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Risk factors associated with anemia of prematurity requiring red blood cell transfusion in very low birth weight infants: a retrospective study

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Abstract

Background Anemia of prematurity (AOP) is prevalent among very low birth weight infants (VLBWIs). Red blood cell (RBC) transfusions, while necessary for managing AOP, have been linked to adverse neonatal outcomes.

Methods This retrospective study analyzed the medical records of 98 VLBWIs (24–31 weeks gestation) admitted to the Chungbuk National University Hospital neonatal intensive care unit. Infants were categorized based on RBC transfusion status and birth weight (< 1000 g and 1000–1499 g). Clinical outcomes between the groups were compared.

Results Of the 98 infants, 35 (35.7%) received RBC transfusions. The RBC transfusion group exhibited significantly higher incidence of bronchopulmonary dysplasia (≥ moderate), prolonged invasive mechanical ventilation, intraventricular hemorrhage (grades 1–2), extended time to full enteral feeding, and extended total parenteral nutrition (TPN) compared to the non-RBC transfusion group. Birth weight was inversely correlated with the number of RBC transfusions ($p = 0.004$). The duration of invasive mechanical ventilation and TPN administration were positively associated with the number of RBC transfusions ($p < 0.001$ and $p = 0.025$, respectively).

Conclusions The RBC transfusion group experienced more comorbidities than the non-transfusion group. Birth weight, duration of invasive ventilation, and duration of TPN were associated with the number of RBC transfusions. Strategies to reduce the duration of invasive ventilation and early discontinuation of TPN may mitigate the need for RBC transfusions in AOP.

Keywords Anemia of prematurity, Red blood cell transfusion, Very low birth weight infants

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Background

Anemia of prematurity (AOP) is a common condition in very low birth weight infants (VLBWIs). Physiologic anemia occurs in healthy term newborns with a nadir around two months of life because of the short lifespan of neonatal red blood cells (RBC), decreased erythropoiesis, and hemodilution with somatic growth [1, 2]. AOP exacerbates physiological anemia due to low blood volume at birth and iatrogenic blood loss during hospitalization. AOP onset is earlier, and recovery is slower compared to physiological anemia in term infants.

Several strategies, including delayed cord clamping (DCC), human recombinant erythropoietin (hrEPO) administration, and minimizing blood withdrawals, have been implemented to mitigate the severity of AOP [3, 4]. RBC transfusion is often employed to improve perfusion and oxygenation in preterm infants with AOP [5, 6]. However, it is recognized as a risk factor for adverse outcomes such as necrotizing enterocolitis (NEC) [7–9], intraventricular hemorrhage (IVH) [10], bronchopulmonary dysplasia (BPD) [7], retinopathy of prematurity (ROP) [11], and in-hospital mortality [11, 12].

There is a lack of consensus regarding the optimal hemoglobin level in preterm infants with AOP and the appropriate threshold for RBC transfusion. Restrictive transfusion thresholds may not be detrimental and could even be associated with fewer neurodevelopmental impairments [13–15]. Consequently, interest in limiting RBC transfusions in neonatal care is increasing. This study aimed to identify risk factors associated with AOP requiring RBC transfusion in VLBWIs. Moreover, it aimed to investigate changes in hemoglobin levels during the first month of life in VLBWIs with AOP, depending on whether RBC transfusions were received.

Methods

Study design and participants

We conducted a retrospective review of medical records of VLBWIs (birth weight < 1500 g) with gestational age (GA) of 24–31 weeks. These infants were born and admitted to the neonatal intensive care unit (NICU) of Chungbuk National University Hospital between January 1, 2016 and August 31, 2021.

To focus on the clinical course of pure AOP, we excluded infants who died or were transferred to other NICUs within 14 days of life, and those who required RBC transfusion for reasons other than AOP, such as massive pulmonary hemorrhage, severe IVH (grades 3–4), or severe pulmonary hypertension.

Routine complete blood count (CBC) tests were performed on days one, three, and seven, and weekly thereafter. Blood gas analysis was conducted daily when respiratory support was required.

During the study period, RBC transfusions were administered according to a guideline based on hemoglobin level and respiratory support status [16]. In our unit, feeding was not routinely discontinued during RBC transfusions.

