Original Research Article

Effect of amoxicillin-clavulanate potassium and potential factors influencing umbilical cord separation time in preterm infants

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Abstract

Purpose: To investigate the effect of amoxicillin-clavulanate potassium and potential factors influencing umbilical cord separation time in preterm infants.

Methods: A total of 151 preterm infants admitted to the Neonatology Department, First Affiliated Hospital of Anhui Medical University, Hefei, China, from November 2020 to June 2021 were selected. Preterm infants were randomly divided into control and study groups. Control group received 2 % povidone-iodine and 75 % ethanol application, followed by gentle pressure with a cotton swab while the study group received amoxicillin-clavulanate potassium applied to the umbilical cord while shaking. The management interventions were stopped after umbilical cord separation in preterm infants, and the difference in umbilical cord separation time between the two groups was compared. Factors associated with preterm birth conditions, hospitalization, and maternal health were identified by univariate and multivariate logistic regression analyses.

Results: The number of cases with umbilical cord separation time > 14 days was significantly higher in the study group compared to control group (p < 0.05). The average umbilical cord separation time in the study group was significantly lower compared to control group (p < 0.05). Univariate analysis revealed that incubator residence time significantly affects umbilical cord separation time in preterm infants (p < 0.05). Logistic multivariate regression analysis identified incubator residence time as the main factor influencing umbilical cord separation time in preterm infants.

Conclusion: The use of amoxicillin-clavulanate potassium shortens umbilical cord separation time, and incubator residence time is the major factor influencing umbilical cord separation in preterm infants. Further studies should expand the study scale and increase the number of samples used.

Keywords: Preterm infants, Umbilical cord separation time, Potential influencing factors, Amoxicillin-clavulanate potassium

INTRODUCTION

Infants born before 37 weeks gestation are termed preterm infants and usually have an increased susceptibility to infections due to underdeveloped immune systems [1]. Studies show that the risk of severe infections is higher in preterm infants with lower gestational age and

birth weight. The umbilical cord, vital for fetal-maternal exchange, undergoes natural detachment after birth, typically within 3 - 7 days for full-term infants [2]. However, in preterm infants, this process may take longer, increasing the risk of infections. Umbilical inflammation, often due to inadequate care or infection, poses significant health risks, particularly for preterm infants with weaker immune systems [3,4]. While the timing of umbilical cord detachment is well-studied in full-term infants, there's less consensus for preterm infants [5,6]. This study aims to investigate the duration of umbilical cord separation in preterm infants and the factors influencing it. Additionally, the study evaluates the efficacy of amoxicillin-clavulanate potassium in promoting umbilical cord detachment in preterm infants.

METHODS

Study population

A total of 151 preterm infants born admitted to the Neonatology Department of a tertiary hospital in Hefei City, China, from November 2020 to June 2021 were selected as study population. The population was randomized into study (76) and control groups (75). Approval for this study was obtained from the Ethics Committee of Anhui Medical University Hospital (approval no. 3253295732), and the study complied with the international guidelines for human studies. Informed consent forms were duly signed by all parents/guardians of the participants.

Inclusion criteria

Gestational age less than 37 weeks with a hospital stay exceeding 48 h for live-born infants; parents of preterm infants with normal cognitive function; capable of comprehending explanations regarding neonatal umbilical care provided by medical staff and willingness of parents of preterm infants to voluntarily participate in the study and cooperate with required procedures.

Treatments

General information

A total of 33 relevant factors were collected, and categorized into three aspects which include; birth characteristics, hospitalization status, and maternal information.

Birth characteristics

These include gender, birth weight, gestational age, age at admission, location of umbilical cord detachment, parity, presence of neonatal respiratory distress syndrome (NRDS), and whether the infant was conceived through *in vitro* fertilization.

Hospitalization status

These include oxygen requirement and method, duration of antibiotics use, incubator residence time, initial and final incubator temperature, duration of phototherapy, white blood cell level at admission, C-reactive protein (CRP) level at admission, Apgar score at 1 and 5 min.

Maternal information

These include maternal age, BMI classification, level of education, residential address, occupation, mode of delivery, presence of gestational diabetes mellitus, gestational hypertension, placenta previa, premature rupture of membranes, gestational infections, other diseases, maternal cardiac arrhythmia, hypothyroidism, history of cesarean section, etc.

