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Postnatal weight gain and retinopathy of prematurity in preterm infants: a population-based retrospective cohort study

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ABSTRACT

Objective: Infants who meet the screening guidelines for retinopathy of prematurity (ROP) based on birth weight and gestational age undergo serial ophthalmological examinations for its detection and treatment. However, <10% of patients require treatment, and less than half develop ROP. Poor postnatal weight gain has been reported to be a strong indicator of ROP development; however, the information regarding this is unclear. Therefore, this study aimed to determine the relationship between postnatal weight gain and ROP development in preterm infants.

Methods: The data of 675 preterm infants with gestational age ≤ 32 weeks, who were hospitalized in our neonatal intensive care unit, were obtained retrospectively from file records. The infants' demographic characteristics, clinical findings, and weekly weight gain (g/kg/day) during the first 8 weeks were recorded. The univariate was used to examine the risk factors for ROP followed by multivariate regression.

Results: The incidence of ROP in the infants included in the study was 41% ($n=278$) and 13.3% ($n=37$) of them required treatment. In the infants of the group that developed ROP, the mean birth weight and gestational age were significantly lower than those in the group that did not develop ROP (973 ± 288 and 1301 ± 349 g, $p=0.001$ and 28.48 ± 1.95 and 30.08 ± 1.60 weeks, $p=0.001$, respectively). As the gestational week and birth weight decreased, ROP development and the risk of ROP-requiring treatment increased. In the infants of the group that developed ROP, the mean weight gain in the postnatal third week was detected as significantly lower compared to those in the group that did not develop ROP (13.9 ± 8.2 and 15.4 ± 6.8 g, $p=0.034$). On multiple logistic regression analysis, birth weight (<750 g) (odds ratio [OR], 8.67; 95% confidence interval [CI], 3.99–18.82, $p=0.001$), blood transfusion (OR, 2.39; 95% CI, 1.34–4.24, $p=0.003$), necrotizing enterocolitis (OR, 4.79; 95% CI, 1.05–26.85, $p=0.045$), bronchopulmonary dysplasia (OR, 2.03; 95% CI, 1.22–3.36, $p=0.006$), antenatal steroid therapy (OR, 1.60; 95% CI, 1.05–2.43, $p=0.028$), surfactant administration (OR, 2.06; 95% CI, 1.32–3.2, $p=0.001$) were independent risk factors for ROP development.

Conclusion: Postnatal weight gain may not be an accurate predictor of ROP development after adjusting for confounding factors. However, the analysis of independent risk factors that influenced the development of ROP revealed a statistically significant effect in cases of low birth weight, blood transfusion, necrotizing enterocolitis, bronchopulmonary dysplasia, and antenatal steroid and surfactant therapies. These findings may help ophthalmologists and neonatologists to pay special attention to this patient group during ROP scanning.

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Introduction

Premature retinopathy (ROP) is a condition that develops because of the abnormal proliferation of retinal vessels in low birth weight (BW) and premature infants, the pathogenesis of which is not completely understood [1]. It is a leading cause of preventable blindness

in children [2]. Although the chance of survival of premature infants with very small gestational age (GA) and BW has increased owing to developments in newborn care, ROP, which can cause vision problems and blindness, occurs more frequently in both developed and developing countries [3]. Although mild ROP forms can self-correct, if severe cases are not treated, they

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may cause retinal scars during decollement and blindness [4]. Therefore, the early diagnosis and treatment of ROP are important to prevent disease progression.

Many guidelines consider BW and GA as important risk factors for identifying infants requiring ROP screening. According to the recommendations of the American Pediatric Academy and the American Academy of Ophthalmology, screening is recommended for all infants whose BW is ≤ 1500 g and/or GA is ≤ 30 weeks as well as for the infants whose GA is > 30 weeks, BW is 1500–2000g, and who have clinical diseases, and who require cardiopulmonary support [5]. This is a simple risk model that includes two factors, GA and BW, and is very sensitive and covers almost all serious ROP cases. However, it has $< 100\%$ sensitivity, and because 5% of infants require treatment, it is not very specific [6–8]. ROP examination is a painful process that may lead to acute events in newborns, including decreased oxygen-saturation levels, increased heart rate, and increased apnea frequency. In addition, unnecessary ROP screening may cause additional health expenditure costs [9], and the limited number of ophthalmologists with experience in ROP may present an obstacle to screening [10]. Therefore, over the last 15 years, efforts have been made to develop better screening criteria by adding other risk factors to BW and GA to identify infants with significant ROP development potential requiring treatment and to reduce the number of infant examinations [11]. The most promising predictive factor is poor postnatal weight gain [12].

