Araştırma Makalesi
Research Article

Can early hemoglobin level and number of blood transfusions predict bronchopulmonary dysplasia

ERKEN HEMOGLOBİN DEĞERİ VE KAN TRANSFÜZYON SAYISI BRONKOPULMONER DİSPLAZİYİ ÖNGÖREBİLİR Mİ?

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ABSTRACT

Background: Currently, no practical biomarker has been discovered for early recognition of the development of bronchopulmonary dysplasia(BPD). This study aimed to evaluate the predictive value of early complete blood count (CBC) indices along with red blood cell transfusion (RBCT) frequency for the development of moderate/severe BPD, and to identify a promising predictive risk model for BPD.

Methods: In this cross-sectional study, one-hundred-sixty-two neonates born before the 32nd weeks of gestation were retrospectively. Predictive role of CBC parameters in the first three postnatal days(PD) and the number of RBCTs on weekly basis were evaluated by univariate/multivariate analysis as well as multivariate data mining processing.

Results: Despite several factors affected BPD development in univariate analysis, gestational age, PD3 haemoglobin level and frequency of RBCT were found to be the independent predictors of BPD in multivariate analysis. The haemoglobin<155 g/L in the PD3 predicted moderate/severe BPD with 60% sensitivity and 88% specificity (AUC 0.80). Having received at least one RBCT during the first three postnatal weeks had AUC 0.81(sensitivity 0.91, and specificity 0.81). During hospitalisation, more than four RBCT predicted moderate/severe BPD with 0.83 sensitivity and 0.93 specificity (AUC0.96). A model including gestational age, PD3 haemoglobin value, and number of RBCT predicted BPD risk with 87% sensitivity and 86% precision using data mining methods.

Conclusion: Results emphasise that even just one blood transfusion in the first weeks is an independent risk factor for BPD. Even though BPD is multifactorial, initial haemoglobin value and RBCT frequency may serve as non-invasive and practical parameters to estimate BPD development risk.

Key Words: Complete blood count; haemoglobin; red blood cell transfusion; bronchopulmonary dysplasia; very preterm infant.

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ÖZ

Giriş: Bronkopulmoner displazi (BPD) gelişiminin erken tanınması için pratik bir biyobelirteç henüz keşfedilmemiştir. Bu çalışma, orta/şiddetli BPD gelişimi için erken tam kan sayımı (CBC) indekslerinin yanı sıra kırmızı kan hücresi transfüzyonu (RBCT) sıklığının hastalığı öngörmedeki değerini ve BPD için umut verici bir öngürücü risk modeli belirlemeyi amaçlamıştır.

Gereç ve Yöntem: Bu kesitsel çalışmada, 32. gebelik haftasından önce doğan 162 yenidoğan retrospektif olarak incelendi. Doğum sonrası ilk üç gündeki (PD) tam kan sayımı parametrelerinin öngörücü rolü ve haftalık bazda RBCT sayısı, tek değişkenli/çok değişkenli analizin yanı sıra çok değişkenli veri madenciliği işleme ile değerlendirildi.

Bulgular: Tek değişkenli analizde BPD gelişimini etkileyen birkaç faktöre rağmen, çok değişkenli analizde gebelik yaşı, PD3 hemoglobin düzeyi ve RBCT sıklığının BPD'nin bağımsız belirleyicileri olduğu bulundu. PD3'teki hemoglobin <155 g/L, %60 duyarlılık ve %88 özgüllükle (EAA 0,80) orta/şiddetli BPD'yi öngördü. Doğum sonrası ilk üç hafta boyunca en az bir RBCT almış olmak, EAA 0,81'e sahipti (duyarlılık 0,91 ve özgüllük 0,81). Hastanede yatış sırasında, dörtten fazla RBCT, 0,83 duyarlılık ve 0,93 özgüllük (AUC0,96) ile orta/şiddetli BPD'yi tahmin etti. Gebelik yaşı, PD3 hemoglobin değeri ve RBCT sayısını içeren bir model, veri madenciliği yöntemlerini kullanarak %87 hassasiyet ve %86 kesinlik ile BPD riskini tahmin etti.

