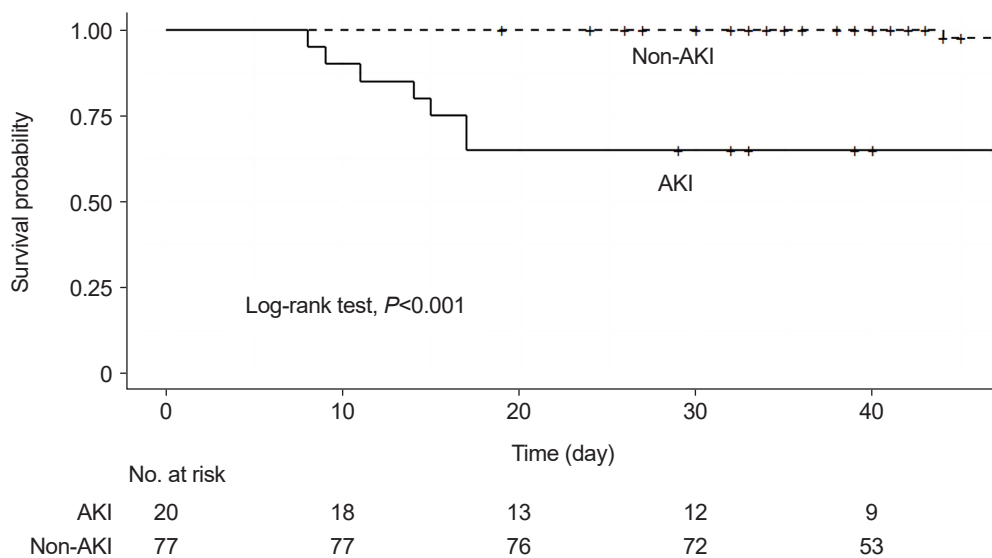

Fig. 2. Kaplan-Meier curves showing the survival probability, expressed as a percentage, following admission for very low birth weight infants, stratified by acute kidney injury.

Table 4. Effects of neonatal characteristics on the probability of death

Variable	Univariable model		Multivariable model	
	HR (95% CI)	P-value	aHR (95% CI)	P-value
Acute kidney injury	9.11 (2.64–31.3)	<0.01	9.72 (2.53–37.4)	<0.01
Gestational age <28 wk	2.08 (0.60–7.31)	0.20	1.08 (0.19–5.91)	0.92
Birth weight <1,000 g	3.10 (0.85–11.3)	0.09	2.42 (0.56–10.4)	0.23
Severe intraventricular hemorrhage[a]	2.28 (0.47–10.9)	0.20	0.53 (0.11–3.29)	0.49
SNAPPE-II >40	3.64 (1.07–12.4)	0.02	1.81 (0.36–9.12)	0.47

HR, hazard ratio; aHR, adjusted HR; CI, confidence interval; SNAPPE-II, Score for Neonatal Acute Physiology with Perinatal Extension-II.
[a]Intraventricular hemorrhage stage 3 or 4.

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al. [15] evaluated three distinct diagnostic tools (AKI network [AKIN], risk, injury, failure, loss, end-stage [RIFLE], and pediatric RIFLE [pRIFLE]) for comparison, while Srinivasan et al. [16] diagnosed AKI in their cohort using the modified-AKIN criteria, relying solely on SCr levels. A critical insight from our analysis is the significant role of urinary output in AKI diagnosis. With 30% of AKI episodes detected solely through urinary output criteria, our study echoes the findings of Burgmaier et al. [14] and Kaddourah et al. [17], highlighting the necessity of rigorous urinary output monitoring in preterm infants for accurate AKI diagnosis.

In our cohort, the routine administration of caffeine, a practice potentially implicated in reducing both the incidence and severity of AKI, introduces a limitation in our ability to isolate this intervention's specific effects on AKI outcomes. This consistent use of caffeine precludes a direct assessment of its protective role against AKI within our study framework. Notably, Harer et al. [18] observed a significant reduction in AKI incidence and severity among 675 infants with a mean GA of 28.9 weeks who received caffeine during their first week of life, reporting AKI rates of 11.2% in the caffeine-treated group compared to 31.6% otherwise. This comparison suggests a potential protective effect of caffeine administration against AKI. Despite our study's methodological constraints, the observed lower incidence of AKI in our cohort might be partially attributed to the prophylactic use of caffeine. Nonetheless, further research is imperative to conclusively determine caffeine's role in AKI prevention among VLBW infants.