ROP pathogenesis involves multiple factors, including retinal oxygen levels, local vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF-1). Clinical studies have shown an association between low postnatal serum IGF-1 levels and increased risk of ROP [13,14]. Serum IGF-1 levels are associated with fetal and postnatal growth, but require blood sampling for measurement and are not routinely used in neonatal intensive care units. In these units, routine weight monitoring and weight gain may be used instead of IGF-1 measurements [12]. Based on this information, Hellstrom et al. first used postnatal weight gain in a predictive model for ROP. In this model, called the Weight and Insulin-Like Growth Factor 1 in Neonatal Retinopathy (WINROP) model, data from 79 Swedish infants were used [15]. While the first algorithm included both postnatal weight measurements and serum IGF-1 levels, later versions included weight gain alone [12]. In another Swedish study, the WINROP model was shown to have 100% sensitivity to the development of severe ROP and reduced the number of examinations by 76% [12]. However, in multiple validity studies, the sensitivity was

consistently lower [16,17]. In a recent multicenter study called postnatal growth and ROP (G-ROP), a new BW, GA, and postnatal growth model was proposed to predict the development of ROP. This new model has shown a 30% decrease in the number of infants requiring screening in North America, as well as 100% sensitivity in type-1 and ROP prediction requiring treatment [18]. In a study conducted in Turkey to test the validity of this G-ROP model, sensitivity was determined to be 88.3% and 91.2% for any stage of ROP and ROP-requiring treatment, respectively, and specificity was determined to be 51.7% and 34.1% for any stage of ROP and ROP-requiring treatment, respectively [19]. While current risk models such as WINROP and G-ROP had 100% sensitivity in the first tests, they were shown to have decreased sensitivity when applied to other populations and skipped certain infants with serious diseases when largely applied. Furthermore, many studies assessing the relationship between postnatal weight gain and ROP based on these models have established different outcomes. While in one study, in the fourth and sixth weeks, low weight gain and weight gain rate were predictive of stage 3+ ROP development [20], another study found a relationship between poor weight gain and severe ROP development in the first postnatal 4 weeks, and this relationship was not observed for weight gain in the sixth week. Furthermore, when multiple logistic regression analysis was performed involving all risk factors for ROP, poor weight gain in the fourth postnatal week was not considered an independent risk factor [21].

Although poor postnatal weight gain has been reported to be a strong indicator of ROP development, information regarding this is unclear. Therefore, this study aimed to determine the relationship between postnatal weight gain and ROP development during the first 8 weeks of life and other potential risk factors for ROP in preterm infants.

Materials and methods

Study group

An observational retrospective study was conducted on premature infants ≤ 32 weeks who were admitted to the level three Newborn Intensive Care Unit (NICU) between 2002 and 2011. The preterm infants were excluded from the study when they could not be examined until complete retinal vascularization, they presented congenital anomalies, died before eye examination or had incomplete medical data.

Maternal and neonatal factors that would affect the development of ROP were obtained retrospectively

from file records: maternal age, consanguineous marriage, mode of delivery, gestation (single or multiple), antenatal steroid therapy, *in vitro* fertilization, premature rupture of membranes (PROM), chorioamnionitis, pre-eclampsia, maternal diabetes mellitus, smoking, gestational age, birth weight, small for GA (SGA), sex, intrauterine growth restriction (IUGR), cardiopulmonary resuscitation, APGAR score at 1 and 5 min, Cord pH, other neonatal factors such as respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH, stage 3–4), hemodynamically significant patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC, ≥ 2), periventricular leukomalacia, sepsis (clinical or proven sepsis), hyperbilirubinemia requiring phototherapy, apnea, postnatal steroid, caffeine or theophylline therapy, thyroxine (fT4) level, Thyroid Stimulating Hormone (TSH) level, thrombocytopenia ($< 100,000/\text{mm}^3$), hyperglycemia (glucose $> 180\text{mg/dL}$), mechanical ventilation, noninvasive ventilation and supplemental O_2 therapy duration (days), parenteral nutrition (PN) duration (days), blood transfusion number, and ROP screening results. The daily measured weights for each infant until the postnatal eighth week was calculated as weekly gain (g/kg/day).

The primary outcome was to assess the effect of postnatal weight gain on the development of ROP during the first 8 weeks. Secondary outcome was to identify the other potential risk factors affecting the development of ROP.

Using the Fenton growth curve, the cases with a birth weight between 10 and 90 percentiles according to the gestational age were called AGA (Appropriate for Gestational Age), and the cases with a birth weight < 10 percentile were called SGA (Small for Gestational Age).

ROP diagnosis and screening

In our unit, on the basis of the recommendations of the American Pediatric Academy and the American Pediatric Ophthalmology and Strabismus Association, all the infants whose birth weight was $\leq 1500\text{g}$ and/or gestational age ≤ 32 weeks, as well as those infants who were born in after 32 weeks and having birth weight between 1500 and 2000g and having clinical problems, and those requiring cardiopulmonary support are screened [22]. However, only babies born at ≤ 32 weeks were included in the study. For the infants born within < 27 weeks, the first ROP examination was performed in the postmenstrual thirty-first week. For the infants born within ≥ 27 weeks, the first ROP examination was performed in the postnatal fourth week. ROP examination was performed with a binocular indirect ophthalmoscope using 20 and 28 diopter lenses

by an ophthalmologist who was proficient in ROP after a lid speculum was inserted. One hour before the examination, 1 drop of 2.5% phenylephrine for mydriasis two to three times at 5-min intervals and 0.5% tropicamide were dripped. The ROP monitoring was decided by the ophthalmologist based on the findings of the first examination. In accordance with the follow-up guideline recommended by the American Academy of Pediatrics and the American Academy of Ophthalmology, complete vascularization of the retina, ROP regression, or retinal examination was performed until treatment was required [23].