Sonuç: Sonuçlar, ilk haftalarda sadece bir kan transfüzyonunun bile BPD için bağımsız bir risk faktörü olduğunu vurgulamaktadır. BPD çok faktörlü olsa da, başlangıç hemoglobin değeri ve RBCT frekansı, BPD gelişme riskini tahmin etmek için invazif olmayan ve pratik parametreler olarak hizmet edebilir.

Anahtar Kelimeler: Tam kan sayımı, hemoglobin, eritrosit transfüzyonu, bronkopulmoner displazi, çok küçük preterm.

Despite developments in health science and technology, mortality and morbidity rates of premature babies are still high. Although most prematurity-related morbidities are multifactorial, the most important factor is still the prematurity itself. Bronchopulmonary dysplasia (BPD) is one of the most source-and-effort-required morbidity among other morbidities of premature babies (1)

Because of the complex pathophysiology of BPD, various factors have been accused and bunch of biomarkers have been proposed. Even though there are efforts to develop specified laboratory methods to predict BPD, these methods are expensive, invasive, or unavailable. On the other hand, risk-scoring systems, including main risk factors such as gestational week, gender and mechanical ventilation requirement, do not allow individual risk analysis (2). Current limitation of specific biomarkers and scoring systems has prompted researchers to determine inexpensive and straightforward tests used frequently in routine clinical practice to foresee BPD.

One of the most common laboratory tests used for preterm infants is complete blood count (CBC), and current data indicate a possible relationship between CBC indices and BPD. Several studies have investigated the relationship between BPD and platelet count as well as indices of platelet functions (3–6). Furthermore, low haemoglobin values in the early neonatal period or/and high transfusion numbers have recently been identified as associated risk factors for BPD development (7). However, the data is inconsistent and inconclusive. In the majority of studies, sample size were insufficient, CBC parameters were

considered alone, and the analysis did not consider confounding factors.

In this study, our objectives were to evaluate the predictive values of CBC indices in the first three postnatal days of life (PD1-3) for BPD development, determine the predictive value of the number of RBCT for BPD development, and create comprehensive risk-scoring systems using data mining methods.

MATERIALS AND METHOD

Study Design

The study evaluated medical records of very preterm infants born between the 24th and 32th of gestational weeks and followed in the tertiary neonatal intensive care unit in the hospital from January 2015 to December 2018. It was approved by the Ethical Committee of Non-invasive Clinical Research of Dokuz Eylul University, Izmir.

Maternal and neonatal data were obtained from patient files and information management system of the hospital. In addition, CBC indices during the first three days of life were recorded. These indices were red-blood-cell count (RBC), haemoglobin (HGB), haematocrit (HTC), mean-corpuscular-volume (MCV), mean-corpuscular-haemoglobin (MCH), mean-corpuscular-haemoglobin-concentration (MCHC), red-blood-cell-distribution-width (RDW), platelet count (PLT), mean-platelet-volume (MPV), plateletcrit (PTC), white-blood-cell count (WBC), absolute-neutrophil count (ANC), lymphocyte count (LYM), monocyte-count (MONO), eosinophil-count (EOS), basophil-count (BASO). If infants had received RBCT treatment before the third day of life, post-transfusion values of the CBC indices were excluded.

BPD was defined as the need for supplemental oxygen or pressure support for at least 28 days of life, and the classification was made at the postmenstrual 36 weeks of age (8,9). Patients resulted with mortality before the 36th postmenstrual week were excluded from the analysis.

21st Intergrowth standards were used to calculate the percentiles and z-scores of body weight, length and head circumference for birth and postnatal growth (10). Extrauterine growth restriction was defined as the z-score of body weight at discharge lower than the -1 standard deviation from birth (11).

Inclusion and exclusion criteria

Infants born between the 24th and 32nd weeks of gestation at the hospital from January 2015 to December 2018 were enrolled in the study. Patients were excluded if any of the following factors existed: transfer to another hospital, major congenital anomaly, blood product transfusion before the third postnatal day of life (PD).

The primary objective was to evaluate the predictive values of CBC indices in the first three postnatal days of life for moderate/severe BPD development. Secondary and further objectives were to evaluate the predictive value of the RBCT frequency for moderate/severe BPD development and to define a promising predictive risk model including selected CBC indices.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 25, and the data-mining process was performed using Orange version 3.18.0. Categorical values were presented as number (n) and percentage (%), while continuous variables were presented as mean (±SD) and median (minimum-maximum), depending on their distribution. Skewness and Kurtosis values, normality tests, and histograms were determined according to the normal distribution of continuous variables. The Chi-squared and Fisher exact tests compared categorical variables among groups. Mann-Whitney U test was used to compare nonparametric variables, and Student T-test was used for comparison between variables with normal distribution.

