

EARLY NEONATAL OUTCOMES IN PATIENTS WITH LATE PRETERM BIRTH

Ahmet KARATAS¹, Mustafa ALBAYRAK², Fatih KESKIN², İsmail BIYIK³, Mesut OKUR⁴,
Cemalettin GUNES⁴, Seyit Ali KOSE⁵

¹ Department of Obstetrics and Gynecology, Abant İzzet Baysal University, School of Medicine, Bolu, Turkey

² Department of Obstetrics and Gynecology, Duzce University, School of Medicine, Duzce, Turkey

³ Department of Obstetrics and Gynecology, Karacabey State Hospital, Bursa, Turkey

⁴ Department of Pediatrics, Duzce University, School of Medicine, Duzce, Turkey

⁵ Department of Obstetrics and Gynecology, Suleyman Demirel University, School of Medicine, Isparta, Turkey

SUMMARY

Objective: Preterm deliveries increased in many countries in recent years. However, despite fetal lung maturity, substantial neonatal morbidity may occur even after 34 weeks of gestation. The aim of this study was to evaluate neonatal morbidity and mortality in women with late preterm births.

Design: Retrospective.

Setting: Duzce University School of Medicine, Departments of Obstetrics and Gynecology and Pediatrics Clinics.

Patients: Medical records of 291 pregnant women and newborns born between the 34^{0/7}-36^{6/7} weeks of gestation were reviewed.

Interventions: The whole population is first divided into two groups as depending on the presence of PPROM or not; and then also divided into three groups based on the gestational age at delivery as 34^{0/7}-34^{6/7} week (Group 1), 35^{0/7}-35^{6/7} week (Group 2), and 36^{0/7}-36^{6/7} week (Group 3).

Main outcome measures: Groups were compared with respect to neonatal complications related to prematurity, and early membrane rupture.

Results: Of the 291 neonates included in the study, 85 were delivered preterm due to PPROM, 206 were non-PPROM group, and 76 were in Group 1, 108 were in Group 2, and 107 were in Group 3. Sepsis rate was higher in Group 1 and 2 compared to Group 3 ($p=0.016$, $p=0.029$). NICU stay period was longer in Group 1 and Group 2 than group 3 ($p=0.028$, $p=0.015$ respectively). Newborns in Group 1 had significantly longer hospital stay than Group 3 ($p=0.010$), and total hospital stay period were significantly higher in newborns with sepsis.

Conclusions: The late-preterm infants especially in earlier weeks represent a significantly higher risk category for neonatal complications, and they have a significantly longer NICU and hospital stay period.

Key words: late preterm birth, preterm premature membrane rupture, neonatal outcomes

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Address for Correspondence: Dr. Ahmet Karataş. Abant İzzet Baysal Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Bolu
Phone: + 90 (374) 253 46 56

e-mail: akaratas1973@hotmail.com

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GEÇ PRETERM DOĞUM OLGULARINDA ERKEN NEONATAL SONUÇLAR

ÖZET

Amaç: Preterm doğumlar son zamanlarda birçok ülkede artış göstermiştir. Fetal akciğerin gelişmiş olmasına rağmen, 34. gebelik haftasından sonra bile ciddi yenidoğan morbiditesi meydana gelebilir. Bu çalışmanın amacı, geç preterm doğum olgularında neonatal morbidite ve mortaliteyi araştırmaktır.

Planlama: Retrospektif.

Ortam: Düzce Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum, Pediatri Klinikleri.

Hastalar: 34^{0/7}-36^{6/7} gebelik haftasında doğum yapan 291 gebe kadın ve yenidoğanlar incelendi.

Girişim: Çalışmaya dahil edilen olgular PPRM varlığı ya da yokluğuna göre öncelikle ikiye ayrıldı. Daha sonra gruplar, tekrar gebelik haftasına göre kendi içlerinde, (34^{0/7}-34^{6/7} hafta olanlar, grup 1; 35^{0/7}-35^{6/7} hafta olanlar, grup 2; 36^{0/7}-36^{6/7} hafta olanlar, grup 3) üçe ayrıldı.

Değerlendirme parametreleri: Gruplar prematürite ve erken membran rüptürü ile ilişkili yenidoğan komplikasyonları açısından karşılaştırıldı.

