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ORIGINAL ARTICLE

Causes and outcomes of respiratory distress in late preterm infants - tertiary neonatal intensive care unit experience

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Summary

Introduction/Aim: Respiratory distress (RD) is the most common cause of morbidity in preterm infants. The current study was undertaken to determine causes of RD in late preterm infants, analyze characteristics of RD regarding gestational age, compare different clinical forms of RD and determine the factors influencing the unfavorable outcome of late preterm infants with RD.

Methods: The study included infants born between 34 0/7 and 36 6/7 weeks of gestation with RD hospitalized at the Institute for Mother and Child Health Care of Serbia „Dr Vukan Cupic". Demographic and clinical characteristics, clinical signs and course of the disease, the occurrence of complications, as well as quantification of disease severity were analyzed. The outcome was assessed through mortality, duration of mechanical ventilation, and length of hospital stay. Patients were ranked and compared according to gestation and type of RD. Descriptive and analytic statistical methods were used for analyzing the results.

Results: The study comprised a total of 65 late preterm newborns with RD, the majority of whom were male (n=44, 67.7%). Respiratory distress syndrome (RDS) (46.2%) and transient tachypnea of the newborn (TTN) (40%) were the most common causes of RD. TTN was most prevalent in neonates in the 36th gestational week, whether RDS was most present before 35th gestational week. The average length of hospital stay was 15 days and mortality in the group was 1.5%.

Conclusion: The most prevalent causes of RD in late preterm infants are RDS and TTN. Late preterm infants represent a vulnerable group of newborns, with a heightened risk of associated morbidity and mortality.

Key words: respiratory distress, late preterm, transient tachypnea of the newborn, respiratory distress syndrome

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INTRODUCTION

Late preterm newborns are born between 34 0/7 and 36 6/7 gestational weeks. They represent 70% of preterm born infants, with a frequency of around 8% of all newborns (1). Physical appearance of late preterm newborns is similar to term infants. However, due to insufficient physiological maturity and usually delayed postnatal adaptation, late preterm newborns are susceptible to specific diseases that can significantly affect the overall neonatal morbidity and mortality. Notably, approximately 50% of late preterm newborns require treatment in neonatal intensive care units (NICUs), and they experience high rates of readmissions, and three times higher mortality compared to full-term newborns (2).

The incidence of respiratory distress (RD) is significantly higher in late preterm than in term newborns and is inversely proportional to gestational age (2, 3). At 34 weeks of gestation, the lung volume is only 50% of the lung volume in a full-term newborn, and alveolar walls are around one-third thicker, contributing to reduced lung compliance (4). The most common causes of RD in late preterm infants include respiratory distress syndrome (RDS), transitory tachypnea of the newborn (TTN), pneumonia, idiopathic persistent pulmonary hypertension, aspiration syndrome, air-leak syndrome.

This research aims to identify the causes of RD in late preterm infants, analyze characteristics of RD in relation to gestational age, compare various clinical forms of RD, and determinate the factors that influence the adverse outcomes of late preterm infants with RD.

MATERIALS AND METHODS

This study is an observational and descriptive retrospective analysis conducted on late preterm newborns with RD who were admitted to the NICU of the Institute for Mother and Child Health Care of Serbia „Dr Vukan Cupic", over a two-year period. The Institute for Mother and Child Health Care of Serbia „Dr Vukan Cupic" is a pediatric hospital providing tertiary-level care in the NICU, but it does not contain a maternity department. The study group included newborns delivered between 34 0/7 and 36 6/7 gestational weeks with the diagnosis of RD. Gestational age was determined according to the mother's last menstrual period. The American College of Obstetricians and Gynecologists' (ACOG) definition of late preterm birth was used (5). The diagnosis of RD was made according to clinical, laboratory, and radiographical findings.

The following demographic and clinical characteristics were analyzed: gender, age, type of delivery, birth weight (BW), Apgar score (AS), small for gestational age (SGA), risk factors for preterm birth, and RD. Additionally, clinical symptoms and signs of RD were observed during hospital stay: type of respiratory pathology, need for supplemental oxygen, intubation and surfactant administration, treatment complications (air leak syndrome, persistent pulmonary hypertension), and co-morbidities. X-ray of the lungs and heart and echocardiography were used to estimate the presence of pulmonary hypertension. Treatment outcome was assessed through survival rate, duration of mechanical ventilation and the length of hospital stay. Patients were compared according to gestational age, and the type of RD.

Disease severity assessment

Disease severity was assessed according to the internationally used scores Score for Neonatal Acute Physiology II (SNAP II) and Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE II) (6).

SNAP II score assesses six parameters: mean arterial pressure, body temperature, the ratio of arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2) (PaO2/FiO2 ratio), serum pH, multiple seizures, and urine output. Normal values are evaluated with zero points, while deviations are evaluated with a minimum of 5 and a maximum of 28 points. SNAPPE II score consists of three additional perinatal variables recognized as important predictors of newborn survival: BW, AS, and SGA. Normal values are evaluated with zero points, whereas alterations are evaluated with 10 to 18 points.

Statistical analysis

Statistical analysis was done using the SPSS Statistics for Windows version 21.0 software program (IBM Corp., Armonk, NY, USA). Descriptive data are presented in the form of measures of central tendency (arithmetic mean, median), measures of variability (standard deviation, percentiles), and relative numbers (structure indicators). Student's t-test, Mann-Whitney U test, One Way ANOVA and Kruskal Wallis test were performed to determine differences between numerical data. Pearson's chi-squared test and Fisher's exact test were used to determine the significance between nominal variables. The association between risk factors and RDS and TTN was evaluated by univariate logistic regression. Differences at $p<0.05$ were considered to be statistically significant.