Univariate and multivariate analysis was performed using independent variables, which were demographic features, complete blood counts and indices, erythrocyte transfusion rates, and dependent variable which was moderate/severe BPD. Predictive cut-off values were assessed for each parameter using ROC analysis as the area under the curve is more than 0.70. $P<0.05$ was determined as statistical significance. Logistic regression analysis was performed to determine the contribution of

each independent variable to the model that was found to be significant in univariate analysis.

In addition, Support Vector Machines, Decision Tree, Random Forest Artificial Neural Network, Naive Bayes, and Logistic Regression algorithms of the datamining process were performed to develop a possible scoring system predicting BPD. Well-known risk factors for each morbidity and aforementioned statistically significant parameters were used in the process.

RESULTS

One hundred seventy-five infants born between the 24th to 32nd weeks of gestation were enrolled. Among these infants, 13 were excluded from the study: 6 infants required transfusion before the third postnatal day, and seven infants were transferred to another hospital. Finally, 162 infants were included in the study.

Maternal, neonatal features

Thirty-two per cent of the infants had maternal comorbidities, which were preeclampsia, gestational diabetes, hypothyroidism, and ablatio placenta. Babies had a median gestational age of 28.6 weeks (24.1 – 31.9) and a median birth weight of 1130 gr (400–2018). In total, 29 infants resulted in mortality. Among these infants, 22 of them died in the first week of life and seven during the latter period. Characteristics of the infants with and without moderate or severe BPD were compared using univariate analysis have been shown in Table 1.

Table 1. Characteristics of Infants with and without Moderate to Severe BPD

	Moderate/Severe BPD		
Features	**No (n:109)**	**Yes (n:24)**	**p**
Birth weight (g)	1211 (±38)	734 (±34)	**< 0.01**
Gestational week	28.9 (±0.2)	25.9 (±0.3)	**< 0.01**
Preeclampsia	40 (%88.9)	5 (%11.1)	0.41
C/s	110 (%84.6)	20 (%15.4)	0.89
Chorioamnionitis	39 (%78)	11 (%22)	0.08
PPROM (>18h)	29 (%82.9)	6 (%17.1)	0.66
Gender (male)	64 (%84.2)	12 (%15.8)	0.45
SGA	28 (%80)	7 (%20)	0.32
Antenatal steroid	91 (%86.7)	14 (%13.3)	0.47
Surfactant therapy	60 (%76.9)	18 (%23.1)	**< 0.01**
Apgar scores			
1st min	6	4	0.69
5th min	8	8	0.76
Delivery room resuscitation	75 (%76.5)	23 (%23.5)	**< 0.01**
NIV (days)	4 (0-49)	28.7 (±2.7)	**< 0.01**
MV (days)	1 (0-63)	37.2 (±2.6)	**< 0.01**
Early onset sepsis	57 (%81.4)	13 (%18.6)	0.24
Late onset sepsis	46 (%65.7)	24 (%34.3)	**< 0.01**
HsPDA	27 (%69.2)	12 (%30.8)	**< 0.01**
IVH2-3	9 (%64.3)	5 (%35.7)	0.056
HGB 1	16.2 (±0.2)	15.1 (±0.4)	**0.037**
HTC1	50.1 (±0.6)	45.9 (19.8-61)	**0.023**
RBC1	4.34 (±0.06)	3.83 (1.74-4.97)	**0.01**
HGB3	15.7 (11.9-20.9)	13.6 (±0.86)	**< 0.01**
HTC3	49.2(±0.93)	38.3 (±3.6)	**< 0.01**
RBC3	4.35 (3.07-5.98)	3.43 (±0.17)	**< 0.01**
Frequency of early (1-3th week) RBCT	0 (0-4)	3 (1-9)	**< 0.01**
Frequency of total RBCT	1 (0-18)	9 (±1)	**< 0.01**
Mortality	26 (%85.2)	3 (%10.3)	0.64