Following NICU protocol, irradiated and leukocyte-filtered RBC were transfused into VLBWIs with AOP who met the transfusion threshold [16] at a volume of 10–15 mL/kg over four hours.

Measurements

We categorized the enrolled infants based on their RBC transfusion status and birth weight (< 1000 g and 1000–1499 g). Clinical manifestations between the non-RBC and RBC transfusion groups were compared. Clinical characteristics included GA, birth weight, sex, Apgar scores at one and five minutes, delivery mode, antenatal steroid use, premature rupture of membranes, pregnancy-induced hypertension, gestational diabetes mellitus, and implementation of DCC at birth. GA was determined using the last maternal menstrual period and adjusted with the Ballard test. Short-term outcomes investigated included death before discharge, BPD (≥ moderate) [17], duration of respiratory supports, IVH (grades 1–2) [18], NEC (≥ Bell's stage 2b) [19], periventricular leukomalacia [20], ROP requiring laser treatment [21], time to full enteral feeding (100 mL/kg), duration of total parenteral nutrition (TPN), and number of hospital days. Hemoglobin levels, hematocrit levels, and number of CBC tests were compared between the two groups.

Statistical analysis

Continuous variables were compared using Student's t-test or Mann–Whitney U test and are presented as mean ± standard deviation. Categorical variables were compared using the Chi-square test or Fisher's exact test and are presented as percentages and frequencies. Using multiple linear regression analysis, we analyzed the association between the number of RBC transfusions and clinical characteristics. SPSS version 27 (SPSS Inc., Chicago, IL) was used for all the statistical analyses. A p value < 0.05 was considered statistically significant.

Results

Clinical characteristics of the infants

During the study period, 134 infants were born and admitted to the NICU. Based on the exclusion criteria, 20 infants (death or transfer), eight with massive pulmonary hemorrhage, seven with severe intraventricular hemorrhage, and one with pulmonary hypertension were excluded. Remaining 98 infants were included.

The mean GA and birth weight were 29^{+0} (24^{+3}-31^{+2}) weeks and 1116 ± 267.4 (540–1470) g, respectively. Thirty-five infants (35.7%) received RBC transfusions

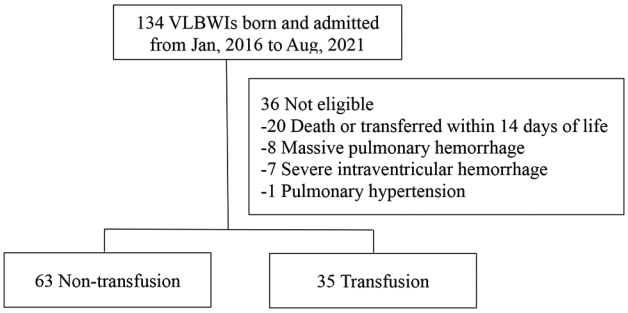

Fig. 1 Flow charts

during NICU hospitalization (Fig. 1). Of these, 34 were extremely low birth weight infants ([ELBWIs], birth weight < 1000 g), and 28 (82.4%) underwent RBC transfusions. Among infants with birth weight of 1000–1499 g, seven (10.9%) received RBC transfusions.

Table 1 presents demographic and clinical data of the infants with AOP, categorized into RBC transfusion and non-transfusion groups. In the overall analysis, the transfusion group had significantly lower GA, birth weight, and Apgar scores, whereas the incidence of pregnancy-induced hypertension was significantly higher compared to the non-transfusion group. However, these significant differences were not observed in subgroup analyses based on birth weight.

Clinical outcomes between the two groups

Table 2 presents the clinical outcomes of infants with AOP, comparing those who received RBC transfusions to those who did not. Mortality and morbidities, including respiratory distress syndrome, BPD (≥ moderate), duration of respiratory support, hypotension, IVH (grades 1–2), NEC (≥ stage 2b), culture-proven sepsis, and ROP requiring laser treatment, were significantly higher in the transfusion group. The time to full enteral feeding, duration of TPN, and number of hospitalization days were also significantly longer in the transfusion group.

These findings were consistent in the subgroup analyses of the incidence of BPD (≥ moderate), duration of invasive mechanical ventilation, incidence of IVH (grades 1–2), time to full enteral feeding, and duration of TPN.