Statistical analysis

All statistical analyses were performed using Number Cruncher Statistical System 2007 (NCSS, Kaysville, UT). The enrolled infants were divided into two groups: infants who developed ROP or those who did not. In addition, to evaluate the impact of risk factors on the severity of ROP, infants who developed ROP were subsequently divided into subgroups: infants who required treatment or those who did not. To identify risk factors, each one was initially analyzed by univariate analysis. We employed Student's *t*-test for intergroup comparisons of normally distributed numerical parameters, and the Mann-Whitney *U* test for intergroup comparisons of non-normally distributed parameters. Pearson's chi-square test, Fisher's exact test, and Yates Continuity Correction test were used to compare qualitative data. Data are presented as the means $\pm$ standard deviation (*SD*), percentages (%), or medians (min-max) as appropriate. Backward stepwise logistic regression analysis using was performed to identify the independent risk factors for ROP development expressed as odds ratios (OR) and 95% confidence intervals (CI). A probability (*p*) value less than 0.01 and 0.05 were considered statistically significant.

Results

A total of 827 preterm infants with a GA of ≤ 32 weeks were admitted to neonatal intensive care unit during the study period. A total of 675 infants were included in the study, and 152 were excluded (Figure 1). The mean GA of all patients included in the study was 29.4 ± 1.9 (23–32) weeks, and the mean BW was 1165 ± 362 (460–2840) g. Of the 675 newborns included in the study, 278 (41%) developed ROP with 19, 253, and 6 in zone-I, -II, and -III diseases, respectively; 115 had stage 1 (41%), 129 had stage 2 (46%), and 32 had stage 3 (11.5%). Aggressive posterior ROP was detected in two infants (0.7%). Of the infants with ROP, 38.5% ($n=111$) were < 28 weeks of

