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Perinatal outcomes and predictors of neonatal mortality in preterm premature rupture of membranes: a tertiary center experience

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Abstract

Background Preterm premature rupture of membranes (PPROM) is a serious obstetric condition associated with increased maternal, fetal, and neonatal morbidity and mortality. It accounts for approximately one-third of all spontaneous preterm births and is associated with complications such as respiratory distress syndrome (RDS), sepsis, pulmonary hypoplasia, and neonatal mortality. Despite significant advances in prenatal care, proper management, particularly in early gestational age, remains unclear. Identifying factors associated with neonatal mortality in PPROM is important to develop therapeutic interventions and improve perinatal outcomes.

Methods This retrospective study examined clinical data and neonatal outcomes in 183 pregnant women with PPROM between the gestational ages of 23 and 36 + 6 weeks who were admitted to a tertiary referral hospital. The study population was categorized into four gestational age cohorts: Group I (23–27 + 6 weeks), Group II (28–31 + 6 weeks), Group III (32–33 + 6 weeks), and Group IV (34–36 + 6 weeks). Neonatal outcomes, including admission to the neonatal intensive care unit (NICU), the incidence of respiratory distress syndrome, the requirement for oxygen and mechanical ventilation, the necessity for surfactant and inotropic support, sepsis, suspected pulmonary hypoplasia, and early and late neonatal mortality were compared between the groups.

Results Group I had the highest CRP values (18.68 ± 21.34), while Group III had the lowest (6.81 ± 5.16). Significant differences were found between the groups in terms of death at discharge, gestational age at delivery, birth weight, and presence of oligohydramnios. The intubated group had higher CRP levels and lower gestational age and birth weight. Of the 14 neonatal deaths, eight occurred in the early neonatal period, corresponding to a mortality rate of 7.6%. The neonatal mortality rate was 63.2% in Group I. No deaths were recorded in Groups II and III. In Group IV, the mortality rate was 2.2%.

Conclusion Neonatal mortality was associated with low gestational age, low birth weight, and oligohydramnios. The predominant cause of early infant deaths was RDS, whereas late neonatal mortality was primarily attributed to sepsis. Specifically, active management options after 34 weeks of gestational age have demonstrated enhancements in neonatal outcomes, underscoring the significance of tailored clinical approaches in cases of PPROM.

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Keywords Resuscitation, Apgar scores, PPROM, Prematurity, RDS, Neonatal mortality, Oligohydramnios

Background

Preterm premature rupture of membranes (PPROM) is defined as rupture of the membranes that occurs before the onset of labor and before 37 weeks gestation. PPROM occurs in 2–5% of all pregnancies and is responsible for approximately one-third of spontaneous preterm births [1–4]. Although pathophysiological mechanisms such as inflammation and oxidative stress play a role in the development of this condition, the etiology is not fully understood [5–9]. Risk factors include low socioeconomic status, smoking, low body mass index (BMI), history of PPROM in the previous pregnancy, multiple pregnancies, nulliparity, cervical abnormalities, genital infections, and polyhydramnios [5–8].

PPROM is a significant condition leading to increased maternal, fetal, and neonatal morbidity and mortality [10–12]. When spontaneous preterm birth and congenital anomalies are excluded, PPROM is an important cause of preterm birth and neonatal deaths associated with prematurity [3, 4, 10, 12]. In addition to prematurity, oligohydramnios and inflammatory processes also lead to adverse neonatal outcomes [7, 12–14]. Neonatal complications such as respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), neonatal sepsis, limb deformities, pulmonary hypoplasia, and neonatal death occur with PPROM [15, 16]. Although attempts are being made to reduce the existing risks of prematurity by extending the interval between membrane rupture and delivery, optimizing the timing of birth is still a challenge for obstetricians today, especially when considering complications such as chorioamnionitis, abruptio placenta, intrauterine cord accidents, fetal distress and maternal sepsis [17, 18]. Due to the improved neonatal practices, the management of PPROM cases in the antenatal period, and the decision on the timing of delivery considering complications, the results regarding perinatal outcomes in studies of cases diagnosed with PPROM vary from center to center [10, 12–16]. Our study aimed to investigate which factors play a vital role in predicting adverse neonatal outcomes in patients with PPROM treated at a tertiary center. We attempted to classify the relationships between perinatal outcomes and predictors through subgroup analyses based on gestational age.

Methods

This retrospective study included pregnant women diagnosed with PPROM between 23 and 36 + 6 weeks of gestation and presented to the perinatology clinic of Ankara Etlik City Hospital between October 2022 and 2023. Ethical approval (number: AEŞH-BADEK-2024-095) was obtained from the Ethics Committee of our hospital before the start of the study. The study's design and protocols were conducted by the Declaration of Helsinki. Initially, 231 patients diagnosed with PPROM were assessed. The patient's gestational ages were calculated using the last menstrual date and confirmed based on the first-trimester Crown-Rump Length (CRL) values. PPROM was diagnosed by direct visualization of the amniotic fluid in the posterior fornix during sterile speculum examination or by positivity of the PROM test (AmniSure test [placental alpha-microglobulin-1] and/or Actim Prom test [insulin-like growth factor binding protein 1]) performed during speculum examination. The exclusion criteria included a history of chronic diseases (e.g., hypertension, diabetes mellitus, autoimmune disorders, chronic kidney disease, and cardiovascular diseases), fetal chromosomal or structural abnormalities, and multiple pregnancies.