Regarding the association between the number of RBC transfusions and clinical characteristics, birth weight was inversely correlated with the number of RBC transfusions. The duration of invasive mechanical ventilation and TPN were positively correlated with the number of RBC transfusions (Table 3).

Hematologic features between the two groups

In the ELBWIs subgroup, the initial hemoglobin level was significantly different between the two groups. The transfusion group underwent additional CBC tests during hospitalization.

RBC transfusions were administered to the transfusion group at an average of 27.6 ± 16.1 days (range 7–76) after birth, with a mean of 3.2 ± 2.3 (1–10) times during hospital stay (Table 4).

A significant difference in hemoglobin levels was observed between the two groups starting with the third CBC test (approximately seven days of life) (Fig. 2).

Table 1 Demographics of enrolled infants

Variable	< 1000 g		1000–1499 g		Total	
	Non-transfusion (*N* = 6)	Transfusion (*N* = 28)	Non-transfusion (*N* = 57)	Transfusion (*N* = 7)	Non-transfusion (*N* = 63)	Transfusion (*N* = 35)
GA (weeks)	28.3 ± 1.4	27.1 ± 2.2	29.3 ± 1.2	28.7 ± 1.4	29.2 ± 1.2	27.5 ± 2.1*
Birth weight (g)	843.3 ± 83.6	779.6 ± 116.1	1295.3 ± 126.8	1234.3 ± 124.7	1252.2 ± 181.6	870.6 ± 217.9*
Male	2 (33.3)	12 (42.9)	29 (50.9)	3 (42.9)	31 (49.2)	15 (42.9)
1-min Apgar score	6.0 ± 2.2	5.1 ± 2.0	6.4 ± 2.3	5.1 ± 2.5	6.4 ± 2.2	5.1 ± 2.1*
5-min Apgar score	8.6 ± 0.9	7.7 ± 1.3	8.4 ± 1.7	7.7 ± 1.6	8.4 ± 1.6	7.7 ± 1.3*
C/sec	5 (83.3)	22 (78.6)	41 (71.9)	6 (85.7)	46 (73.0)	28 (80.0)
Antenatal steroids	4 (66.7)	21 (75.0)	50 (87.7)	4 (57.1)	54 (85.7)	25 (71.4)
PROM	2 (33.3)	10 (35.7)	29 (50.9)	2 (28.6)	31 (49.2)	12 (34.3)
Pathologic chorioanmnionitis	1 (16.7)	13 (46.4)	30 (52.6)	1 (14.3)	31 (49.2)	14 (40.0)
PIH	2 (33.3)	12 (42.9)	6 (10.5)	2 (28.6)	8 (12.7)	14 (40.0)*
GDM	0 (0)	2 (7.1)	11 (19.3)	0 (0)	11 (17.5)	2 (5.7)
DCC	0 (0)	0 (0)	3 (5.3)	0 (0)	3 (4.8)	0 (0)

*P-value < 0.05

Mean ± SD (range)

GA, gestational age; PROM, premature rupture of membranes; PIH, pregnancy-induced hypertension; GDM, gestational diabetes mellitus; DCC, delayed cord clamping