Umbilical cords of preterm infants were ligated 0.5 - 1.0 cm away from the umbilical ring without delayed cord clamping.

Umbilical cord management during hospitalization

The medical team was responsible for daily examination of the umbilical cords, and accurately recording the time of umbilical cord detachment. For preterm infants whose umbilical cords have not detached at the time of discharge, specialized nursing staff provide relevant knowledge and education to their parents. The specific measures for umbilical cord management during hospitalization are as follows:

Ward environment and item management

The temperature in the ward was maintained at 24 – 26 °C, and humidity at 45 – 55 %. The air in the ward was disinfected twice daily for 2 h each using an air disinfection machine. The air was ventilated at least twice a day, for 30 min each time. Cotton and cloth items used by preterm infants were washed and subjected to high-temperature disinfection. Disposable items and disinfectants were handled according to established regulations.

Incubator management

Relative humidity in the incubator (Ningbo Davi incubator model YP-90) was maintained at 55 –

65 %. Sterile injection water in the incubator was replaced daily, and the internal and external component of the incubator was cleaned daily. The incubator and its light-shielding cover were replaced and thoroughly disinfected weekly.

Umbilical cord management

In the control group, umbilical cord management involved the use of 2 % povidone-iodine (Shanghai Yunjia Huangpu Pharmaceutical Co., Ltd., National Drug approval no. H31021416) and 75 % ethanol (Guilin Lijing Pharmaceutical Supplies Co., Ltd., Guilin Food and Drug Administration Certificate no. 0032). Study group was treated with amoxicillin-clavulanate potassium dry suspension (Guangzhou Baiyunshan Pharmaceutical Group Co., Ltd. Baiyunshan Pharmaceutical Factory, National Drug approval no. H20041109). The suspension was drawn into a 5 mL syringe, the needle was thereafter removed with the nipple positioned directly over the umbilicus dropping the solution. The umbilicus was gently shaken with the index finger and thumb of the left hand, allowing the solution to be absorbed slowly, following strict sterile procedures. For smaller infants, the diaper was folded back to expose the remaining part of the umbilical cord. Ideally, the umbilical cord of preterm infants should not come in contact with water. If it becomes wet, sterile cotton swabs should be promptly used to dry it. Before and after umbilical cord detachment, if bleeding or exudate occurred from the umbilicus, caregivers provided timely care. Specific measures for umbilical cord care include cleaning the umbilical fossa and surrounding tissues with 3 % hydrogen peroxide (Guangdong Hengjian Pharmaceutical Co., Ltd., National Drug approval no. H44023919), followed by disinfection of the umbilical fossa with 0.5 % iodophor (Shenzhen Andon Health Co., Ltd.) until the area is clean and free from discharge. If the umbilical cord becomes contaminated with feces, urine, or other substances, the care personnel promptly clean and disinfect the cord.

Personnel management

The obstetrics and neonatology healthcare professionals involved in umbilical cord management for preterm infants in this study receive standardized training in umbilical cord management at the hospital. For preterm infants discharged from the obstetrics department and re-admitted to the neonatology department, umbilical cord management followed protocols used for in-hospital preterm infants during their stay in the obstetrics department and after admission to the neonatology department.

Follow-up

For preterm infants whose umbilical cords have not yet detached at the time of discharge, the care professionals conducted daily follow-up until the umbilical cord detachment was complete.

Evaluation of parameters/indices

Observation of umbilical cord detachment during hospitalization

During hospitalization period, nursing staff were responsible for closely observing the time of umbilical cord detachment for both groups of preterm infants. This observation was conducted systematically and diligently to accurately record the duration of cord attachment. Nursing staff were trained to recognize signs of cord detachment and document the exact time it occurred. This ensures precise data collection and allows for comparison between the two groups of preterm infants. Any variations or anomalies in the process were noted and documented accordingly to maintain data integrity.

Telephone follow-up after discharge

Following discharge from the hospital, a structured telephone follow-up procedure was implemented to monitor the umbilical cord detachment status. Trained healthcare professionals conducted follow-up calls to inquire about the progress of cord detachment and to address any concerns or queries raised by mothers and family members. The follow-up process is systematic and thorough, ensuring that all relevant information regarding cord detachment was accurately obtained after discharge. Any complications or delays in cord detachment are noted during these follow-up calls for further investigation and management.