All PPROM cases were managed after the initial examination based on gestational age according to current guidelines [17, 18]. All pregnant women with PPROM between 23 and 33 + 6 weeks who did not require urgent delivery were admitted to the hospital and followed up with a prenatal care plan that included laboratory tests, non-stress tests (NSTs), and ultrasound examinations for symptoms and signs of complications such as chorioamnionitis, placental abruption, fetal distress, oligohydramnios, and preterm labor. In all patients admitted to our clinic with a diagnosis of PPROM, vital signs, daily NST, and biophysical profiles were monitored every 4 h; white blood cell counts were checked twice a week. The latent period was defined as the time from the onset of PPROM to spontaneous delivery or induction of labor at 34 + 0 weeks or recommended delivery before 34 + 0 weeks due to obstetric complications such as suspected chorioamnionitis, placental abruption or a non-reassuring fetal heart rate.

All patients with PPROM received 1 g Azithromycin orally and 2 g Ampicillin intravenously every 6 h for the first 48 h after admission to the hospital. Thereafter, 875 mg of Amoxicillin was administered orally every 12 h for 5 days. In all cases, two doses of 12 mg intramuscular Betamethasone were administered 24 h apart to induce fetal lung development. Magnesium sulfate was administered for neuroprotection to all patients who underwent preterm labor or required delivery due to obstetric indications before a gestational age of 32 weeks, per guidelines. Patients who had no further complications and reached a gestational age of 34 weeks were delivered either by induction of labor or cesarean section, according to obstetric indications. However, if clinical signs and

symptoms of chorioamnionitis or deterioration of fetal well-being occurred, conservative treatment was discontinued, and delivery was performed based on obstetric indications without prolonging the pregnancy beyond a gestational age of 34 weeks. The clinical diagnosis of chorioamnionitis was made if two or more of the following criteria were present together with maternal fever (37.8 °C or 100.4 °F):

- Maternal tachycardia (> 100 beats/minute),
- Fetal tachycardia (˃ 160 beats/minute)
- Uterine tenderness
- Purulent or foul-smelling vaginal discharge
- Leukocytosis in maternal whole blood count (> 15,000 cells/mm3) present [19].

The PPROM cases were divided into four groups depending on the gestational ages: Group I ($23–27^{+6}$ weeks), Group II ($28–31^{+6}$ weeks), Group III ($32–33^{+6}$ weeks), and Group IV ($34–36^{+6}$ weeks). Maternal and neonatal data, including demographic characteristics, laboratory values, clinical observations, amniotic fluid status, presence of placental abruption and chorioamnionitis, time of birth, and mode of delivery, were obtained from the patient's electronic health records and medical files. Assessment of short and long-term neonatal outcomes, including intraventricular hemorrhage [(IVH), grade 3, 4], bronchopulmonary dysplasia (BPD), 1st and 5th minute Apgar scores, need for resuscitation, neonatal intensive care unit (NICU) stay (days), respiratory distress syndrome (mild, severe), duration of oxygen requirement, duration of mechanical ventilation, surfactant requirement, need for inotropic support, development of sepsis, suspicion of pulmonary hypoplasia, periventricular leukomalacia, early and late neonatal death, and necrotizing enterocolitis (NEC) was determined from the records. NEC was included as a parameter without staging. Early neonatal death refers to death occurring within the initial 7 days of life, and late neonatal death refers to death occurring after the first week of life. Pulmonary hypoplasia was suspected in infants exhibiting extreme immaturity, severe respiratory failure, and inadequate response to maximal mechanical ventilation. The diagnosis relied on clinical suspicion instead of histopathologic validation.

The data for the statistical analyses were done using IBM SPSS Statistics 27.0 (IBM Corp. Armonk, NY). The Kolmogorov–Smirnov test assessed how well the data fit the normal distribution. Parametric methods were used for normally distributed measurements. The "ANOVA" test (F-table value) was used to compare the measured values of three or more independent groups using parametric methods. Non-parametric methods were used for non-normally distributed measurements. In accordance with the nonparametric methods, the "Mann–Whitney U" test (Z-table value) was used to compare the measured values of two independent groups, and the "Kruskal–Wallis H" method (χ2-table value) was used to compare the measured values of three or more independent groups. Pearson χ2 cross-tabulations were used when examining the relationships between the two qualitative variables. If the p-value was below 0.05, statistical significance was assumed. The Bonferroni correction was applied for binary comparisons of variables with significant differences for three or more groups. As part of this correction, the significance threshold was set at 0.05 / 6 = 0.0083, as six pairwise comparisons were carried out. Values with $p \leq 0.0083$ were considered statistically significant.

Results

A total of 231 patients with a diagnosis of PPROM were identified from our hospital's electronic records. Of these, five were excluded from the study due to multiple pregnancies, seven due to type two diabetes mellitus or gestational diabetes, six due to hypertensive disease, and three due to congenital fetal anomalies. In addition, 15 patients who had given birth in another hospital and 12 with missing neonatal data were excluded from the final analysis. After these exclusions, 183 patients were included in the study (Fig. 1).

Table 1 shows the comparison of the demographic and clinical findings of the groups. There were no significant differences between the groups regarding maternal age, parity, number of live-born neonates, and BMI. A statistically significant difference between the groups was found in the latency period, with group IV having the lowest latency period and group II having the highest ($p = 0.001$). Patients in group I had the lowest Apgar scores at 1 and 5 min ($p = 0.001$). Notably, 11 (57.9%) of the patients in Group I had a gestational age between 23 + 0 and 24 + 6 weeks. Group I had the highest CRP values, and Group III had the lowest ($p = 0.027$). There was no significant difference in prenatal WBC counts across the groups ($p = 0.320$). Group I had the highest need for NICU admission and the highest rates of O2 requirement, and mechanical ventilation requirement, whereas Group IV demonstrated the lowest ($p = 0.001$).