Table 2 Clinical outcomes of enrolled infants

Variable	< 1000 g		1000–1499 g		Total	
	Non-transfusion (*N* = 6)	Transfusion (*N* = 28)	Non-transfusion (*N* = 57)	Transfusion (*N* = 7)	Non-transfusion (*N* = 63)	Transfusion (*N* = 35)
Mortality	0 (0)	3 (10.7)	0 (0)	0 (0)	0 (0)	3 (8.6)*
RDS	6 (100)	27 (96.4)	44 (77.2)	7 (100.0)	50 (79.4)	34 (97.1)*
Air leak syndrome	0 (0)	1 (3.6)	0 (0)	0 (0)	0 (0)	1 (2.9)
BPD (≥ moderate)	1 (16.7)	18/25 (72.0)*	10 (17.5)	6 (85.7)*	11 (17.5)	24 (75.0)*
Invasive mechanical ventilation (days)	1.0 ± 1.3	27.8 ± 27.7*	1.7 ± 1.8	4.4 ± 3.6*	1.7 ± 1.7	23.1 ± 26.4*
Non-invasive ventilation (days)	30.8 ± 21.9	50.3 ± 39.0	20.4 ± 18.4	44.7 ± 21.3	21.4 ± 18.8	49.1 ± 35.9*
Hypotension	0 (0)	18 (64.3)*	1 (1.8)	0 (0)	1 (1.6)	18 (51.4)*
IVH (grade 1–2)	1 (16.7)	19 (67.9)*	17 (29.8)	6 (85.7)*	18 (28.6)	25 (71.4)*
PVL	0 (0)	1 (3.6)	2 (3.5)	0 (0)	2 (3.2)	1 (2.9)
NEC (≥ Stage 2b)	0 (0)	6 (21.4)	0 (0)	0 (0)	0 (0)	6 (17.1)*
Culture proven sepsis	2 (33.3)	13 (46.4)	1 (1.8)	3 (41.9)*	3 (4.8)	14 (40.0)*
ROP requiring laser treatment	0 (0)	4 (14.8)	0 (0)	2 (28.6)*	0 (0)	6 (17.6)*
Timing of full enteral feeding (days)	9.3 ± 4.5	28.1 ± 18.8*	7.4 ± 4.6	19.1 ± 8.4*	7.6 ± 4.6	26.1 ± 17.3*
TPN duration	20.7 ± 10.8	52.3 ± 27.2*	10.7 ± 9.3	49.6 ± 23.6*	11.7 ± 9.8	51.7 ± 26.2*
HD	91.2 ± 24.6	107.8 ± 55.3	67.8 ± 16.7	91.1 ± 12.2*	70.0 ± 18.7	104.4 ± 50.0*

*P-value < 0.05

Mean ± SD (range)

RDS, respiratory distress syndrome of newborn; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; TPN, total parenteral nutrition; HD, hospital day

Table 3 Association between the number of red blood cell transfusions and clinical characteristics

Variables	β ± SE	Partial R^2	*P*-value
GA (weeks)	-0.197 ± 0.356	0.227	0.666
Birth weight (g)	-0.002 ± 0.001	0.433	0.004
Invasive mechanical ventilation (days)	0.056 ± 0.010	0.632	< 0.001
Timing of full enteral feeding (days)	0.009 ± 0.013	0.427	0.480
TPN duration (days)	0.017 ± 0.007	0.481	0.025
HD (days)	-0.007 ± 0.005	0.208	0.127

GA, gestational age; TPN, total parenteral nutrition; HD, hospital days

Discussion

This study aimed to identify risk factors associated with AOP requiring RBC transfusion in VLBWIs and compare hemoglobin trend changes between the two groups with or without RBC transfusion.

One-third of VLBWIs received RBC transfusions, with a rate of 82.4% in ELBWIs. Subgroup analyses based on birth weight revealed that BPD (≥ moderate), duration of invasive mechanical ventilation, IVH (grades 1–2), time to full enteral feeding, and duration of TPN administration were associated with RBC transfusion in VLBWIs. The initial hemoglobin level was also linked to RBC transfusion in ELBWIs.

The RBC transfusion rate in VLBWIs was lower than that reported in previous studies (50–70%) [22, 23], likely due to different inclusion criteria and study timing.

Table 4 Hematologic features of enrolled infants

Variable	< 1000 g		1000–1499 g		Total	
	Non-transfusion (*N* = 6)	Transfusion (*N* = 28)	Non-transfusion (*N* = 57)	Transfusion (*N* = 7)	Non-transfusion (*N* = 63)	Transfusion (*N* = 35)
Initial Hb, g/dL	19.5 ± 1.6	17.0 ± 2.7*	17.4 ± 2.2	17.3 ± 1.5	17.6 ± 2.2	17.1 ± 2.5
Initial Hct,	56.1 ± 9.7	52.7 ± 8.3	53.0 ± 6.4	52.7 ± 4.7	53.2 ± 6.7	52.7 ± 7.7
No. of CBC tests	12.2 ± 3.5	19.2 ± 8.1*	10.0 ± 2.7	16.4 ± 3.6*	10.2 ± 2.9	18.7 ± 7.5*
Hb at the 1st RBC transfusion	-	8.3 ± 1.2	-	7.5 ± 1.0	-	8.1 ± 1.2
Hct at the 1st RBC transfusion	-	25.1 ± 3.6	-	22.4 ± 3.0	-	24.5 ± 3.6
No of RBC transfusion	-	3.6 ± 2.4	-	1.4 ± 0.5	-	3.2 ± 2.3
Timing of the 1st RBC transfusion (HD)	-	26.5 ± 16.3	-	32.1 ± 15.5	-	27.6 ± 16.1