Analysis using self-made questionnaire

A self-made questionnaire was developed and utilized to conduct a comprehensive statistical analysis of the time of umbilical cord detachment in preterm infants and its associated factors. The questionnaire was designed to collect structured data such as gestational age, birth weight, maternal factors, and any medical interventions received during hospitalization period. The questionnaire ensures systematic data collection and facilitates identification of factors influencing cord detachment time through statistical analysis. Data obtained from the questionnaire was analyzed using appropriate statistical methods to determine any significant correlations or

associations between variables and the time of cord detachment. This rigorous analysis allows for a deeper understanding of the factors influencing cord detachment in preterm infants to inform future clinical practice and management protocols.

Statistical analysis

Data were entered using Epidata 3.1 software for double data entry and analyzed using Statistical Packages for Social Sciences (SPSS 24.0 software). Qualitative data was described using frequency and composition ratios, and intergroup comparison was conducted using chi-square test. Quantitative data that follow normal distribution were described using mean and standard deviation, while non-normally distributed quantitative data were described using median and interquartile range. Intergroup comparison was conducted using rank sum test. Logistic regression analysis was used to determine main influencing factors for time of umbilical cord detachment in preterm infants. $P < 0.05$ was considered statistically significant.

RESULTS

Umbilical cord detachment time

Average umbilical cord detachment time in study group was significantly lower compared to control group ($p < 0.05$). Also, number of cases with umbilical cord detachment time > 14 days was significantly higher in study group compared to control group ($p < 0.05$).

Univariate analysis

Univariate analysis results revealed that infant weight, gestational age, age at admission, presence of neonatal respiratory distress syndrome (NRDS), use of antibiotics, duration in the incubator, initial incubator temperature, duration of phototherapy, Apgar score at 1 minute, maternal education level had a significant impact on umbilical cord detachment time ($p < 0.05$). On the other hand, infant gender, location of cord detachment, parity, in vitro fertilization status, oxygen therapy and delivery method, final incubator temperature, white blood

cell count and C-reactive protein level at admission, Apgar score at 5 minutes, maternal age, BMI classification, residential address, occupation, mode of delivery, presence of gestational diabetes, gestational hypertension, placenta previa, premature rupture of membranes, gestational infections, other medical conditions, maternal history of arrhythmia, hypothyroidism, and cesarean section history showed no significant effect on umbilical cord detachment time ($p > 0.05$; Table 2).

Multivariable logistic regression analysis of factors influencing umbilical cord detachment time

Factors that were statistically significant in the univariate model were selected as independent variables, and the assignment of values for these variables is shown in Table 3. Through multivariable logistic regression analysis, it was found that the duration of time spent in the incubator was the main factor influencing umbilical cord detachment time in premature infants ($p < 0.05$; Table 4; Figure 1).

DISCUSSION

The umbilical cord is a tubular structure that connects the fetus and placenta in mammalian animals, and it is made up of two arteries and one vein [7]. The umbilical cord serves multiple purposes. It not only supplies the fetus with oxygen, and nutrients, and eliminates waste products, but it also acts as a toy for fetal movement within the mother's body [8,9]. After birth, the umbilical cord naturally detaches itself. Normally, the residual umbilical cord in newborns detaches within approximately 3-7 days, but there are cases where the detachment time exceeds 10 days or even longer, and it is rare for a fetus to have a delayed detachment time of more than 30 days [10]. Umbilical cord in newborns is a cloudy white color, composed of Wharton's jelly between blood vessels. After the infant is born, the umbilical cord is ligated, resulting in loss of moisture from the Wharton's jelly. The residual end of the umbilical cord dries up and detaches, eventually healing to form the umbilical stump [11].