When analyzed by birth weight, there were 16 infants with extremely low birth weight (ELBW) (< 1000 g) and 12 infants with very low birth weight (VLBW) (1000–1500 g). Only 31% of the infants in the ELBW group survived, and the average stay in the intensive care unit was 23.3 ± 9.5 days. In the VLBW group, 91.6% of the infants survived, and the average NICU stay was 44.0 ± 6.1 days. In addition, PPROM occurred in 11 of the 16 infants in the ELBW group at a gestational age between 23 + 0 and 24 + 6 weeks.

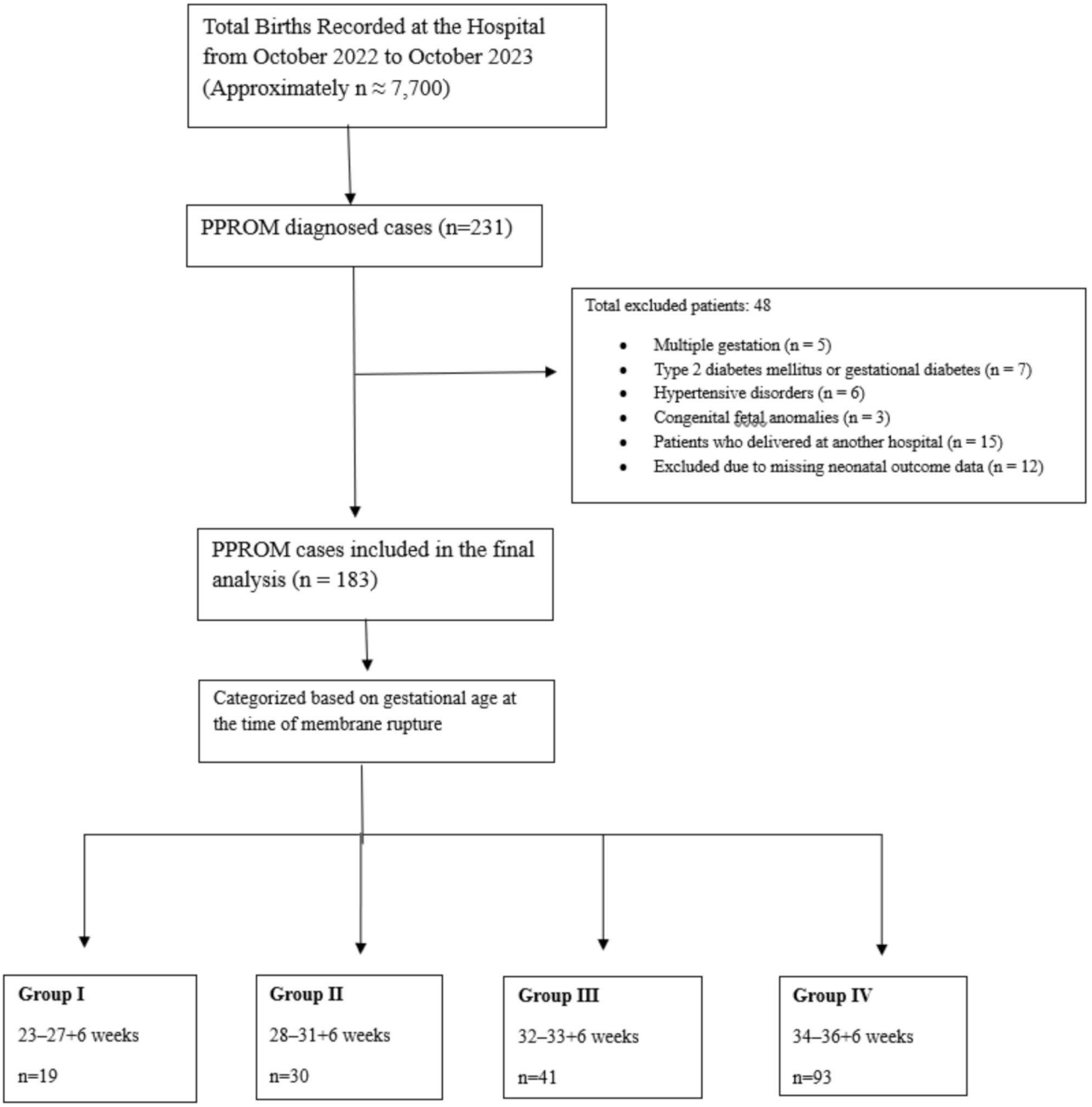

Fig. 1 The Flowchart illustrates the selection process of the study population, detailing the inclusion and exclusion criteria and the classification based on gestational age at the time of preterm premature rupture of membranes (PPROM)

In the assessment of obstetric complications and medication status (Table 2), there were no statistically significant differences between the groups with regard to chorioamnionitis, placental abruption, spontaneous labor, and fetal distress. Oligohydramnios occurred more frequently in earlier gestational ages, with the highest rate in Group I ($p = 0.001$). The pairwise comparisons for the parameters exhibiting statistically significant differences between the groups in Table 2 were evaluated utilizing the Bonferroni correction. Post-correction, substantial differences were seen between Group I and Group IV, Group II and Group IV, and Group III and Group IV across all variables, except for completed neuroprotection between Group III and Group IV ($p < 0.001$).