Sonuç: Çalışmaya dahil edilen ikiyüz doksanbir olgunun 85'i PPRM nedeniyle erken doğum yapmıştı. 206'sı PPRM olmayan gruptaydı, ve 76'sı 1.grup, 108'i 2. grup, 107'si de 3.grupta yer aldı. Sepsis oranı, birinci ve ikinci grupta üçüncü gruba göre daha yüksekti ($p=0.016$, $p=0.029$). Yenidoğan yoğunbakım ünitesinde (YDYB) kalış süresi 3. gruba oranla, 1. ve 2.grupta daha yüksekti (sırasıyla $p=0.028$, $p=0.015$). Birinci gruptaki yenidoğanlar, üçüncü gruptakilere göre anlamlı olarak daha uzun hastanede kalış süresine sahipti ($p=0.010$), ve toplam hastanede kalış süresi sepsisli yenidoğanlarda anlamlı olarak daha yüksekti.

Yorum: Özellikle daha erken gebelik haftalarında olan, geç preterm yenidoğanlar, yenidoğan komplikasyonları için anlamlı olarak daha fazla risklidirler, ve anlamlı olarak yenidoğan yoğun bakımda ve hastanede daha uzun kalış süresine sahiptirler.

Anahtar kelimeler: geç preterm doğum; preterm erken membran rüptürü; yenidoğan sonuçları

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INTRODUCTION

Prematurity is the leading cause of neonatal morbidity and mortality⁽¹⁾. Preterm delivery is described as the birth on or before the 37th weeks of gestation following the onset of the mother's last menstrual period^(2,3). Late-preterm birth is defined as birth between the 34^{0/7} and 36^{6/7} weeks of gestation⁽⁴⁾. Up to 60-70% of these preterm births occurred between the 34-36 weeks' of gestation indicating that late preterm births form a substantial proportion of the preterm births⁽⁵⁾. Data from the United States showed that the rate of late preterm deliveries rose by 20%, from 6.8% to 8.1%, between 1990 and 2006⁽⁶⁾. Late preterm newborns, although they are not evaluated in high risk category, have increased risk of short and long term morbidity and mortality, and they are reported to constitute an important community problem⁽⁷⁾.

Preterm PROM is associated with increased rates of neonatal and maternal infection and is responsible for nearly one-third of these pre-term deliveries in high-

income countries⁽⁸⁾. Although a more or less consensus exists on the management of preterm labor between 34 and 37 weeks due to PPRM where a higher risk of chorioamnionitis for the mother and the fetus exists⁽⁹⁻¹¹⁾, substantial neonatal morbidity may occur even after 34 weeks of gestation despite lung maturity⁽¹²⁾.

The aim of this study was to analyze late preterm delivery and compare the early neonatal morbidity and mortality based on the gestational age weeks and presence of PPRM. As far as we know this is the first study on this issue in Turkey.

MATERIALS AND METHODS

This study was carried out in the Departments of Obstetrics and Gynecology and Neonatology of Duzce University School of Medicine. We retrospectively collected the antepartum and intrapartum records of 291 singleton pregnancies and neonatal outcomes delivered between 34 - 36^{6/7} weeks of gestation,

spontaneous or indicated, from January 2009 to December 2011. The study protocol was approved by the University Non-invasive Human Research Ethics Committee.

Demographic characteristics including maternal age, pre-existing maternal medical problems such as hypertensive disorders, heart diseases, renal disease, infections such as chorioamnionitis or pyelonephritis, and other pregnancy-specific complications gestational age at delivery, birth weight, vaginal and cesarean delivery rates were recorded. Diagnosis of preterm PROM was made in the presence of leakage of clear fluid from the cervical channel or accumulation of fluid in the posterior fornix during dry speculum examination, and a positive nitrazine and ferning test or a positive placental alpha microglobulin-1 (PAMG-1) (Amniosure, International LLC, USA)⁽¹³⁾. A single dose of 12 mg betamethasone (1ml/ampul Chronodose Celestone, Schering-Plough) was injected to 25 pregnant women those excluded maternal infection in both groups.