BPD: Bronchopulmonary dysplasia; C/S: C section; PPROM: Prolonged premature prelabour rupture of membranes; SGA: Small for gestational age; NIV: Non-invasive ventilation; MV: Mechanical ventilation; HsPDA: Hemodynamic significant patent ductus arteriosus; IVH2-3: Intraventricular hemorrhage grade 2 and 3; HGB1: Hemoglobin of first postnatal day; HTC1: Hematocrit of first postnatal day; RBC1: Red blood cell count of first postnatal day; HGB3: Hemoglobin of third postnatal day; HTC3: Hematocrit of third postnatal day; RBC3: Red blood cell count of third postnatal day; RBCT: Red blood cell transfusion

CBC-indices and outcomes

All 162 infants had CBC records on postnatal days of life (PD) 1-3 . Of those records, 160 belonged to PD1 and 64 belonged to PD3. Since 29 patients were excluded from the analysis because of mortality before the 36th postmenstrual week, only 133 of these infants were included in the analysis. Thirty-five (21.6 %) out of 133 evaluated infants were diagnosed with BPD. Of those infants, 18 (11. 1%), 6 (3.7%), and 11 (6.8%) were classified as severe, moderate and mild BPD, respectively. Therefore, 24 out of 133 babies were diagnosed with moderate/severe BPD.

Analysis, performed to evaluate the relationship between BPD and CBC-indices, pointed out that median HGB, HCT and RBC values on PD3 were significantly lower in patients diagnosed with moderate/severe BPD (Table 1). Median RBC, HGB, HCT, PLT and PCT values were significantly lower in infants with moderate/severe BPD than in infants with mild BPD or without BPD. Median HGB level lower than 155 g/L in PD3 showed 88% sensitivity and 60% specificity, and HCT lower than 39.2% in PD3 showed 94% specificity on ROC analysis. Further, the median MCH was higher in the moderate/severe BPD group. MPV in PD1-3 did not have a relationship with BPD. The predictive values of early CBC-indices for the BPD according to the ROC analysis have been given in Table 2.

Table 2. Predictive Values of CBC-indices and RBCT frequency for moderate/ severe BPD development by ROC Analysis

CBC-indices and RBCT Counts	**Cut-off**	**AUC**	***P***	**95% CI**	**Sensitivity**	**Specificity**
Moderate/Severe BPD						
RBC (10^{12} cells/L)	4.11	0.913	<.001	0.821 - 1.000	0.60	1
HGB (g/L)	155	0.801	.004	0.634 - 0.968	0.60	0.88
HTC (volume fraction)	39.2	0.805	.004	0.656 - 0.954	0.94	0.55
PLT ($\times 10^9$/L)	172	0.737	.023	0.596 - 0.879	1	0.52
PTC (volume fraction)	0.16	0.711	.044	0.565 - 0.857	1	0.41
MCV (fl)	38.9	0.751	.017	0.587 - 0.914	0.66	0.78
Total RBCT Counts	4	0.957	<.001	0.924 – 0.990	0.83	0.93
1 - 3 week	1	0.895	<.001	0.845 – 0.946	0.91	0.81
3 - 12 week	2	0.938	<.001	0.897 – 0.978	0.73	0.88

PTC, plateletcrit; RBC, red blood cell's count; HGB, hemoglobin; HTC, hematocrit; PLT, platelet's count; MCV, mean corpuscular volume; BPD, bronchopulmonary dysplasia; RBCT, red blood cell transfusion

The frequency of RBCT was assessed on weekly basis. According to the clinical protocol, the decision of RBCT has been taken by the consultant neonatologist in NICU and generally 15 cc/kg of appropriate packed erythrocyte suspension has been transfused based on guidelines. Generally, median transfusion frequency per infant was 1 (0-18). Forty-four infants received erythrocyte transfusion in the first week of life after PD1-3. Eighty-three of them received transfusion in the first three weeks, and 65 babies were transfused between 3 and 12 weeks of life. RBCT rate was significantly higher in the group diagnosed with moderate or severe BPD. ROC analysis of RBCT frequency for predicting moderate/severe BPD development have been shown in Table 2. Having received at least one RBCT during the first three PN weeks had AUC 0.90 with a sensitivity of 0.91 and a specificity of 0.81. For total RBCT count , a cut-off level "4 " had AUC 0.96 with a sensitivity and specificity of 0.83 and 0.93 respectively.