The relationships between the groups and neonatal complications are shown in Table 3. Patients in whom PPROM occurred at earlier gestational ages had higher rates of resuscitation and surfactant requirement and development of RDS. In Group I, all newborns who experienced early neonatal death or death at discharge had

Table 1 Comparison of demographic and clinical findings across groups

Variables	Group I (23–27^{+6}) (*n*:19)	Group II (28–31^{+6}) (*n*:30)	Group III (32–33^{+6}) (*n*:41)	Group IV (34–36^{+6}) (*n*:93)	*p*-value *
Gravidity, (median [IQR])	2.0[3.0]	2.0[1.3]	3.0[2.5]	2.0[2.0]	**0.039 [III-IV]**
Parity, (median [IQR])	1.0[2.0]	1.0[2.0]	1.0[2.0]	0.0[1.0]	0.206
Number of live-born neonates, (median [IQR])	1.0[2.0]	1.0[2.0]	1.0[2.0]	0.0[1.0]	0.256
Abortus, (median [IQR])	0.0[1.0]	0.0[1.0]	0.0[1.0]	0.0[0.0]	**0.049 [III-IV]**
Maternal Age (years), Mean ± SD	27.79 ± 5.23	28.30 ± 5.88	29.85 ± 6.11	27.23 ± 5.91	0.136
BMI (kg/m2), Mean ± SD	26.42 ± 4.03	28.43 ± 5.51	28.37 ± 6.01	28.35 ± 4.06	0.379
Latency period (days), (mean ± SD)	6.68 ± 14.60	12.73 ± 17.91	3.97 ± 8.97	0.30 ± 0.72	**0.001 [I, II, III-IV] [II-III]**
GA at delivery (week), (mean ± SD)	25.54 ± 2.82	31.87 ± 2.92	33.48 ± 1.32	35.37 ± 0.96	**0.001 [I-II, III, IV] [II-III, IV] [III-IV]**
Birth weight (g), (mean ± SD)	901.00 ± 413.64	1803.00 ± 598.51	2206.95 ± 487.55	2561.59 ± 333.14	**0.001 [I-II, III, IV] [II-III, IV] [III-IV]**
Apgar score at 1 min, (median [IQR])	3.0[4.0]	7.5[2.0]	8.0[1.0]	9.0[1.0]	**0.001 [I-II, III, IV] [II, III-IV]**
Apgar score at 5 min, (median [IQR])	6.0[4.0]	9.0[1.0]	9.0[1.0]	10.0[1.0]	**0.001 [I-II, III, IV] [II, III-IV]**
CRP (mg/dL), (mean ± SD)	18.68 ± 21.34	17.12 ± 21.64	6.81 ± 5.16	9.43 ± 11.03	**0.027 [I-III]**
Prenatal WBC count(per microliter), (mean ± SD)	14806.31 ± 6161.09	13325.0 ± 4175.79	12256.58 ± 3917.72	12441.83 ± 3898.17	0.320
NICU admission (days), (mean ± SD)	27.05 ± 38.15	23.03 ± 25.87	11.63 ± 32.33	2.23 ± 5.83	**0.001 [I, II, III-IV]**
O2 requirement (days), (mean ± SD)	24.21 ± 36.24	12.13 ± 19.43	6.95 ± 31.81	1.09 ± 4.77	**0.001 [I-III, IV] [II-III, IV] [III-IV]**
MV requirement (days), (mean ± SD)	7.89 ± 11.90	1.03 ± 4.20	5.19 ± 31.83	0.42 ± 2.52	**0.001 [I-II, III, IV]**

Note: Prenatal white blood cell (WBC) count refers to the maternal blood sample collected on the day of delivery

* "ANOVA" test (F-table value) statistics were used to compare the measured values of three or more independent groups for normally distributed data. The Kruskal–Wallis H test (χ2-table value) was used to compare the measured values of three or more independent groups for data that did not have a normal distribution

Abbreviations: BMI; body mass index, GA; gestational age, CRP; C reactive protein, WBC; white blood cells, NICU; neonatal intensive care unit, MV; mechanical ventilation

Abbreviations: BMI; body mass index, GA; gestational age, CRP; C reactive protein, WBC; white blood 514 cells, NICU; neonatal intensive care unit, MV; mechanical ventilation

Table 2 Comparison of the presence of prenatal complications and medication status between the groups

Variables	Group I (23–27^{+6}) (*n*:19)	Group II (28–31^{+6}) (*n*:30)	Group III (32–33^{+6}) (*n*:41)	Group IV (34–36^{+6}) (*n*:93)	*p*-value*
Completed antibiotic treatment, (*n*, %)	10(52.6%)	23(76.7%)	24(58.5%)	13(14.0%)	**0.001 [I; II, III- IV]**
Chorioamnionitis, (*n*, %)	2(10.5%)	2(6.7%)	1(2.4%)	2(2.2%)	0.272
Placental Abruption, (*n*, %)	2(10.5%)	2(6.7%)	-	1(1.1%)	0.062
Fetal Distress, (*n*, %)	2(10.5%)	4(13.3%)	7(17.1%)	6(6.5%)	0.284
Oligohydramnios, (*n*, %)	14(73.7%)	13(43.3%)	17(41.5%)	8(8.6%)	**0.001 [I, II, III-IV]**
Spontaneous labor, (*n*, %)	15(78.9%)	22(73.3%)	29(70.7%)	68(73.1%)	0.930
Completed Betamethasone treatment, (*n*, %)	11(57.9%)	23(76.7%)	24(58.5%)	12(12.9%)	**0.001 [I, II, III-IV]**
Completed Neuroprotection, (*n*, %)	19(100.0%)	21(70.0%)	2 (4.9%)	-	**0.001 [I, II-III] [II, II-IV]**

* "Pearson–χ2 cross tables" were used to examine the relationships between two qualitative variables

RDS at any stage. Two patients in group I and one patient in group IV had severe RDS. Group I had the highest sepsis rate at 42.1%, and Group III had the lowest ($p < 0.001$). Suspicion of pulmonary hypoplasia and NEC were found only in Group I ($p < 0.001$). IVH was found in 26.3% of patients in Group I and 10.0% of patients in Group II, while no cases were found in the other groups. Early infant mortality was found in 8 patients, all of whom belonged to group I. Death at discharge was observed in 4 patients in Group I and two patients in Group IV. In pairwise comparisons utilizing Bonferroni correction, Group I exhibited significantly higher rates of resuscitation and surfactant requirements, RDS, early infant mortality, and death at discharge relative to the other groups ($p < 0.001$). Moreover, sepsis, IVH, suspected pulmonary hypoplasia, and BPD were significantly more prevalent in