Table 1: Umbilical cord detachment time

Group	Number of cases (n)	Umbilical cord shedding time (days)		
		<7	*7-14*	*>14*
Control	75	0	32	43
Study	76	4	43	29
χ^2	-	2.270	2.922	5.563
P-value	-	0.131	0.087	0.018

Table 2: Univariate analysis of factors influencing umbilical cord detachment time

Normal information	Number of cases (n)	Shedding time (days)			χ^2/H	*P*-value
		0-7	*7-14*	*>14*		
Gender					0.813	0.666
Male	72	2	33	37		
Female	79	2	42	35		
Premature baby weight					13.069	0.042
<1000g	5	0	0	5		
<1500g	31	0	11	20		
<2500g	94	4	51	39		
≥2500g	21	0	13	8		
gestational age					15.993	0.014
<28w	5	0	0	5		
28-31 +6 w	29	0	12	17		
32-33 +6 w	42	0	18	24		
34-36 +6 w	75	4	45	26		
Length of admission (age)					9.040	0.011
<24h	145	3	70	72		
≥24h	6	1	5	0		
Where the umbilical cord fell off					3.990	0.136
In the courtyard	82	4	42	36		
Outside the Hospital	69	0	33	36		
Parity					4.228	0.121
Single birth	73	2	30	41		
Twins and above	78	2	45	31		
Do you have NRDS					14.651	0.001
Have	45	0	13	32		
None	106	4	62	40		
Whether it is a test tube baby					0.062	0.969
Have	75	2	38	35		
None	76	2	37	37		
Oxygen inhalation method					10.771	0.096
None	62	4	36	22		
Oxygen in the box	47	0	20	27		
Non-invasive ventilator	39	0	18	21		
Invasive ventilator	3	0	1	2		
Whether to use antibiotics					25.040	0.000
No	82	4	52	26		
Use time <7days	31	0	15	16		
Use time ≥7days	38	0	8	30		
Incubator residence time	151	4	75	72	55.752	0.000
Entering temperature	151	4	70	72	14.138	0.001
Final temperature	151	4	70	72	2.691	0.260
Phototherapy duration	151	4	75	72	11.162	0.004
Admission white blood cells	151	4	75	72	1.703	0.427
Admission CRP	151	4	75	72	2.131	0.345
Apgar1 minute degree					16.421	0.003
Normal	116	4	67	45		
Mild suffocation	29	0	6	23		
Severe suffocation	6	0	2	4		
Apgar 5 minutes degree					2.648	0.618
Normal	141	4	72	65		
Mild suffocation	9	0	3	6		
Suffocation	1	0	0	1		
Maternal age					6.414	0.378
20-30	52	1	21	30		
30-40	94	3	53	38		
40-50	4	0	1	3		
≥50	1	0	0	1		

Table 2: Univariate analysis of factors influencing umbilical cord detachment time *(continued)*

Normal information	Number of cases (n)	Shedding time (days)			χ^2/H	P-value
		0-7	*7>14*	*>14*		
Maternal BMI grade					4.439	0.350
Normal weight	26	0	12	14		
Overweight	88	4	41	43		
Obesity	37	0	22	15		
Education level					10.336	0.035
Junior high school and below	60	2	26	32		
High School and Technical Secondary School	37	0	14	23		
College and above	54	2	35	17		
Family residence					0.619	0.734
Town	121	3	62	56		
The countryside	30	1	13	16		
Nature of the work					6.127	0.190
Brain power	59	2	35	22		
Physical strength	21	0	7	14		
Unemployed	71	2	33	36		
Mode of delivery					2.357	0.308
Caesarean section	121	2	61	58		
Natural childbirth	30	2	14	14		
Presence of gestational diabetes					4.473	0.107
Have	52	1	32	19		
None	99	3	43	53		
Presence of gestational hypertension					4.035	0.133
Have	41	1	15	25		
None	110	3	60	47		
Presence of placenta previa					1.491	0.474
Have	9	0	3	6		
None	142	4	72	66		
Premature rupture of membranes					1.233	0.540
Have	28	0	13	15		
None	123	4	62	57		
Pregnancy infection					0.431	0.806
Have	9	0	4	5		
None	142	4	71	67		
Presence of other diseases					0.296	0.862
Have	10	0	5	5		
None	141	4	70	67		
Whether there is pregnancy complicated with arrhythmia					2.186	0.335
Have	5	0	1	4		
None	146	4	74	68		
Are you suffering from hypothyroidism					2.052	0.358
Have	17	1	6	10		
None	134	3	69	62		
Whether there is a history of cesarean section					1.005	0.605
Have	15	0	9	6		
None	136	4	66	66		