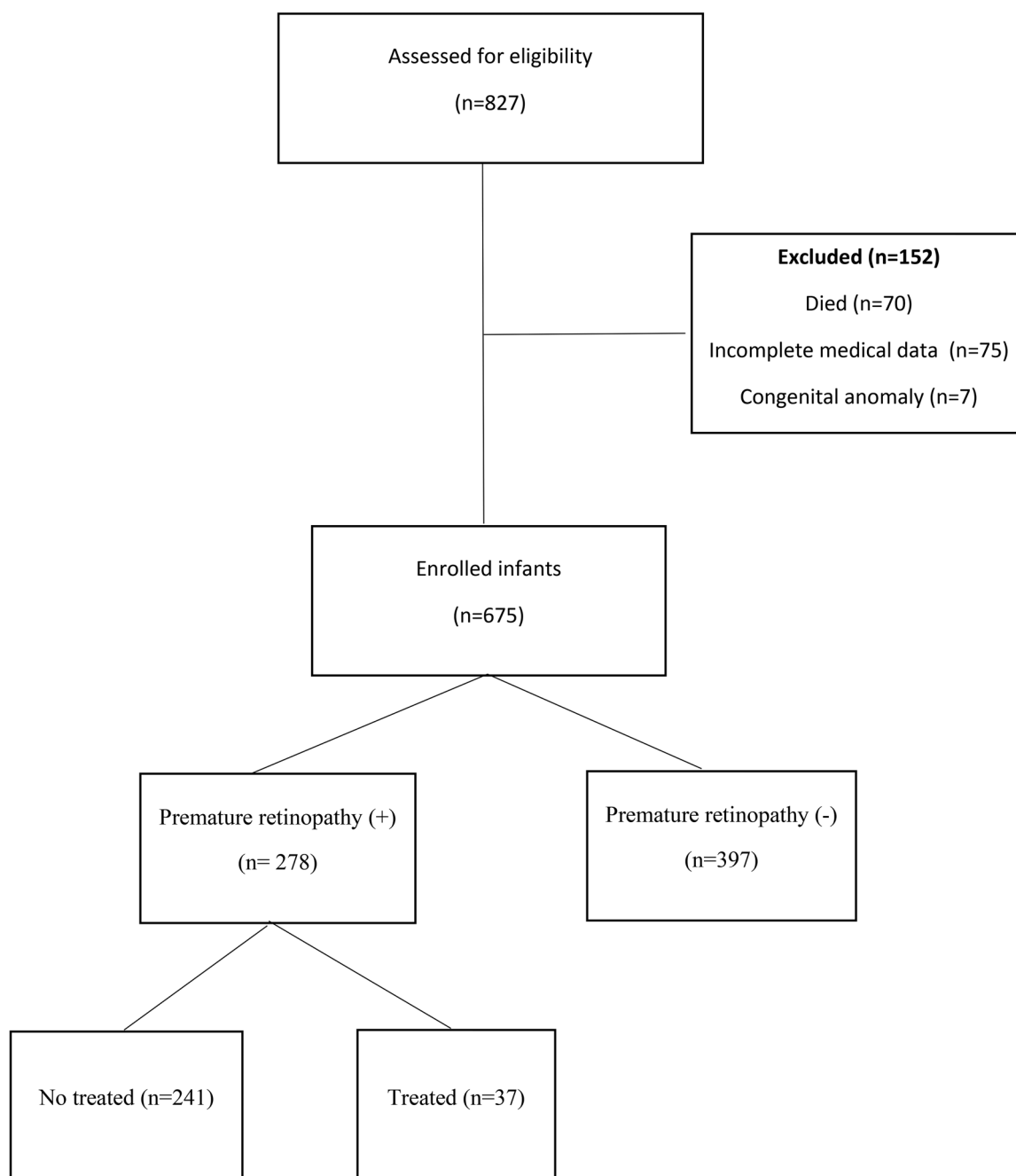


Figure 1. Flow diagram of the study.

gestational age, and 57.5% ($n=160$) had a BW <1000 g. Further, 37 (13.3%) of 278 infants with ROP received treatment. Among the infants who received treatment, 81% ($n=30$) were treated with laser photocoagulation, 2.7% ($n=1$) with cryotherapy, and 16.2% ($n=6$) required both treatments (laser photocoagulation and intravitreal anti-VEGF).

Univariate analysis identified various factors as significant risk factors for ROP development. The demographic characteristics and the clinical results of mothers and infants are presented in Table 1. In the infants of the ROP-developing group, the mean BW and GA were

significantly lower than those in the group that did not develop ROP (973 ± 288 and 1301 ± 349 g, $p=0.001$ and 28.48 ± 1.95 and 30.08 ± 1.60 weeks, $p<0.001$, respectively). In the infants of the group that developed ROP, IUGR, cardiopulmonary resuscitation, SGA, and antenatal steroid use rates were significantly higher than those in the group that did not develop ROP ($p=0.012$, $p=0.001$, $p=0.001$, and $p=0.031$, respectively). The mean Apgar scores at the first and fifth minutes were significantly lower ($p=0.001$). The rates of RDS, surfactant administration, BPD, IVH, PDA, NEC, sepsis, apnea, postnatal steroid therapy, thrombocytopenia, and hyperglycemia

Table 1. Univariate analysis of risk factors for the development of ROP.