Logistic regression analysis was performed to test the effect of gestational age, HsPDA, surfactant replacement treatment, the number of the first three weeks' RBCT, and HGB level on PD1, on moderate to severe BPD development. Moderate/severe BPD was found to be significantly associated with decreased gestational age

(adjusted OR:0.61, p<0.01) and increased number of the first three weeks' RBCT (adjusted OR:2.7, p<0.01). HsPDA (adjusted OR:0.47, p:0.6), HGB1 (adjusted OR:0.33, p:0.33) and surfactant treatment (adjusted OR:1.69, p:0.5) were not found to be significant.

The utility of complete blood counts and indices to estimate BPD was also evaluated by the data-mining process. In the data-mining model of moderate/severe BPD, the Naive-Bayes method had the highest predictive value by using parameters including gestational week, birth weight, invasive mechanically ventilation duration, RBCT during first three weeks , LOS, HB on PD3 (Figure 1).

Figure 1.

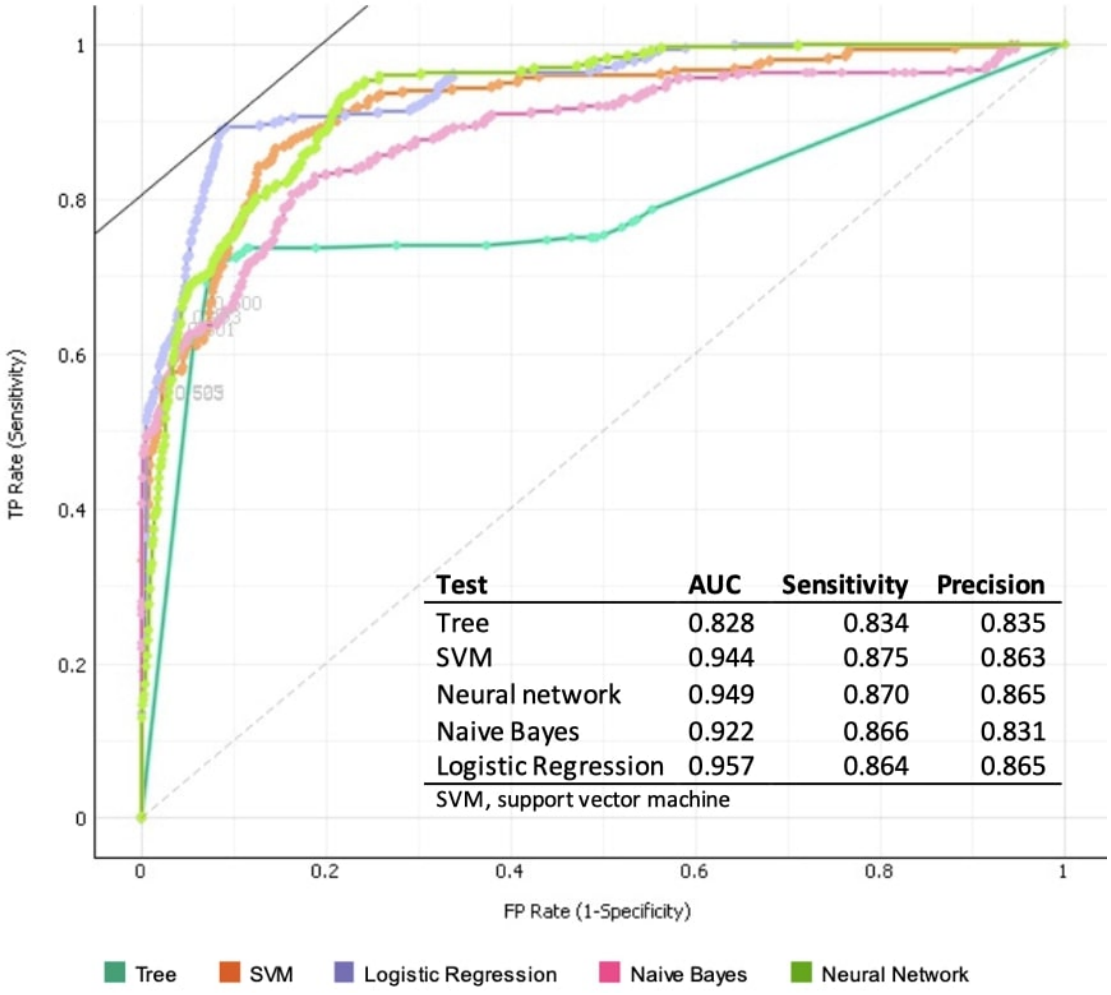

Figure 1. ROC curve (Receiver Operating Characteristic) in datamining processing demonstrating the performence of the prediction model. Model included gestational week, invasive mechanically ventilation duration, RBCT(red blood cell transfusion) during first three weeks, LOS (late onset sepsis), HB on PD3 (haemoglobin on postnatal day 3).

DISCUSSION

Recent evidence suggests a relationship between lower haemoglobin (HGB) levels with BPD. However, this study evaluates the value of CBC indices and the RBCT frequency in predicting BPD from a holistic perspective. The main results suggest a significant relationship between BPD with early haemoglobin levels and RBCT frequency. Even one RBCT in the first three weeks was found to be independently related with increased risk for moderate to severe BPD.

As supported by other studies, the study emphasises that early lower HGB level was mainly related to moderate/severe BPD. Since haemoglobin F (HGBF) is dominant in the early postnatal period, lower haemoglobin means lower HGBF. Hellström W. et al. showed that lower haemoglobin and HGBF were associated with an increase in BPD frequency in the early postnatal period, supporting our study12. Because HGBF's oxygen-holding capacity is higher than adult haemoglobin A (HGBA1), HGBF is expected to cause less fluctuation in the level of free oxygen radicals in the blood. It is thought that since erythrocyte suspensions used in the treatment include adult HGBA1 instead of HGBF, it causes more fluctuations in free oxygen and increases oxidative damage. Additionally, recurrent rates of RBCT are associated with increasing non-transferrin-bound iron overload, causing an impact on the immune system, nitric oxide-induced vasoregulation, and oxidative stress in vulnerable preterm babies (13).