P < 0.05: Statistically significant

A study indicated that delayed detachment of residual umbilical cord in newborns causes significant mental and psychological burdens for mothers and their families [12]. Moreover, it poses a significant risk of umbilical cord infection in newborns. When the residual end of the umbilical cord in an infant fails to detach for an extended period, it becomes an open wound susceptible to microbial invasion and proliferation. This may lead to life-threatening local or systemic infections. Premature infants are live-born infants with a gestational age of less than 37 weeks. Due to lower gestational age, low birth weight, thin skin, and reduced

Table 3: Assignment of values for independent variables

Independent variable	Assignment method
Gestational age	<28weeks means 1; 28-31 +6 weeks means 2; 32-33 +6 weeks means 3; 34-36 +6 weeks means 4
Admission time	<24h=1; ≥24h=2
Do you have NRDS?	yes=1; no=2
Premature baby weight	<1000g=1; <1500g=2; <2500g=3; ≥2500g=4
Use of antibiotics	None=1;<7d=2;≥7d=2
1 minute Apgar score	Normal = 1; Mild asphyxia = 2; Severe asphyxia = 3
Education level of pregnant mother	Junior high school and below = 1; high school and technical secondary school = 2; junior college and above = 3
Umbilical cord shedding time	<7d =1, 7-14d =2, >14d=3
Time in box	Original value entry
Entering temperature	Original value entry
Phototherapy duration	Original value entry

Table 4: Multivariable logistic regression analysis of factors influencing umbilical cord detachment time (*df =1*)

| Variable	β	S.E	Wald	P-value	95% CI Lower limit	95% CI Upper limit
Incubator residence time (h)	0.018	0.004	23.581	0.000	0.138	0.427
Into the box temperature (°C)	0.054	0.411	0.017	0.895	-0.751	0.859
Phototherapy duration (h)	-0.017	0.013	1.746	0.186	-0.043	0.008
Gestational age						
<28w	13.504	0.000	.	.	13.504	13.504
28-31 +6 w	-1.638	1.159	1.997	0.158	-3.911	0.634
32-33 +6 w	-1.156	0.638	3.286	0.070	-2.406	0.094
34-36 +6 w	Reference category					
Admission time						
<24h	2.142	1.168	3.361	0.067	-0.148	4.432
≥24h	Reference category					
Do you have NRDS?						
Yes	-0.535	0.689	0.603	0.438	-1.885	0.815
No	Reference category					
Apgar1 minute degree						
Normal	-0.003	2.207	0.000	0.999	-4.330	4.323
Mild suffocation	1.317	2.174	0.367	0.545	-2.944	5.579
Severe suffocation	Reference category					
Weight						
<1000g	17.251	0.000	.	.	17.251	17.251
<1500g	-.812	1.247	0.424	0.515	-3.257	1.632
<2500g	-1.005	0.768	1.712	0.191	-2.510	0.500
≥2500g	Reference category					
Whether to use antibiotics						
No	-0.749	0.746	1.007	0.316	-2.212	0.714
Use time <7day	-0.444	0.743	0.358	0.550	-1.900	1.011
Use time ≥7day	Reference category					
Education level						
Junior high school and below	0.527	0.518	1.036	0.309	-0.488	1.543
High School and Technical Secondary School	1.068	0.604	3.123	0.077	-0.116	2.252
College and above	Reference category					
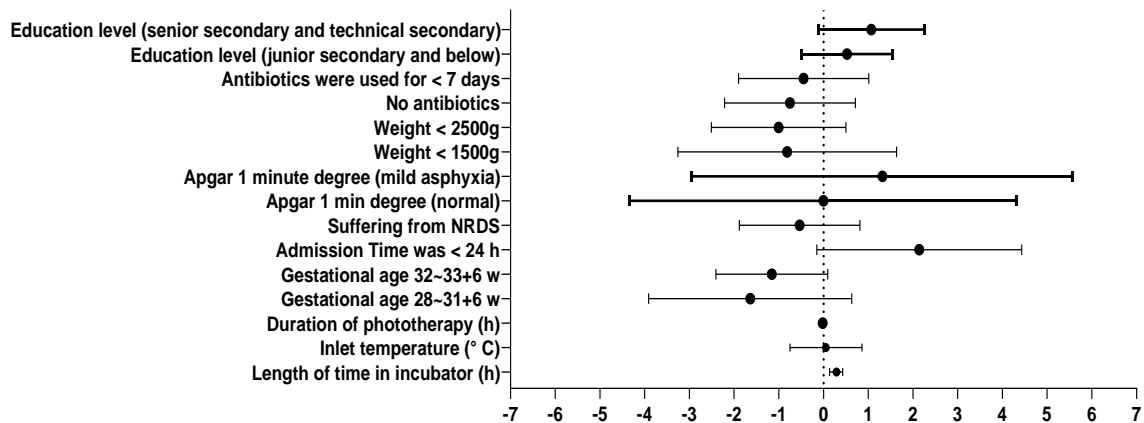
Figure 1: Forest plot of multivariable logistic regression analysis examining factors impacting umbilical cord detachment time in premature infants