Table 3 Examining the relationships between gestational week and neonatal complications

Variables	Group I (23–27^{+6}) (*n*:19)	Group II (28–31^{+6}) (*n*:30)	Group III (32–33^{+6}) (*n*:41)	Group IV (34–36^{+6}) (*n*:93)	*p*-value*
Delivery Type, (*n*, %)					
Vaginal	6(31.6%)	10(33.3%)	13(31.7%)	49(52.7%)	**0.049**
C/S	13(68.4%)	20(66.7%)	28(68.3%)	44(47.3%)	
Sex, (*n*, %)					
Female	8(42.1%)	11(36.7%)	16(39.0%)	43(46.2%)	0.765
Male	11(57.9%)	19(63.3%)	25(61.0%)	50(53.8%)	
Resuscitation Requirement, (*n*, %)	16(84.2%)	6(20.0%)	4(9.8%)	1(1.1%)	**< 0.001 [I-II, III, IV] [II-IV]**
RDS (all grades), (*n*, %)	16(84.2%)	5(16.7%)	3(7.3%)	2(2.2%)	**< 0.001 [I-II, III, IV]**
Severe RDS	2(10.5%)	-	-	1(1.1%)	0.079
Surfactant Requirement, (*n*, %)	14(73.7%)	5(16.7%)	3(7.3%)	1(1.1%)	**< 0.001 [I-II, III, IV]**
Requirement for Inotrope Support, (*n*, %)	6 (31.6%)	-	1(2.4%)	3(3.2%)	**< 0.001 [I-II, III, IV]**
Sepsis, (*n*, %)	8(42.1%)	4 (13.3%)	2 (4.9%)	5(5.4%)	**< 0.001 [I-III, IV]**
IVH, (*n*, %)	5(26.3%)	3(10.0%)	-	-	**< 0.001 [I-III, IV]**
NEC, (*n*, %)	3(15.8%)	-	-	-	**< 0.001 [I-IV]**
Suspicion of Pulmonary hypoplasia, (*n*, %)	3(15.8%)	-	-	-	**< 0.001 [I-IV]**
BPD, (*n*, %)	4(21.1%)	3(10.0%)	-	1(1.1%)	**< 0.001 [I-III, IV]**
Early neonatal Death, (*n*, %)	8 (42.1%)	-	-	-	**< 0.001 [I-II, III, IV]**
Death at discharge, (*n*, %)	4(63.2%)	-	-	2(2.2%)	**< 0.001 [I-II, III, IV]**

Note: RDS classification: Mild RDS was defined as respiratory distress requiring ≤ 30% FiO_2 with CPAP support, without significant retractions or grunting. Severe RDS was defined as respiratory distress requiring ≥ 40% FiO_2, mechanical ventilation, or surfactant therapy, with pronounced clinical and radiological findings

* "Pearson-χ2 cross" was used to examine the relationships between two qualitative variables

Abbreviations: C/S; caesarean section, RDS; respiratory distress syndrome, IVH; intraventricular hemorrhage, NEC; necrotizing enterocolitis, BPD; Bronchopulmonary dysplasia

Group I compared to Group III. Marked disparities were noted between Group II and Group IV regarding resuscitation and surfactant requirements.

Analysis of the causes of early neonatal death and death at discharge by groups revealed that RDS was the primary cause of death in Group I. Among the 19 infants in this cohort, 12 died (either early or at discharge), and all were diagnosed with RDS at any stage. Among the 12 infants who died, 9 had oligohydramnios, while 3 were suspicion of pulmonary hypoplasia. All newborns with suspected pulmonary hypoplasia demonstrated oligohydramnios. Furthermore, two cases exhibited IVH (grade 2), and four individuals presented with sepsis. No neonatal deaths were recorded in Groups II and III. In Group IV, there were two deaths at discharge, both attributed to sepsis and requiring inotropic support, indicating septic shock.

A comparison of clinical parameters according to death at discharge is shown in Table 4. In neonates that died at discharge, birth weight and gestational age were significantly lower, but the incidence of oligohydramnios was higher ($p < 0.001$, $p < 0.001$, and $p = 0.002$, respectively). The presence of placental abruption, fetal distress, chorioamnionitis, and duration of latency period did not differ between the groups.

The relationship between death at discharge status and neonatal complications is shown in Table 5. All grades of RDS, rates of severe RDS, the need for surfactant, inotropic support, the presence of sepsis, and suspicion of pulmonary hypoplasia were significantly higher in the group with death at discharge. No significant difference was found between the groups with regard to fetal sex, IVH, NEC, or BPD.

Table 6 shows the comparison of different parameters depending on the resuscitation status. There were no significant differences in maternal age, latency, or prenatal WBC count between patients with and without resuscitation needs. High CRP levels and lower gestational age and birth weight were observed in the intubated group ($p = 0.007$, $p < 0.001$ and $p < 0.001$, respectively).