Neonatal outcome data related to prematurity included transient tachypnea of the newborn (TTN), apnea of prematurity, respiratory distress syndrome (RDS), neonatal sepsis, hypoglycemia, jaundice, total number of phototherapy days and the neonatal intensive care unit (NICU) stay of neonate, total length of the hospital stay, and neonatal mortality. Diagnostic criteria for each neonatal morbidity were set by neonatologists as follows: (1) apnea of prematurity: prolonged respiratory pause (20 seconds or longer) accompanied by cyanosis, pallor or bradycardia; (2) TTN: clinical and radiographic features identified during the first hours of life, followed by characteristic resolution during the subsequent 24-48 hours; (3) hypoglycemia: blood glucose level below 40 mg/dL; (4) hyperbilirubinemia based on gestational week and birth weight; (5) neonatal sepsis: positive blood culture and clinical manifestations.

The discharge criteria for preterm infants included satisfactory suction upon breast-feeding assessed by experienced nursing personnel accompanied by adequate weight gain.

The first aim of this study is to evaluate the early neonatal morbidity in late preterm newborns, and the second one is to evaluate the impact of membrane rupture to neonatal morbidity.

Statistical analysis

The Statistical Package for Social Sciences (SPSS for Windows Version 19.00, Chicago, IL, USA) program was used for assessment of the results. The distribution of data analyzed using the Shapiro-Wilks test according to which suitable parametric and non-parametric tests were selected. The parametric data are given as arithmetic means \pm standard deviation (SD) and non-parametric data are given as median (minimum-maximum). Pearson chi-square test was used to compare categorical variables. When there were more than two groups, one way ANOVA and Kruskal Wallis tests were used. In the comparison of the groups, the univariate variance analysis was used in variables with normal distribution (Oneway-ANOVA test), while the Post Hoc test (Tukey-HSD) and Bonferroni correction was used for multiple comparisons ($\alpha^*=0.05/3=0.017$), respectively. Mann Whitney U test was used in cases showing a statistical difference between the two groups. A p value of < 0.05 was regarded as significant.

RESULTS

Late preterm birth rate was 6.7% (291/4301) in three-years period. Of the 291 neonates included in the study, 85(2%) were delivered with PPRM, and 206(4.7%) without PPRM.

Totally, 80 women presented with some sort of complicated obstetric maternal problem besides the preterm delivery in both groups. Preeclampsia was the most frequent condition and was diagnosed in 65 women in total. Only preeclampsia, maternal infection and antibiotherapy administration rate were statistically different between non-PPROM and PPRM groups (Table I). Maternal infection was diagnosed in 12 women, four women with chorioamnionitis and eight with pyelonephritis and antibiotherapy rates were higher in PPRM compared to non-PPROM group as expected.

Caesarean section rate was higher in non-PPROM group compared to PPRM group (65.5% vs. 35.3%, $p=0.001$) (Table II). Considering neonatal complications, neonates sepsis rate were similar between groups: 10 (11.7%) in PPRM group and 15 (7.2%) in non-PPROM group ($p=0.215$). Other parameters related to morbidity including Neonatal Intensive Care Unit (NICU) and total hospital stay periods were also statistically similar.

Table I: Demographic characteristics and systemic problems of women with and without premature rupture of membranes.

	Premature rupture of membranes		
	PROM (n=85)	No PROM (n=206)	P
	Mean ± SD	Mean ± SD	
	n (%)	n (%)	
	M (min- max)	M (min- max)	
maternal age (year)	28.3 ± 6.9 (17 - 43)	27.5 ± 5.7 (16 - 46)	0.445
≤ 19	9 (10.6)	17 (8.3)	0.067
> 19 - < 35	60 (70.6)	169 (82)	
≥ 35	16 (18.8)	20 (9.7)	
Gravidity			
1	32 (38)	81 (39)	0.790
≥2	53 (62)	125 (61)	
Preeclampsia	4 (4.7)	61 (29)	0.001
Chronic hypertension	1	7	
Maternal infection	7 (8.2)	5 (2.4)	0.023
Antibiotic therapy	20 (23.5)	9 (4.4)	0.001
Diabetes	-	2	
Cardiac disease	-	2	
Renal disease	-	2	
Hypothyroidism	-	1	
Hyperthyroidism	-	1	

Mean ± SD: Mean ± standart deviation, n (%): number (percentage).