subcutaneous fat, premature infants have a higher risk of umbilical cord infections [13].

Previous studies have shown that promoting early detachment of umbilical cord in premature infants not only effectively prevents infection, but also has potential benefits for their physical health and overall development [14]. Amoxicillin-clavulanate potassium is a combination antibiotic medication comprising amoxicillin and potassium clavulanate. Amoxicillin is a broad-spectrum antibiotic belonging to the penicillin class of drugs with antibacterial properties. Potassium clavulanate is a β-lactamase inhibitor that effectively inhibits enzymes produced by bacteria, thereby enhancing antibacterial activity of amoxicillin. Amoxicillin-clavulanate potassium is commonly used to treat infections in the respiratory tract, urinary tract, skin, and soft tissues. It has particularly good efficacy against bacteria that produce β-lactamase [15].

This study revealed that treating umbilical cord remnants with amoxicillin-clavulanate potassium promotes early drying, detachment, and healing. Furthermore, among the 76 premature infants in the study group treated with amoxicillin-clavulanate potassium, no adverse reactions were observed. This result suggests that amoxicillin-clavulanate potassium is safe in promoting umbilical cord detachment. The reason for this is that the concentration of amoxicillin-clavulanate potassium used in this study is low, and the amount of topical medication is minimal, thus minimizing the possibility of systemic adverse reactions in premature infants.

Previous clinical studies have addressed the timing and influencing factors of umbilical cord detachment in full-term newborns [16]. However,

there's a dearth of clinical reports on this topic concerning premature infants. Understanding these aspects is crucial for preventing adverse effects like umbilical cord infections and improving premature infants' prognosis. This study also revealed that factors like weight, gestational age, age at admission, NRDS presence, antibiotic use, incubator duration, initial temperature, phototherapy duration, Apgar score, and maternal education level significantly affected umbilical cord detachment time ($p < 0.05$).

Multivariate logistic regression analysis identified incubator residence time as the primary influencing factor ($p < 0.05$). Premature infants often experience hypothermia after birth due to immature thermoregulation [17], requiring incubator use for warmth, which mimics the uterine environment and helps minimize discomfort [18]. However, high humidity in incubators, though beneficial for premature infants, may delay umbilical cord detachment [19], potentially increasing the risk of bacterial proliferation. Hence, strict aseptic procedures and heightened awareness of disinfection are crucial during incubator use for premature infants to reduce risk of infection. Additionally, individualized assessment of incubator necessity and duration is vital to mitigate risk of delayed umbilical cord detachment.

Limitations of this study

There are still some limitations in this study. Due to constraints in time, operational space, and the number of included samples, this study did not conduct a comparative analysis of the specific bacterial infection situation in premature

newborns. In future, efforts should be to expand the study scale and increase number of samples.

CONCLUSION

Application of amoxicillin-clavulanate potassium facilitates early detachment of umbilical cord in preterm infants, thereby alleviating parental concerns and burdens. Furthermore, variables such as premature infant weight, gestational age, age at admission, presence of Neonatal Respiratory Distress Syndrome (NRDS), antibiotic usage, duration in the incubator, initial incubator temperature, duration of phototherapy, Apgar score at 1 min, and maternal education level affects umbilical cord detachment time. Among these factors, incubator residence time emerges as the primary determinant affecting umbilical cord detachment time in premature infants.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of Anhui Medical University Hospital (approval no. 3253295732).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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