*P-value < 0.05

Mean ± SD (range)

Hb, hemoglobin; Hct, hematocrit; RBC, red blood cell; HD, hospital days

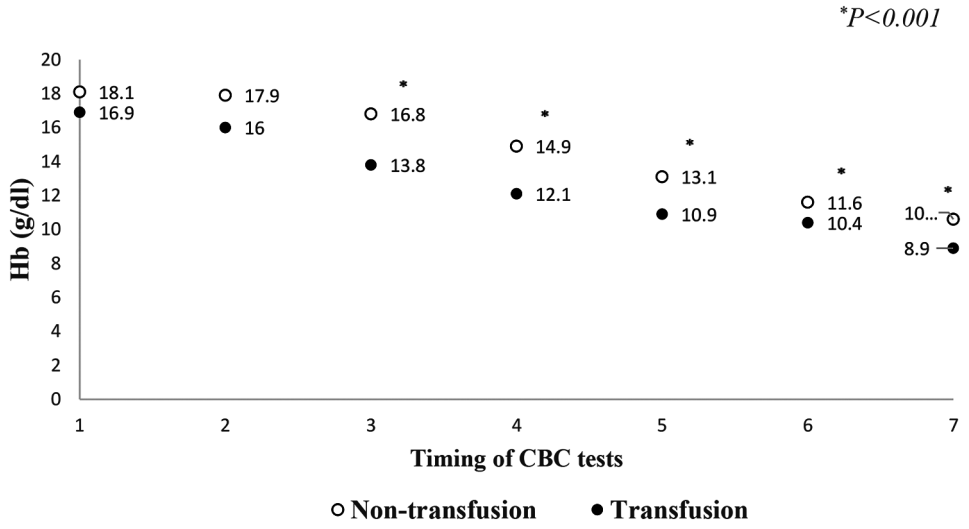

Fig. 2 Trends in hemoglobin levels between the non-transfusion and transfusion groups

Despite excluding infants with massive blood loss conditions, such as massive pulmonary hemorrhage and severe IVH, the RBC transfusion rate in ELBWIs was similar to previous findings [24–26], suggesting that birth weight is a crucial factor in AOP requiring RBC transfusion.

Other factors, including BPD, duration of mechanical ventilation, duration of TPN, and initial hemoglobin level, aligned with previous studies [22, 23]. Among the significant continuous variables, birth weight was negatively correlated with the number of RBC transfusions, while the duration of invasive ventilation and TPN were positively correlated. These findings suggest that reducing the duration of invasive mechanical ventilation and early discontinuation of TPN could potentially be modifiable factors to decrease exposure to RBC transfusion.

Several studies have reported that preterm infants who undergo RBC transfusion may experience poor clinical outcomes, including BPD, severe IVH, NEC, sepsis, and ROP. RBC transfusion is considered a risk factor for adverse prognosis in preterm infants.

In this study, the incidence of NEC was significantly higher in the transfusion group compared to the non-transfusion group. Among the six infants with NEC, four received RBC transfusions prior to NEC development; however, there was a one-month gap between NEC and RBC transfusion. Subgroup analysis revealed no significant differences between the two groups. Recent research suggests that severe anemia may contribute more to NEC development than RBC transfusions [9, 27, 28].

Regarding culture-proven sepsis, only three of 14 infants in the RBC transfusion group received RBC transfusions before the onset of sepsis.

The role of RBC transfusion as a risk factor for poor outcomes in preterm infants remains uncertain. The initial hemoglobin levels and number of phlebotomies were significantly different between the two groups. However, hemoglobin levels between the two groups showed became significantly different after the third laboratory test, corresponding to one week of life. These findings suggest that infants with rapidly progressing AOP may require RBC transfusion later. Strategies to reduce transfusion include efforts to reduce the cumulative amount of blood sampling [29, 30], DCC or umbilical cord milking to increase the blood volume of infants at birth [31, 32], and hrEPO treatment to prevent AOP requiring RBC transfusions [3, 33, 34].