M (min - max): Median (minimum- maximum).

When we stratified the whole group based on the gestational age at delivery, 76 (26%) were at 34^{0/7}-34^{6/7} (Group 1), 108 (37%) were at 35^{0/7}-35^{6/7} (Group 2), and 107 (36%) were at 36^{0/7}-36^{6/7} (Group 3) gestational weeks (Table III). There were no differences in maternal age, gravidity patterns, rates of preeclampsia, maternal diabetes, and chorioamnionitis between the groups. However, rupture of membrane was significantly higher only in Group 2 than the Group 3 (for Group 2 vs. Group 3, P=0.013). Caesarean delivery rate was similar among groups (61.8%, 51.9%, 57.9%, respectively). RDS and necrotising enterocolitis (NEC) rate did not differ among the groups. Among the 291 neonates there was no mortality and none had intraventricular haemorrhage. Sepsis rate was higher in Group 1 and 2 with 11 newborns in each group compared to Group 3 in which three newborns were detected with sepsis (14.5%, 10% and 2.8%, respectively; p=0.016, p=0.029). Also, the number of

Table II: Birth and neonatal morbidity data in those women with and without premature rupture of membranes.

	Premature rupture of membranes		
	PROM (n=85)	No PROM (n=206)	P
	Mean ± SD	Mean ± SD	
	n (%)	n (%)	
	M (min- max)	M (min- max)	
Applicant week	35.2 ± 0.8	35.2 ± 0.9	0.584
Steroid	6 (7.1)	19 (9.2)	0.549
Gestational age (week)	35.2 ± 0.8	35.4 ± 0.85	0.152
Cesarean rate	30 (35.3)	135 (65.5)	0.001
Birth weight (g)	2460 ± 265	2400 ± 304	0.194
Transient tachypnea	4 (4.7)	12 (5.8)	0.703
Respiratory distress syndrome	2 (2.3)	6 (2.9)	0.791
Pneumonia	3 (3.5)	4 (1.9)	0.422
Hypoglycemia	7 (8.2)	20 (9.7)	0.694
Sepsis	10 (11.7)	15 (7.2)	0.215
Necrotizing enterocolitis	1 (1.2)	1 (0.5)	0.516
Phototherapy	16 (18.8)	40 (19.4)	0.907
Phototherapy (day)	2 (1 - 7)	2 (1 - 7)	0.975
NICU need newborn (n)	26 (30.5)	57 (28)	0.616
Stay in NICU (day)	5 (2 - 23)	6 (1 - 18)	0.603
Stay in hospital (day)	8 (2 - 30)	7 (2 - 28)	0.580
Ventilator use	0	0	
Intraventricular hemorrhage	0	0	

Mean ± SD: Mean ± standart deviation, n (%): number (percentage).

M (min - max): Median (minimum- maximum), NICU: Neonatal Intensive Care Unit.

newborns needing NICU was higher in Group 1 (32, 42%) and Group 2 (38, 35%) compared to Group 3 (13, 12%) (p < 0.001). Additionally, NICU stay period was longer in Group 1 (6 days, mean: 1-13) and Group 2 (6 days, mean: 3 -13%) compared to Group 3 (4.2 ± 2.1 days) (p=0.028 for Group 1 and 3, p=0.015 for Group 2 and 3). When total hospital stay was evaluated, newborns in Group 1 had significantly longer hospital stay than Group 3 (p=0.010). Newborn sepsis, maternal infection and antibiotherapy rates were similar among the groups. However, vaginal birth rate (59% vs. 36% respectively; p=0.029), RDS rate (12% vs. 2% respectively; p=0.003) and total hospital stay period (11 vs. 6 days respectively; p < 0.001) were significantly higher in newborns with sepsis compared to newborns without sepsis.

Table III: Maternal demographic characteristics, birth and neonatal morbidity data according to the week of delivery.