	Infants (n=675)		p	Infants with ROP (n=278)		
	ROP (–) (n=397)	ROP (+) (n=278)		No treated (n=241)	Treated (n=37)	p
Maternal factors						
Maternal age, (years)	29.8±5.90	30±5.47	^a 0.569	30±5.5	29±5.3	^b 0.418
Consanguineous marriage, n (%)	43 (11)	39 (14)	^a 0.172	34 (14.5)	5 (14)	^a 0.927
Antenatal steroid, n (%)	211 (%56)	163 (64)	^a 0.031	143 (65)	20 (62.5)	^b 0.963
IUGR, n (%)	78 (21)	78 (29)	^a 0.012	67 (29)	11 (32.4)	^b 0.855
Cesarean delivery, n (%)	337 (85)	229 (84)	^a 0.668	204 (86)	25 (69)	^b 0.963
In vitro fertilization, n (%)	61 (15)	40 (14)	0.741	37 (15.4)	3 (8)	^b 0.359
Premature rupture of membranes, n (%)	84 (22)	58 (22)	^a 0.998	46 (20)	12 (33)	^b 0.107
Chorioamnionitis, n (%)	10 (2.6)	9 (3.4)	^b 0.758	7 (3)	2 (5.7)	^e 0.336
Multiple gestation	92 (23)	69 (25)	^a 0.621	58 (24)	11 (30)	^b 0.590
Preeclampsia, n (%)	141 (37)	98 (37)	^a 0.618	87 (37.5)	11 (31.4)	^e 0.659
Diabetes mellitus, n (%)	23 (6)	18 (7)	^b 0.846	16 (7)	2 (%5.7)	^e 1.000
Smoking, n (%)	24 (6.5)	21 (8)	^a 0.465	17 (7.5)	4 (12)	^e 0.494
Neonatal factors						
Gestational age (week)	30.08±1.60	28.48±1.95	^c 0.001	28.7±1.8	27.2±2.3	^c 0.001
Birth weight (g)	1301±349	973±288	^c 0.001	1000±288	781±198	^c 0.001
Male, n (%)	194 (% 48.9)	138 (% 49.6)	0.843	119 (49)	19 (51)	^b 0.963
SGA, n (%)	81 (20)	100 (36)	^a 0.001	81 (33.6)	19 (51.4)	^b 0.056
Cord pH	7.28±0.11	7.29±0.11	^c 0.224	7.30±0.1	7.24±0.1	^c 0.061
Cardiopulmonary resuscitation, n (%)	70 (18)	136 (51)	^a 0.001	107 (46)	29 (81)	^b 0.001
Apgar score 1.min	6±2	5±2	^d 0.001	5.4±2.1	4±1.9	^d 0.001
Apgar score 5.min	8±1 (9)	7±1 (8)	^d 0.001	7.6±1.5	6.4±1.7	^d 0.001
Respiratory distress syndrome, n (%)	137 (35)	186 (69)	^a 0.001	153 (66)	32 (91)	^b 0.004
Bronchopulmonary dysplasia, n (%)	49 (14)	121 (48)	^a 0.001	91 (42)	30 (91)	^e 0.001
Intraventricular hemorrhage (Stage 3–4), n (%)	11 (3)	31 (12)	^b 0.001	23 (10.5)	8 (23.5)	^e 0.046
Patent ductus arteriosus, n (%)	79 (%22)	109 (%43)	^a 0.001	90 (41)	19 (58)	^b 0.102
Necrotizing enterocolitis (Stage-2–3), n (%)	2 (0.6)	12 (5)	^b 0.001	6 (3)	6 (19)	^e 0.002
Periventricular leukomalacia, n (%)	8 (2.3)	8 (3.3)	^b 0.627	6 (3)	2 (6.5)	^e 0.274
Sepsis, n (%)	224 (61)	222 (84)	^a 0.001	188 (82.5)	34 (97)	^b 0.048
Hyperbilirubinemia, n (%)	362 (95)	255 (97)	^b 0.163	222 (97.4)	33 (97)	^e 1.000
Apnea, n (%)	100 (28)	138 (55)	^a 0.001	117 (54)	21 (66)	^b 0.280
Postnatal steroid therapy, n (%)	36 (10)	87 (35)	^a 0.001	64 (30)	23 (74)	^b 0.001
Caffeine or theophylline, n (%)	86 (25)	73 (29)	^a 0.206	65 (30)	8 (26)	^b 0.792
Thyroxine (pmol/L)	14.1±3.5	12.5±3.2	^d 0.001	12.6±3.2	11.5±3.1	^d 0.057
Thyroid Stimulating Hormone (mUI/L)	3.89±8.9	3.39±10.6	^d 0.001	3.66±11.4	1.68±2.2	^d 0.001
Thrombocytopenia (< 100,000/mm ³), n (%)	115 (34)	124 (52)	^a 0.001	102 (49)	22 (71)	^b 0.035
Hyperglycemia, n (%)	15 (4.3)	30 (12)	^b 0.001	23 (11)	7 (21)	^e 0.093
Mechanical ventilation duration (days)	2.26±5.92	10.59±22.19	^a 0.001	7.95±16.4	28±40	^d 0.001
Noninvasive ventilation duration (days)	2.5±4.6	7.6±9.6	^c 0.001	7±8.8	12±13	^d 0.003
Oxygen therapy (days)	4.3±9.5	10.1±13.4	^c 0.001	8.9±12	18.2±18	^d 0.009
Surfactant administration, n (%)	137 (35)	186 (69)	^a 0.001	153 (65.7)	33 (92)	^b 0.003
Parenteral nutrition duration (days)	12.48±9.2	20.17±20	^d 0.001	12.5±9	20±20	^d 0.032
Blood transfusion, (number)	1.51±2.11	4.22±4.04	^a 0.001	3.7±3.6	7.6±4.9	^d 0.001

^aPearson's chi-square test.^bYates continuity correction test.^cStudent's *t*-test.^dMann–Whitney *U* test.^eFisher's exact test.

The values are presented as mean±standard deviation. IUGR, intrauterine growth restriction; ROP, retinopathy of prematurity; SGA, small for gestational age.

were significantly higher in the infants of the group that developed ROP than those in the group that did not ($p=0.001$). The mean duration of mechanical ventilation and oxygen therapy, mean duration of total parenteral nutrition, and number of blood transfusions were significantly higher in the infants of the group that developed ROP than those in the group that did not develop ROP ($p=0.001$). The free T4 (FT4) and thyroid-stimulating hormone (TSH) levels were significantly lower ($p=0.001$) in the infants who developed ROP than those in the infants who did not. There were no significant differences based on maternal age, consanguineous marriage, cesarean delivery, multiple

pregnancies, *in vitro* fertilization, preeclampsia, diabetes, PROM, chorioamnionitis, smoking, sex, cord pH, periventricular leukomalacia, hyperbilirubinemia, caffeine intake, or theophylline therapy for ROP development ($p>0.05$; Table 1).

In the infants who developed ROP, the mean daily postnatal weight gain at the third, fourth, and fifth postnatal weeks was lower than that in those who did not develop ROP. A statistical significance was observed in the third week ($p=0.034$). In the infants of the ROP-developing group, the mean weight gain in the sixth and seventh weeks was significantly higher than that in those of the group that did not develop ROP

($p=0.049$ and $p=0.017$, respectively), and no significant difference was found between the two groups in terms of mean weight gain in the first, second, and eighth weeks ($p>0.05$; Table 2).