Even though the accepted anaemia level of HGB is lower than 135 g/L and the generally accepted required transfusion limit level of HGB is lower than 120 g/L, this study reveals that an HGB level lower than 155 g/L in PD3 is related to moderate/severe BPD with high sensitivity and specificity. Duan Jun et al. found the same cut-off level in PD3 for this morbidity (14). It is also known that delayed umbilical cord clamping improves clinical outcomes of preterm infants, at least via increasing blood volume and HGB levels (15).

The median values of CBC-indices of PD1-3 were similar to the previously defined values (16). Studies have investigated the relationship between CBC-indices (RDW and MPV are the most studied parameters) and morbidities of prematurity. However, PDA, BPD, and ROP were the most common morbidities studied in this manner, and the literature on this issue needs to be more consistent (5,17,18).

The retrospective design and small sample size are the most critical limitations of this study. Delayed cord clamping has been increasingly used at the moment of birth, and the protocol of our obstetric clinic allows 30 seconds before clamping. Although it is used in routine practice, the impact of delayed cord clamping on CBC values and morbidities could not be analysed in the study owing to retrospective design and insufficient data.

The most crucial difference between our study and existing studies is that it comprehensively deals with the effect of many CBC indices on BPD. Additionally, the data-mining method evaluated the relationship between different confounding data and their impact on the BPD. Finally, the results indicated that early haemoglobin level in. The first three PDs and frequency of RBCT in the first weeks are promising parameters that would be a substantial part of the scoring systems predicting the morbidities of prematurity.

Conclusion

The study suggested that the lower erythrocyte mass and the higher RBCT frequency are independent risk factors for BPD development. Even though BPD is multifactorial, and prematurity is still the most critical risk factor, combining the early HGB level with other clinical risk factors, including gestational age, birth weight, prolonged invasive ventilation, and RBCT frequency may serve as a helpful clinical score for predicting it. Further prospective studies, including larger samples, are needed to clarify these results.

Disclosure

Any financial support has received for the study.

Author Contribution

C.A. and F.T. designed the study; C.A , Y.A., N.D. collected data; P.K performed the statistical analysis N.D. and H.O conceptual advice. CA wrote the first draft of the study. F.T. supervised the whole study process. All authors read and approved the final manuscript.

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