	Delivery week			P
	34 ^{0/7} -34 ^{6/7} n=76 (% 26) Mean ± SD n (%) M (min - max)	35 ^{0/7} -35 ^{6/7} n=108 (% 37) Mean ± SD n (%) M (min - max)	36 ^{0/7} -36 ^{6/7} n=107 (% 36) Mean ± SD n (%) M (min - max)	
Maternal age (year)	28 ± 5.4 (17 - 42)	27.8 ± 6.3 (17 - 46)	27.5 ± 6.4 (16 - 41)	0.782
≤19	4 (5.3)	9 (8.3)	13 (12.1)	0.386
> 19 - < 35	64 (84.2)	87 (80.6)	78 (72.9)	
≥35	8 (10.5)	12 (11.1)	16 (15)	
Gravidity				
1	26 (34.2)	40 (37)	47 (44)	0.368
≥2	50 (65.8)	68 (63)	60 (56.1)	
Preeclampsia	16 (21.1)	18 (16.7)	31 (29)	0.091
Maternal infection	1 (1.3)	5 (4.6)	6 (5.6)	0.336
Antibiotic therapy	6 (7.9)	16 (14.8)	7 (6.5)	0.101
Rupture of membrane	22 (29)	40 (37)	23 (21)	0.043 b 0.044 c 0.013
Steroid use	12 (15.8)	6 (5.6)	7 (6.5)	0.032 a 0.021 b 0.043
Cesarean rate	47 (61.8)	56 (51.9)	62 (57.9)	0.383
Birth weight (g)	2270 ± 321	2415 ± 285	2520 ± 234	<0.001 a 0.003 b <0.001 c 0.021
Transient tachypnea	5 (6.6)	8 (7.4)	3 (2.8)	0.298
Sepsis	11 (14.5)	11 (10)	3 (2.8)	0.016 b 0.016 c 0.029
Necrotizing enterocolitis	1 (1.3)	1 (0.9)	0	0.530
Respiratory distress syndrome	5 (6.6)	2 (1.9)	1 (0.9)	0.055
Hypoglycemia	7 (9.2)	13 (12)	7 (6.5)	0.301
Hypothermia (n)	19 (25)	23 (21.3)	14 (13.1)	0.104
Phototherapy (das)	2 (1 - 7)	2 (1 - 4)	3.1 ± 1.6	0.05 c 0.048
NICU need newborn (n)	32 (42)	38 (35.2)	13 (12.1)	<0.001 b <0.001 c <0.001
Stay in NICU (days)	6 (1 - 13)	6 (3 - 13)	4.2 ± 2.1	0.042 b 0.028 c 0.015
Stay in hospital (days)	8.5 (2 - 30)	8.74 ± 4.3	5 (2 - 20)	0.015 b 0.010

Mean ± SD: Mean ± standart deviation, n (%): number (percentage).

M (min - max): Median (minimum-maximum), NICU: Neonatal Intensive Care Unit,

a: 34^{0/7}- 34^{6/7} vs. 35^{0/7}-35^{6/7} weeks, b: 34^{0/7}- 34^{6/7} vs. 36^{0/7}-36^{6/7} weeks, c: 35^{0/7}- 35^{6/7} vs. 36^{0/7}- 36^{6/7}. Oneway-ANOVA test, Post Hoc Tukey- test and bonferroni correction was used for multiple comparisons ($\alpha^*=0.05/3=0.017$).

DISCUSSION

Late preterm births account for two thirds of all preterm births, and one third of these women present with

PPROM⁽¹⁴⁾. In our study, late preterm birth rate (6.7%) was found to be consistent with the literature⁽⁶⁾. During a 3 year period, 85 (2%) of the 4301 deliveries were in the PPRM group and 206 (4.7%) were in the group

that did not develop PPROM. There is no study from our country that investigates late preterm deliveries, but in one study which investigated pregnancies that did or did not develop PPROM before the 34th gestational week found a rate of 3.7% and 9.6%, respectively⁽¹⁵⁾.

Besides an increase in various neonatal complications in short term such as TTN, RDS, intraventricular haemorrhage, NEC, hypoglycemia, hyperbilirubinemia, neonatal sepsis, and need for NICU, these infants are also at risk for long term complications such as compromised lung function later in life⁽¹⁶⁻¹⁸⁾.

Although we did not observe several severe neonatal complications such as broncho-pulmonary dysplasia, pulmonary haemorrhage and intraventricular haemorrhage in our study, this might be explained by the small sample size and relatively low frequency of these complications, especially in later gestational preterm births.