During the study period, DCC was not actively performed in VLBWIs; only three infants received DCC. Increasing initial hemoglobin levels could be an effective way to reduce exposure to RBC transfusions.

VLBWIs, particularly ELBWIs, are critically ill patients. Exposure to invasive devices, such as prolonged ventilator care and central line catheters for TPN, can induce inflammatory conditions in preterm infants. Nutritional crisis and preterm birth lead to iron deficiency in these infants. These factors are associated with the pathophysiology of anemia in chronic diseases, also known as inflammatory anemia.

BPD, the most common chronic disease in preterm infants, is also called chronic lung disease. Diagnosing anemia in chronic diseases can be challenging. However, the treatment options are similar to those for AOP, including RBC transfusion, iron supplementation, and hrEPO administration. Treating the underlying disease is crucial [35, 36].

Neonatal medicine has recently focused on reducing morbidities in preterm infants. Multifactorial quality improvements, such as gentle respiratory care and early discontinuation of parenteral nutrition, can decrease the need for RBC transfusion in preterm infants.

Controversies exist regarding the hemoglobin threshold for RBC transfusion in preterm infants. Recent studies suggest that a high hemoglobin threshold does not improve neonatal outcomes, and a restrictive transfusion threshold is considered harmless [26, 37–39].

In addition to known factors associated with RBC transfusion in VLBWIs, including GA, birth weight, initial hemoglobin level at birth, and comorbidities, the NICU institution is another factor [22, 23, 25]. The RBC transfusion threshold can vary among NICUs.

In this study, we observed that chronic factors such as prolonged ventilator therapy and extended duration of TPN were associated with the number of RBC transfusions. Reducing the frequency of RBC transfusions by improving these chronic factors may indicate an improvement in NICU quality.

This study had several limitations. First, its single-center, retrospective, and uncontrolled observational design limited its scope. The small number of enrolled infants may restrict the generalizability of the results, and the data was skewed towards ELBWIs. Larger-scale studies are needed for further investigation. However, this is challenging due to varying RBC transfusion protocols across units [13–15, 22] and the numerous factors influencing neonatal outcomes [7, 11].

We did not accurately measure iatrogenic blood loss volumes or other hematological values such as ferritin, iron, transferrin, and hepcidin. Nevertheless, we observed that the duration of invasive ventilation and TPN could be modifiable factors associated with AOP requiring RBC transfusion.

Conclusions

This study found that infants who received RBC transfusions had more comorbidities. Birth weight, duration of invasive ventilation, and duration of TPN were associated with the frequency of RBC transfusions. Reducing the duration of invasive ventilation and early discontinuation of TPN could potentially prevent the need for RBC transfusions in AOP.

Abbreviations

AOP	Anemia of prematurity
VLBWI	Very low birth weight infant
RBCs	Red blood cells
DCC	Delayed cord clamping
hrEPO	human recombinant erythropoietin
NEC	Necrotizing enterocolitis
IVH	Intraventricular hemorrhage
BPD	Bronchopulmonary dysplasia
ROP	Retinopathy of prematurity
GA	Gestational age
NICU	Neonatal intensive care unit
CBC	Complete blood count
TPN	Total parenteral nutrition
ELBWI	Extremely low birth weight infant

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Author contributions

SY conceptualized and designed the study, performed the initial analyses, and drafted the initial manuscript. YK collected the data and reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Data availability

Data supporting the findings of this study are available from the corresponding author (dalen@chungbuk.ac.kr) upon request.

Declarations

Ethics approval and consent to participate

Data collection was approved by the Institutional Review Board of Chungbuk National University Hospital (IRB No. 2024-04-020). The Institutional Review Board waived the requirement for informed consent for this retrospective chart review. All methods were performed in accordance with relevant guidelines and regulations.

Chungbuk National University Hospital Institutional Review Board members

Bo Ra Son (Chairperson), Jin Young Yoo, Woong Choi, Eun Young Lee, Sun Gil Kwon, Yong Dae Kim, Won Seop Kim, Dong Hee Ryu, Tae Su Lee, Hee Bok Chae, Youn Soo Hahn, Hong Gu Her, Gook Mi Shin, In Sook Hong, Chul Woo Lee, Woong Gil Choi, Seung Park, Yong June Kim, and Ki wook Jung.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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