All significant risk factors affecting ROP were evaluated using a backward stepwise logistic regression analysis. The analysis was conducted on 160 infants with all risk factors. Taking as reference the birth weight of babies over 1250g; BW (1000–1249g) (odd ratio [OR], 2.58; 95% confidence interval [CI], 1.51–4.43, $p=0.001$), BW (750–999g) (OR, 4.91; 95% CI, 2.78–8.66, $p=0.001$), BW (<750g) (OR, 8.67; 95% CI, 3.99–18.82, $p=0.001$), blood transfusion (OR, 2.39; 95% CI, 1.34–4.24, $p=0.003$), necrotizing enterocolitis (OR, 4.79; 95% CI, 1.05–26.85, $p=0.045$), bronchopulmonary dysplasia (OR, 2.03; 95% CI, 1.22–3.36, $p=0.006$), antenatal steroid therapy (OR, 1.60; 95% CI, 1.05–2.43, $p=0.028$), surfactant administration (OR, 2.06; 95% CI, 1.32–3.2, $p=0.001$) were independent risk factors for ROP development (Table 3).

When we evaluated the effect of risk factors on the severity of ROP, the mean BW and GA, apgar scores at the first and fifth minutes and TSH levels were significantly lower in the infants of the ROP-requiring treatment group than those in the ROP group that did not require treatment ($p=0.001$). The rates of RDS, surfactant administration, BPD, IVH, NEC, sepsis, postnatal steroids, thrombocytopenia, the mean duration of mechanical ventilation and oxygen therapy, mean duration of total parenteral nutrition, and number of blood transfusions were significantly higher in the infants of the group that ROP-requiring treatment than those in the group that did not ($p<0.01$).

Table 2. Comparison of the daily weight gain in non-ROP and ROP groups according to weeks.

	ROP (–) ($n=397$)	ROP (+) ($n=278$)	p
Weight gain at 1th week	-9.6 ± 8.11	-8.7 ± 9.1	$^a0.517$
Weight gain at 2th week	13.1 ± 8.1	13.2 ± 9.8	$^a0.687$
Weight gain at 3th week	15.4 ± 6.8	13.9 ± 8.2	$^a0.034$
Weight gain at 4th week	16.4 ± 6.8	15.6 ± 8.7	$^a0.861$
Weight gain at 5th week	15.7 ± 7.1	14.6 ± 8.8	$^a0.180$
Weight gain at 6th week	14.5 ± 7.5	16 ± 7.7	$^a0.049$
Weight gain at 7th week	13.8 ± 7.3	15.5 ± 7.8	$^a0.017$
Weight gain at 8th week	12.1 ± 8.2	14.1 ± 8.4	$^a0.098$

a Mann–Whitney U test. ROP, retinopathy of prematurity.

Table 3. Independent risk factors for retinopathy of prematurity.

Variables	Odds ratio	95 % CI	p
Birth weight (< 750g)	8.67	3.99–18.82	0.001**
Birth weight (750–999g)	4.91	2.78–8.66	0.001**
Birth weight (1000–1249g)	2.58	1.51–4.43	0.001**
Blood transfusion	2.39	1.34–4.24	0.003**
Necrotizing enterocolitis	4.79	1.05–26.85	0.045*
Bronchopulmonary dysplasia	2.03	1.22–3.36	0.006**
Antenatal steroid therapy	1.60	1.05–2.43	0.028*
Surfactant administration	2.06	1.32–3.2	0.001**

CI, confidence interval. * $p<0.05$; ** $p<0.01$.

There were no significant differences based on maternal age, consanguineous marriage, antenatal steroid, IUGR, cesarean delivery, multiple pregnancies, *in vitro* fertilization, preeclampsia, maternal diabetes, PROM, chorioamnionitis, smoking, gender, Cord pH, PDA, periventricular leukomalacia, hyperbilirubinemia, apnea, hyperglycemia, thyroxine level and caffeine intake, or theophylline therapy ($p>0.05$) (Table 3). No difference was found in the comparison of daily weight gain according to weeks in the treated and untreated ROP group ($p>0.05$) (Not shown).

Discussion

The results of our study indicate that postnatal weight gain in the third week was significantly lower among infants with ROP; however, when all the risk factors for ROP development in the univariate analysis were included in the logistic regression, poor postnatal weight gain did not arise as an independent risk factor. In our cohort of preterm infants, certain well-defined premature morbidities were more common in infants with ROP. The association between poor postnatal weight gain and ROP may be attributed to common postnatal risk factors that cause them. We consider that poor weight gain lost significance in logistic regression as it was a result of other clinical comorbidities rather than an independent risk factor for ROP.

This is in contrast to the findings of many studies indicating that poor postnatal weight gain is a predictive factor for the development of ROP. Wallace et al. suggested that poor postnatal weight gain (g/day) in the first 6 weeks was an independent risk factor for the development of severe ROP [24]. Similarly, Cabañas Poy et al. demonstrated that GA and poor postnatal weight gain during the first 6 weeks of life were significantly associated with the need for treatment in infants with ROP, and postnatal weight gain at 6 weeks was predictive of the need for ROP treatment [25]. Meanwhile, a multicenter study reported that poor weight gain on postnatal day 28 was an independent risk factor for the development of severe ROP [26].

Contrary to these studies and supporting our findings, Rao et al. reported no relationship between postnatal weight gain in the fourth, fifth, and sixth weeks and severe ROP development in very low BW infants [27]. Similarly, a prospective cohort study of 487 very low BW infants found that weight gain in the first 4 weeks of life was not a significant predictor of ROP [21]. Lundgren et al. showed that after the target oxygen saturation range increased from 88%–92% to

91%–95%, the predictive effect of postnatal weight gain for ROP-requiring treatment decreased [28].