Discussion

PPROM is still responsible for the majority of preterm births and is associated with neonatal morbidity and mortality [1, 3, 4, 10–12, 20]. The exact pathogenesis of the condition is not yet fully understood. However, mortality and morbidity rates vary by ethnicity and center

Table 4 Comparison of the parameters according to neonatal death at discharge

Variables	Neonatal Death at Discharge		*p*-value*
	No (*n*:169)	Yes (*n*:14)	
Maternal Age (years), (mean ± SD)	28.01 ± 6.04	28.71 ± 4.46	0.559
BMI (kg/m2), (mean ± SD)	28.21 ± 4.89	27.64 ± 3.65	0.786
Latency period (days), (mean ± SD)	3.83 ± 10.71	3.71 ± 7.90	0.759
GA at delivery (week), (mean ± SD)	33.97 ± 2.49	25.86 ± 4.49	**< 0.001**
Birth weight (g), (mean ± SD)	2288.78 ± 566.59	936.85 ± 590.57	**< 0.001**
CRP (mg/dL), (mean ± SD)	10.85 ± 14.44	13.65 ± 12.69	0.222
Completed antibiotic treatment, (*n*, %)			
No	104 (61.5%)	9 (64.3%)	0.839
Yes	65 (38.5%)	5 (35.7%)	
Chorioamnionitis, (*n*, %)			
No	163 (96.4%)	13 (92.9%)	0.501
Yes	6 (3.6%)	1 (7.1%)	
Abruptio Placenta, (*n*, %)			
No	164 (97.0%)	14 (100.0%)	0.514
Yes	5 (3.0%)	-	
Fetal distress, (*n*, %)			
No	150 (88.8%)	14 (100.0%)	0.185
Yes	19 (11.2%)	-	
Oligohydramnios, (*n*, %)			
No	126 (74.6%)	5 (35.7%)	**0.002**
Yes	43 (25.4%)	9 (64.3%)	

* The "Mann–Whitney U test" statistic (Z-table value) was used to compare the measured values of two independent groups of data that did not have a normal distribution

Abbreviations: BMI; body mass index, GA; gestational age, CRP; c reactive protein

[21, 22]. The most critical factors for mortality and morbidity of preterm infants are still the gestational age and birth weight [12, 23]. Therefore, the main goal in managing PPROM cases is to reduce these important risk factors with an expectant management approach, except for urgent obstetric reasons between 23 and 34 weeks gestation. However, the susceptibility to many maternal and fetal complications, such as intrauterine fetal demise and fetal distress, hypoxic events, maternal sepsis, and atony, increases. This situation has led to the need for research and development of methods to identify and predict risk factors that influence mortality and morbidity. To this end, we designed our study to determine the factors influencing early and late neonatal mortality by analyzing the clinical data and perinatal outcomes of patients with PPROM admitted to a tertiary care center.

Given this information, we analyzed our cases in four groups according to gestational age. There was no significant difference between the groups regarding maternal age, BMI, parity, or number of living children. As expected, the number of admissions to the NICU decreased, and Apgar scores increased with advancing gestational age.

When evaluating the latency period, the shortest latency was observed in Group IV due to active labor management, while the longest latency period was in Group II. Despite previous studies suggesting a correlation between latency and neonatal mortality, our findings did not indicate significant differences, which differ from prior research findings [15, 16]. In the literature, research investigating the impact of latency period on neonatal outcomes typically compares groups according to the median latency period. In our study, average latency times were assessed based on gestational weeks. This methodological discrepancy is a potential reason why a significant relationship between the latency period and newborn mortality could not be established. Moreover, the observation that 50.8% of our patient cohort was within the 34–36 + 6 gestational ages and the implementation of active management during delivery resulted in a reduced average latency period. The limited cases of PPROM occurring in early gestational weeks may have also influenced the absence of a statistically significant difference in newborn death.

The prematurity and low birth weight contribute to probable respiratory problems and inadequate fetal immunity. Oxygen requirement and intubation were more frequent at lower gestational ages than at higher gestational ages, which was expected in line with the literature [12, 15, 16]. CRP levels were also elevated in earlier gestational age groups, while maternal prenatal WBC levels were similar. Despite the high incidence of subclinical infections in the lower gestational age, two cases of late neonatal mortality due to sepsis in group IV were documented in our study. These data emphasize the occurrence of infection-related problems in this period of

Table 5 Investigation of the relationship between death at discharge status and neonatal complications

Variables	Neonatal Death at Discharge		*p*-value*
	No (*n*:169)	**Yes (*n*:14)**	
Sex, (*n*, %)			
Female	71(42.0%)	7(50.0%)	0.561
Male	98(58.0%)	7(50.0%)	
RDS (all grades), (*n*, %)			
No	155(91.7%)	2(14.3%)	**< 0.001**
Yes	14(8.3%)	12(85.7%)	
Severe RDS, (*n*, %)			
No	168(99.4%)	12(85.7%)	**< 0.001**
Yes	1(0.6%)	2(14.3%)	
Surfactant Requirement, (*n*, %)			
No	157(92.9%)	3(21.4%)	**< 0.001**
Yes	12(7.1%)	11(78.6%)	
Inotrope Support, (*n*, %)			
No	164(97.0%)	9(64.3%)	**< 0.001**
Yes	5(3.0%)	5(35.7%)	
Resuscitation Requirement, (*n*, %)			
No	155 (91.7%)	1 (7.1%)	**< 0.001**
Yes	14 (8.3%)	13 (92.9%)	
Sepsis, (*n*, %)			
No	156(92.3%)	8(57.1%)	**< 0.001**
Yes	13(7.7%)	6(42.9%)	
IVH, (*n*, %)			
No	163(96.4%)	12(85.7%)	0.059
Yes	6(3.6%)	2(14.3%)	
NEC, (*n*, %)			
No	167(98.8%)	13(92.9%)	0.092
Yes	2(1.2%)	1(7.1%)	
Suspicion of Pulmonary hypoplasia, (*n*, %)			
No	169(100.0%)	11(78.6%)	**< 0.001**
Yes	-	3(21.4%)	
BPD, (*n*, %)			
No	161(95.3%)	14(100.0%)	0.405
Yes	8(4.7%)	-	