In contrast with findings from other studies, our data did not demonstrate a significant association between AKI and the duration of MV, potentially attributable to the variance in MV frequency across different cohorts [14,19]. This discrepancy underscores the complexity of AKI risk factors and the need for further research to clarify these relationships.

The association between higher SNAPPE-II scores and AKI, while not surprising given the score's indication of increased morbidity, highlights the vulnerability of neonates with elevated SNAPPE-II scores to AKI. This association, consistent with the literature, reinforces the importance of comprehensive risk assessment in neonates to mitigate AKI risks [14,20].

Our investigation highlights AKI as a significant independent risk factor for increased mortality among neonates, reinforcing the vital need for stringent monitoring and management of AKI within NICU settings. The observed hazard ratio for mortality in neonates with AKI versus those without was

9.72 ($P<0.01$), a finding that resonates with the broader body of literature on the topic. Notably, Jetton et al. [2] identified AKI as an independent predictor of mortality, with an odds ratio of 4.6 (95% CI, 2.5–8.3; $P<0.001$), while Askenazi et al. [21] reported an association between AKI and an elevated risk of bronchopulmonary dysplasia and mortality, evidenced by a relative risk of 1.7 (95% CI, 1.2–2.4; $P<0.02$) in a cohort of 122 preterm infants. These studies collectively underscore the critical impact of AKI on neonatal outcomes, underscoring our findings and advocating for enhanced vigilance in AKI detection and care in the NICU environment.

While our study did not find a significantly higher frequency of AKI in extremely premature or extremely low birth weight infants compared to some literature, this may highlight variability in AKI risk across different neonatal populations [3,22]. Jetton et al. [2] reported the incidence of AKI at 48% among neonates born at less than 29 weeks gestation, affecting 131 out of 273 infants in this group. This rate was the most significant compared to other gestational age groups in the total studied population of 2,022 infants. Our study had a small absolute number of extremely premature (n=21) and extremely low birth weight infants (n=28), which may explain why we did not observe a statistically significant difference in the occurrence of AKI in these groups. Furthermore, Wu et al. [22] described significant heterogeneity among studies reporting the prevalence of AKI. This comparison underscores the critical need for expansive, multicenter studies to more accurately determine the risk factors and incidence rates of AKI in various neonatal groups, thereby enhancing our understanding and management of this condition in neonatal intensive care settings.

This study's strengths lie in its focused assessment of AKI incidence in VLBW infants within a middle-income setting and the employment of strict AKI definitions incorporating both SCr and urinary output criteria. However, its limitations include the single-center design and a sample size that may not capture the full spectrum of AKI severity. Additionally, the absence of renal ultrasound data to assess total renal volume and cortical thickening limits our understanding of renal health in these neonates. These factors suggest caution in generalizing the findings and highlight the need for multicenter, larger-scale studies to validate and expand upon our findings.

Our investigation confirms a significant incidence of AKI among VLBW infants, with AKI serving as a notable risk factor

for increased mortality. These findings emphasize the critical need for meticulous AKI diagnostics, incorporating both creatinine and urinary output assessments, to improve outcomes in this vulnerable population.

Ethical statements

The research protocol received approval from the Institutional Review Board of Hospital Geral de Caxias do Sul (IRB No. 12142/2017). The informed consent was obtained from mothers or guardians of the VLBW infants for study participation.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: VCS, LFP
Data curation: LFP, LLK, SAB, RFSC
Formal analysis: LSS, VCS
Investigation: VCS, LFP, BFA
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Project administration: VCS, LFP
Visualization: LFP, LLK, SAB, RFSC, BFA, LSS, VCS
Writing-original draft: VCS, LFP
Writing-review & editing: VCS, LFP
All authors read and approved the final manuscript.

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