The two predominantly known risk factors for the development of ROP are GA and BW [29]. In our study, BW and GA were significantly lower in patients who developed ROP and ROP-requiring treatment. As GA and BW decreased, the incidence of ROP and ROP-requiring treatment increased. Multiple logistic regression analysis identified low BW as an independent risk factor for ROP development. While having a BW <750 g increases the development of ROP by a factor of 8.67, having a BW 750–999 g increases it by a factor of 4.91, having a BW 1000–1249 g increases it by a factor of 2.58. Similarly, in many studies, BW was reported to be a risk factor for both ROP development and ROP-requiring treatment [30,31]. In a multicenter Cryotherapy for Retinopathy of Prematurity study in which 4099 infants whose BW was <1251 g were included, low BW and GA were found to be related to threshold ROP development [32]. In this study, it was concluded that every 100-g increase in BW decreased the threshold ROP development by 27%, while an increase in GA by every 1 week decreased the threshold ROP development by 19% [32].

Several studies have reported that lower Apgar scores, which are a general indicator of poor neonatal health, may be associated with higher ROP [25]. However, on multivariate regression analysis, the relationship was not significant in most cases, as observed in our study. Furthermore, in our study, neonatal cardiopulmonary resuscitation was associated with increased risks of ROP development and ROP-requiring treatment. In addition to the underlying systemic disease necessitating resuscitation, the possibility of worsening of the patient's general condition or periods of post-cardiopulmonary resuscitation hypoxia followed by hyperoxia is likely related to abnormal retinal vascular development in these patients.

Antenatal steroid therapy was an independent risk factor for ROP in our study; however, no significant difference was found between ROP patients requiring treatment and those who did not. The effect of antenatal steroid use on ROP development is controversial. In a meta-analysis, antenatal steroid use was reported to reduce ROP development and the risk of progression to severe ROP [33]. However, another study involving 7200 infants conducted in Sweden showed that antenatal steroid treatment increased ROP development by 1.57 times [34]. In other studies, no association was found between antenatal steroid administration and ROP development [35]. Antenatal steroids are administered to pregnant women at risk of premature birth because it accelerates fetal lung maturation and

reduces RDS as well as other neonatal morbidities, such as NEC and IVH. In our study, the development of ROP may not be directly related to antenatal steroid use; however, antenatal steroid use is more likely due to the lower gestation weeks of this group of infants.

Many studies have suggested that neonatal respiratory diseases are closely associated with the development of ROP [1]. RDS and apnea are associated with an increased risk of ROP in our study. RDS is caused by a surfactant deficiency; therefore, newborns with RDS may require mechanical ventilation and oxygen therapy. In addition, infants with apnea require mechanical ventilation and oxygen treatment. However, apnea was not associated with ROP-requiring treatment.

Some studies have suggested that surfactant administration is closely associated with ROP [1], which may be interpreted as a higher risk for ROP in infants with RDS-requiring treatment. In this study, we found that surfactant administration was associated with a higher risk of ROP development and ROP-requiring treatment. It was also found to be an independent risk factor on multivariate analysis. Similarly, BPD was associated with an increased risk of ROP development and ROP-requiring treatment. Additionally, BPD was found to be an independent risk factor for the development of ROP. These cases involved patients with chronic respiratory disease, in whom episodes of desaturation and subsequent hyperoxia were frequent during oxygen treatment, which could explain the increased risk. Additionally, postnatal steroid therapy is associated with a higher risk of ROP development and ROP-requiring treatment. Similarly, several studies on preterm infants have reported a significant association between postnatal steroid administration and an increased risk of ROP [36]. As the incidence of BPD is higher in infants who develop ROP, steroid use could be high owing to BPD being a main indication for its use.

In our study, severe IVH was associated with the development of ROP and ROP-requiring treatment. IVH and ROP have similar characteristics. In both cases, incidence increased with decreasing GA and BW. IVH develops because of the fragility of germinal matrix vessels and fluctuations in cerebral blood flow [1]. ROP is caused by immature retinal vascularization and unstable oxygen treatment [1].

In infants with PDA, decreased perfusion due to systemic blood flow bypass may cause retinal hypoxia and predispose them to developing ROP [1]. PDA has been associated with ROP development, but no relationship was found with ROP-requiring treatment in our study. Unlike our study findings, other studies have found that PDA is an independent risk factor for ROP [25].

The pathophysiology of NEC may involve innate immune responses against the gut microbiota, leading to inflammation. Animal models have shown that systemic inflammation affects retinal angiogenesis, suggesting a possible relationship between NEC and ROP [1]. In our study, a significant relationship was found between NEC and the development and treated ROP. NEC has also been identified as an independent risk factor for ROP. Similarly, Fundora et al. reported that infants with surgical NEC, especially early surgical NEC, were at a higher risk of ROP and severe ROP [37].