Note: RDS classification: Mild RDS was defined as respiratory distress requiring ≤ 30% FiO_2 with CPAP support, without significant retractions or grunting. Severe RDS was defined as respiratory distress requiring ≥ 40% FiO_2, mechanical ventilation, or surfactant therapy, with pronounced clinical and radiological findings

* "Pearson χ2 cross" was used to examine the relationships between two qualitative variables

Abbreviations: RDS; respiratory distress syndrome, IVH; intraventricular hemorrhage, NEC; necrotizing enterocolitis, BPD; Bronchopulmonary dysplasia

Table 6 Comparison of several parameters according to resuscitation status

Variables	Resuscitation		*p* Value*
	No (*n*:156)	**Intubated (*n*:27)**	
Maternal Age (years), (mean ± SD)	28.29 ± 6.01	26.74 ± 5.31	0.258
BMI (kg/m2), (mean ± SD)	28.49 ± 4.86	26.29 ± 4.05	**0.018**
Latency Period (days), (mean ± SD)	3.92 ± 11.11	3.26 ± 5.99	0.102
GA at Delivery (weeks), (mean ± SD)	34.33 ± 2.13	27.69 ± 4.09	**< 0.001**
Birth Weight (g), (mean ± SD)	2366.45 ± 504.95	1139.04 ± 551.20	**< 0.001**
CRP (mg/dL), (mean ± SD)	9.74 ± 12.56	18.78 ± 20.48	**0.007**
Prenatal WBC count (per microliter), (mean ± SD)	12547.37 ± 3949.16	14195.93 ± 5649.19	0.344

Note: Prenatal white blood cell (WBC) count refers to the maternal blood sample collected on the day of delivery

* The "Mann–Whitney U test" statistic (Z-table value) was used to compare the measured values of two independent groups of data that did not have a normal distribution

Abbreviations: BMI; body mass index, GA; gestational age, CRP; c reactive protein, WBC; white blood cells

pregnancy. The observed pattern of increased late neonatal mortality and morbidity in Group I compared to Group II is consistent with findings in the literature [12, 15, 16].

PPROM occurring at an earlier gestational age correlates with higher neonatal complications due to loss of protective function of the amniotic membrane and reduced amniotic fluid content. Yan et al. documented RDS and neonatal sepsis rates of 24% and 13.5%, respectively, for PPROM occurring between 24–and 27 + 6 weeks [16]. Elevated rates were noted in our analysis, likely because cases in Group I were included at 23 weeks, and 57.9% of these patients did not complete antenatal steroid treatment, while 52.6% did not receive comprehensive antibacterial therapy before spontaneous labor. Nevertheless, our neonatal complication rates are consistent with those in the study by Yan et al. [16].

Predicting neonatal outcomes in PPROM cases and identifying newborns with unfavorable prognostic factors is of significant therapeutic relevance, and this concern is the primary outcome measure in numerous studies. In their study of the impact of PPROM on neonatal outcomes, Tanir et al. identified gestational age, Apgar scores, and umbilical cord blood pH as independent predictors of neonatal outcomes in PPROM [24]. Goya et al. demonstrated that normal amniotic fluid volume, normal cervical length, and negative vaginal cultures serve as protective factors against unfavorable neonatal outcomes [25]. Our study confirms previous findings and shows that the surviving newborns have a higher birth weight and gestational age and that oligohydramnios occur less frequently. Coolen et al. found that oligohydramnios increased the incidence of chorioamnionitis and NICU admissions but were not directly related to infant death [26]. This inconsistency may be due to methodological differences, as their study only included PPROM cases between 30 and 36 weeks and excluded earlier gestational ages. Our study included a broader range (23–36 + 6 weeks) and thus allowed a more thorough analysis of protracted oligohydramnios and its impact on neonatal development.

In line with the guidelines recommendations, patients diagnosed with PPROM are usually hospitalized and followed up [17, 18]. These patients are at risk of complications, including chorioamnionitis, preterm labor, fetal distress, placental abruption, and sepsis. A study conducted by Yu et al. demonstrated a prevalence of 3.3% for fetal distress, 2.2% for placental abruption, and 17.8% for chorioamnionitis in cases with PPROM [15]. Wahabi et al. discovered a chorioamnionitis rate of 4.7% in patients with PPROM [27]. In our investigation, the prevalence of clinical chorioamnionitis was 3.8%, aligning with the findings of Wahabi et al. and labor was induced in 2.7% of patients due to placental abruption and in 10.3% of patients due to fetal distress. Nonetheless, our documented frequency of clinical chorioamnionitis diverges from earlier investigations [21, 25, 28]. This discrepancy may be attributed to variations in inclusion criteria and clinical chorioamnionitis diagnostic thresholds. Moreover, the absence of histopathological confirmation may have limited the identification of subclinical cases. However, it does not fully account for our cohort's lower frequency of clinically confirmed chorioamnionitis.

Furthermore, in our cases, inotropic support was more frequently required in conjunction with sepsis, i.e., in group I. While our study did not specifically categorize septic shock as a separate variable, the need for inotropic support in septic neonates may indicate hemodynamic instability consistent with septic shock. IVH was predominantly seen in Groups I and II due to extreme prematurity and low birth weight, and suspicion of pulmonary hypoplasia was associated with oligohydramnios, especially in Group I. No early neonatal deaths were observed in group IV. However, two cases of death at discharge were recorded in this group. Between the 24th and 33 + 6 gestational ages, implementing the management protocols defined in international guidelines and providing effective neonatal intensive care suggest that neonatal mortality during this period can be reduced [17, 18]. However, between the 32nd and 33 + 6 gestational ages, a balance must be maintained between the risks of premature birth and infectious complications. In our clinic, these patients are monitored with antibiotic therapy to prolong the latency period. The loss of the protective effect of the intact membranes can increase the risk of an ascending infection. Therefore, in line with current guidelines, we do not take an expectant approach to PPROM cases at or after 34 weeks but opt for active management [17, 18].