The RDS incidence in this study were found as 6.6%, 1.9% and 0.9% at 34th, 35th and 36th weeks respectively. Robertson et al.⁽¹⁹⁾ reported the RDS incidences as 13.7%, 6.4% and 3.3% at 34th, 35th and 36th weeks respectively in the largest multicentre study conducted so far. This may partially be explained by improvement in NICU facilities during the last 20-year time span between two studies. The higher incidence of sepsis in our study compared to study of Robertson et al. (14.5% vs. 3.5%, 13% vs. 2.2%, and 3.7% vs. 1.2 for corresponding gestational weeks respectively) might be explained by possible lower socioeconomic status of our population. RDS, hypoglycemia, hyperbilirubinemia, and neonatal sepsis were the major causes of NICU need and prolonged hospital stay in our study.

Newborns born at 34th and 35th completed gestational weeks were followed up in NICU longer compared to those born at 36th weeks. In addition, the total hospital stay was longer in newborns born at completed 34th weeks compared to newborns born at 35th and 36th gestational weeks in our study. Similarly to our study, Lubow et al.⁽²⁰⁾ reported NICU stay period as 67%, 30% and 12%, and the total hospital stay means as 8±7, 3±4 and 3±4 days for 34th, 35th and 36th weeks for gestational weeks, respectively.

Microbial pathogens have been reported to be recovered from the amniotic cavity in 10-15% of the cases with spontaneous PROM and in 32-35% of women with

PPROM^(21,22). We do not routinely investigate the GBS colonization in our clinic, but, GBS carriage during pregnancy has been estimated to be 10 - 30% in most population based on previous studies⁽²³⁾. Transmission of organism to the neonates can occur vertically or, rarely by hematogenous dissemination. More than 98% of the cases of early-onset GBS sepsis are the consequence of vertical transmission from the genital tract of the mother to the infant⁽²⁴⁾. Neonatal transmission rate of 60% had been calculated in one study⁽²⁵⁾. In line with this, the sepsis rate was significantly higher in newborns delivered vaginally than those delivered by caesarean in this study.

Empiric antibiotic therapy following PPROM reduces risk of neonatal respiratory distress, intra-ventricular haemorrhage and confirmed neonatal sepsis. Cousens et al.⁽²⁶⁾ were reported a 39% reduction in incidence of neonatal sepsis (95% CI 23-52%, P<0.001) with antibiotic therapy for PPROM among newborns born following PPROM. Not only PPROM, but also preeclampsia is defined as factors which increase neonatal morbidity in late preterm period⁽²⁷⁾. Although we have not looked at morbidity rates based on whether or not preeclampsia, 61 of 65 women were in non-PPROM group with preeclampsia.

We analysed only the short-term neonatal morbidity of late-preterm births during the stay of the newborn in the nursery. As stated by Kotecha et al.⁽¹⁸⁾ late preterm infants are at increased risk of respiratory morbidity in the neonatal period with a higher incidence of unavoidable and urgent respiratory interventions, such as mechanical ventilation and treatment with antibiotics, steroids and surfactant for early respiratory infections and insufficiency; thus they may also be at risk of compromised long term lung function later in their lives. Recently, two papers concluded that the burden of prematurity can be decreased if elective late preterm delivery is eliminated, and birth should be considered only if the risk of continuation the pregnancy exceeds the neonatal risks related to early birth^(7,28).

In conclusion, although late preterm infants are at increased risk for short and long-term morbidity and possibly mortality and they are also an important burden to the community and they are often not viewed as in high-risk category. However, they deserve a considerable attention and care for increased short and long term complications and mortality rates, which may be costly when overlooked. This study showed that the late-

preterm infants represent a significantly higher risk category for neonatal complications especially in earlier weeks, and they cause significantly longer NICU and hospital stay periods. In addition, the length of hospital stay increases even more in the presence of sepsis. Vigorous efforts should be put into practice for the detection for early neonatal infectious complications such as colonization and treatment of GBS infections in late preterm deliveries. Delivery should be induced only if risk assessment shows definitive risk in continuation of pregnancy and elective delivery in near term pregnancies should be avoided.

Because of the small number of cases in our study, we could not evaluate the neonatal morbidities according to the gestational weeks. This issue needs to be investigated in a larger patient population.

Conflict of Interest

We declare that we have no conflict of interest

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