Many studies have indicated that sepsis was closely related to the appearance of the development of retinopathy [1,25]. In our study, sepsis was a risk factor for the development of ROP and ROP-requiring treatment. Systemic inflammation can disrupt angiogenesis and hypotension, and fluctuations in oxygen saturation can affect retinal perfusion, leading to retinal ischemia [1].

Studies on the effects of thyroid hormones on angiogenesis have shown that thyroid hormones increase angiogenesis, especially by increasing the pro-angiogenic factor levels. Therefore, it is reasonable to assume a relationship between thyroid hormone levels and ROP [38]. TSH and FT4 levels were significantly lower in infants who developed ROP; however, only TSH levels were significantly lower in infants with ROP-requiring treatment in our study. Coşkun et al. found that TSH measurements were significantly lower in the group with ROP than the measurements in those without ROP. In addition, FT4 levels were significantly lower in those in the treated group than that in those in the non-treated ROP group. However, after multivariate analysis, thyroid hormone levels were not independent risk factors for ROP development [39]. In another study, no relationship was observed between thyroid function and ROP development [40].

Hyperglycemia is associated with increased mortality and morbidity in preterm infants [41]. In our study, hyperglycemia was found to be associated with the development of ROP, but not with ROP-requiring treatment. Similarly, several studies reporting mean blood glucose concentrations in infants with different ROP statuses have suggested a relationship between hyperglycemia and ROP [1]. However, some studies have reported no association between hyperglycemia and ROP [42].

Platelets store, transport, and deliver several key angiogenesis regulators, including VEGF. Therefore, a possible role of platelets in the pathogenesis of ROP can be hypothesized. If platelets provide a mean to sequester accumulating VEGF and temper retinal angiogenesis, thrombocytopenia could permit a greater degree of unregulated retinal neovascularization when IGF-1 levels increase and activate accumulated VEGF [1]. In our study,

thrombocytopenia was associated with the development of ROP and ROP-requiring treatment. Similar to our findings, Choręziak et al. also found a relationship between thrombocytopenia and the development of ROP [43]. In addition, Vinekar et al. reported spontaneous resolution of aggressive posterior ROP after correction of thrombocytopenia with platelet transfusion [44]. Considering thrombocytopenia as a potential risk factor for ROP development, the authors proposed platelet transfusion as a new treatment strategy for ROP [44].

The mean duration of oxygen therapy was significantly longer in infants with ROP and those with ROP-requiring treatment. Regarding assisted ventilation, we found that any modality duration (mechanical ventilation or noninvasive ventilation) was related to the development of ROP and ROP-requiring treatment.

This study indicates that blood transfusion has a strong effect on ROP development and is its independent risk factor. Transfusions may increase the retina's exposure to oxygen due to the low oxygen affinity of adult hemoglobin, catalyze the formation of iron-loaded reactive oxygen species, and may lead to ROP development by accelerating oxidative damage [1]. Although many studies have shown that blood transfusion is a risk factor for ROP development [25], some have reported that a restricted transfusion policy does not reduce ROP development [45].

In our study, the mean duration of parenteral nutrition was significantly higher among infants with ROP and those with ROP-requiring treatment. Similarly, some studies have indicated that prolonged parenteral nutrition is a risk factor for ROP [1]. However, a Turkish randomized controlled study showed that fish oil lipid emulsions were associated with a lower incidence of any-stage ROP [46]. Because parenteral nutrition containing soybean oil was used in our study, a comparison could not be made with lipid emulsions containing fish oil.

Different, supportive, and conflicting conclusions have been reported in clinical studies regarding the risk factors affecting ROP development. The differences in the demographic characteristics of the infants included in the study, such as race, ethnicity, GA, and BW; protocols applied in the neonatal intensive care unit between the hospitals or countries studied; clinical outcomes such as survival rate and premature morbidities; clinical experience of ophthalmologists; diagnostic disputes between ophthalmologists; and changes in ROP screening and treatment guidelines over time may well lead to different outcomes in these clinical trials. Therefore, prospectively designed studies with standardized study groups are needed to identify the risk factors affecting the development of ROP.

The main strength of our study is that it is the most comprehensive study evaluating the risk factors in the development of ROP among the studies conducted till date. However, this study has some limitations. First, this was a retrospective study. Second, we assumed that poor postnatal weight gain was caused by low serum IGF-1 concentration. However, serum IGF-1 concentrations have not yet been measured in clinical practice. In addition, the data are from one center, indicating that a specific population is not adequately reflected. Thus, prospective multi-center cohort studies on relationships between postnatal weight gain and ROP are warranted.

Postnatal weight gain, as predicted in previous studies, may not be an accurate predictor of ROP development after adjusting for confounding factors based on our study. However, the analysis of independent risk factors that influenced the development of ROP revealed a statistically significant effect in cases of low birth weight, blood transfusion, necrotizing enterocolitis, bronchopulmonary dysplasia, and antenatal steroid and surfactant therapies. These findings may help ophthalmologists and neonatologists to pay special attention to this patient group during ROP scanning.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author, [initials]. The data

are not publicly available due to [restrictions e.g. their containing information that could compromise the privacy of research participants].

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