According to the studies on neonatal mortality in PPROM cases in the literature, the infant mortality rate at a gestational age of ≤ 28 weeks was reported by Gezer et al. to be 53.6% [12], while Yu et al. reported neonatal mortality in this period at 50% [15]. In our study, neonatal mortality was higher in group I at 63.2%. This discrepancy may be attributed to methodological differences, as the studies by Yu et al. and Gezer et al. categorized cases as < 28 weeks but did not specify the lowest gestational age in their cohorts; this may affect the direct comparability of neonatal mortality rates. In addition, this difference may have been influenced by the fact that 57.9% of patients in group I had a gestational age between 23 and 24 + 6 weeks.

Overall, 92.9% of patients with neonatal mortality in our study required resuscitation, while 91.7% of patients who survived did not require. The risk of neonatal death was 17.491 times higher in patients who needed resuscitation than in those who did not. In the patients who

died in the early neonatal period, the gestational age ranged between 23 and 27 + 6 weeks. All of these patients had RDS of varying severity, with two cases classified as severe. Four patients were diagnosed with anhydramnios, and pulmonary hypoplasia was suspected in these patients due to severe immaturity and failure to receive ventilatory support despite mechanical ventilation. Six patients belonged to the late neonatal death group (death at discharge). Four belonged to Group I, and two to Group IV. In group I, all newborns who died had clinical RDS findings. In the two cases in group 4 who died in the late neonatal period, sepsis was the main contributing factor to mortality rather than severe respiratory complications.

Of the 16 extremely low birth weight infants (ELBW, < 1000 g), the survival rate was 31%, with an average NICU duration of 23 days. Conversely, the survival percentage for the 12 very low birth weight (VLBW, 1000–1500 g) newborns was 91.6%, accompanied by an average NICU duration of 44 days. The reduced duration of NICU hospitalization for ELBW newborns is attributable to the elevated early postnatal mortality rate (43.7%). Moreover, 11 of the 16 ELBW infants PPROM occurred between gestational ages of 23–24 + 6 weeks, and the high incidence of spontaneous labor in this cohort may have influenced these outcomes.

In our study, low gestational age, low birth weight, and oligohydramnios were significantly more common in neonates who did not survive, indicating a possible association with neonatal mortality. However, there was no significant difference in the incidence of placental abruption, fetal distress, and chorioamnionitis between the surviving and non-surviving neonates. RDS was significantly more common in non-surviving neonates compared to survivors. In addition, suspected pulmonary hypoplasia was more commonly associated with early neonatal deaths, whereas sepsis and the need for inotropic support were prevalent in late neonatal deaths. Although these results suggest possible clinical implications, further studies with larger samples are needed to confirm these observations.

One of the strengths of our study is the comprehensive analysis of the effects of PPROM on neonatal outcomes over a wide range of gestational ages (23–36 + 6 weeks). Dividing the patients into four groups based on gestational age allowed us to understand age-related differences in morbidity and mortality risk. In addition, our thorough evaluation of important perinatal variables such as birth weight, need for resuscitation, latency period, and maternal inflammatory markers provides essential information for neonatal prognosis. The in-depth analysis of factors such as the RDS, surfactant requirements, and sepsis increases the clinical significance of our work.

There are several limitations of this study. First, the retrospective design limits data collection and standardization. Second, The number of cases is limited because our hospital was only recently established. Especially, the fact that nearly half of the patients in Group I were between 23 and 24 + 6 gestational age may have impacted the study findings. Our study focused on the assessment of neonatal outcomes in PPROM cases. However, due to the relatively small number of cases between 23 and 33 + 6 weeks compared to those between 34 and 36 + 6 weeks, it was limited to perform group analyses for neonatal outcomes. A comprehensive study with week-specific cohorts in a larger dataset will obtain a more accurate result.

Conclusion

In summary, our study demonstrates the influence of gestational age, birth weight, and neonatal complications on mortality in PPROM. It demonstrates the importance of expectant management in the early weeks of gestation and supports the role of active management after 34 weeks of gestation in improving neonatal outcomes. The increased incidence of oligohydramnios in non-surviving infants indicates a possible relationship with adverse outcomes. Although our results are consistent with the literature, methodological differences and patient distribution should be considered when interpreting neonatal mortality rates. Prospective studies with larger cohorts are needed to improve PPROM management and better define risk factors.

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Author contributions

R.T.A. and K.Y.Y. and C.O.U. conceptualization; D.S.K., B.H. and M.A. resources; M.A. and F.G. data curation; Ö.Ö. and M.A. formal analysis; K.Y.Y. and R.T.A. supervision; B.H. and D.S.K. validation; C.O.U. and F.G. investigation; Ö.Ö. visualization; M.A. and F.G. methodology; R.T.A. writing-original draft; R.T.A. and K.Y.Y. writing-review and editing. All authors read and approved the final manuscript.

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Data availability

The data supporting this study are available from the corresponding authorsupon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted following the principles outlined in the Declaration of Helsinki, with ethical approval obtained from the Ankara Etlik City Hospital Clinical Research Ethics Committee No. 1 (approval number: AEŞH-BADEK-2024-095). Given the study's retrospective nature, the Ethics Committee of Ankara Etlik City Hospital granted a waiver for informed consent.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors certify that there are no conflicts of interest with any financial organization regarding the material discussed in the manuscript.

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