RESULTS

The study included 65 late preterm newborns with RD, and the majority of them were male (n=44, 67.7%). In order to assess their characteristics, type of RD and therapy strategy, newborns were divided into three groups according to gestational week: 34 – 34+6 (group I), 35 – 35+6 (group II) and 36 – 36+6 (group III) **(Table 1)**. BW was significantly different between groups, with low-

Table 1. Characteristics of the study participants according to the gestational week.

	All N=65 N (%)	Group I 34–34+6 GW N=16 N (%)	Group II 35–35+6 GW N=14 N (%)	Group III 36–36+6 GW N=35 N (%)	p
BW	2815.8 ±399.5	2533.7 ±379.0	2770.0 ±209.8	2963.1 ±399.4	**0.001**
BW<10 percentile	2 (3.1)	1 (6.3)	0 (0)	1 (2.9)	0.609
BW>90 percentile	7 (10.8)	1 (6.3)	0(0)	6 (17.1)	0.413
Twins	6 (9.2)	2 (12.5)	1 (7.1)	3 (8.6)	0.863
Cesarean section	31 (47.7)	8 (50)	7 (50)	16 (45.7)	0.942
Maternal morbidity	24 (36.9)	8 (50)	4 (28.6)	12 (34.3)	0.428
PPROM	3 (4.6)	2 (12.5)	1 (7.1)	0 (0)	0.125
Antenatal corticosteroids	6 (9.2)	2 (12.5)	4 (28.6)	0 (0)	**0.007**
AS 1 minute	8 (7-9)	8 (6-8)	8.5 (8-9)	9 (7-9)	**0.040**
AS 5 minute	9 (8-10)	8 (6-9)	9 (8-9.5)	9 (8-10)	**0.054**
AS 5 ≤ 7	14 (21.5)	4 (25.0)	3 (21.4)	7 (20.0)	0.922
Resuscitation in delivery room	7 (10.8)	2 (12.5)	2 (14.3)	3 (8.6)	0.816

GW – gestational week; BW – birth weight; PPROM – preterm premature rupture of the membranes; AS – Apgar score

Table 2. Types of the RD among study participants according to the gestational week.

	All N=65 N (%)	Group I 34–34+6 GW N=16 N (%)	Group II 35–35+6 GW N=14 N (%)	Group III 36–36+6 GW N=35 N (%)	p
RDS	30 (46.2)	13 (81.3)	8 (57.1)	9 (25.7)	**0.005**
TTN	26 (40)	2 (12.5)	5 (35.7)	19 (54.3)	
Others	9 (13.8)	1 (6.3)	1 (7.1)	7 (20.0)	

GW – gestational week; RDS – respiratory distress syndrome; TTN – transient tachypnea of the Newborn

est BW in the group born between 34 and 34+6 weeks (p=0.001). The use of antenatal corticosteroids was most frequently recorded in group II (p=0.007). AS in 1st and 5th minute were lowest in group I (p=0.040 and p=0.054, respectively) **(Table 1)**.

Causes of RD among all included participants were RDS (n=30, 46.2%), TTN (n=26, 40%), amniotic fluid aspiration (n=2, 3.1%), persistent pulmonary hypertension of the newborn (PPHN) (n=1, 1.5%), meconium aspiration syndrome (MAS) (n=2, 3,1%), and pneumothorax (n=4, 6,1%). Most common type of RD in the group born between 34 and 34+6 weeks was RD, and among infants born between 36 and 36+6 weeks it was TTN (p=0.005) **(Table 2)**. Univariant logistic regression showed 8,15-fold higher risk for RDS in infants born before 35 weeks. Newborns with BW below 2500 g had a 3,47-fold increased risk for developing RDS.

As for the therapy used, only surfactant administration was significantly different between study groups, commonly used in the group born between 34 and 34+6 gestational weeks (p=0.005). Pneumothorax occurrence was statistically most frequent in group II (p=0.013). PPHN frequency was similar across groups (p=0.258) **(Table 3)**.

Table 3. Therapeutic procedures and their duration across groups according to the gestational week.

	All N=65 N (%)	Group I 34–34+6 GW N=16 N (%)	Group II 35–35+6 GW N=14 N (%)	Group III 36–36+6 GW N=35 N (%)	p
Surfactant	12 (18.5)	17 (43.8)	3 (21.4)	2 (5.7)	**0.005**
MV	37 (56.9)	9 (56.3)	11 (78.6)	17 (48.2)	0.159
MV duration	7 (3-8)	8 (2-12)	7 (4-8)	5 (2-7)	0.144
O2 duration	3 (2-5)	4 (2-6)	3.5 (2.5-5)	3 (2-5)	0.603
Pneumothorax	11 (16.9)	2 (12.5)	6 (42.9)	3 (8.6)	**0.013**
PPHN	13 (20)	1 (6.3)	4 (28.6)	8 (22.9)	0.258

GW – gestational week; MV – mechanical ventilation; PPHN - persistent pulmonary hypertension of the newbor

Table 4. Therapeutic procedures and their duration according to the type of RD

	RDS N=30		TTN N=29		Others N=9		P
	N	%	N	%	N	%	
Surfactant	11	36.7	0	0	1	11.1	**0.002**
MV	23	76.7	7	26.9	7	77.8	**<0.001**
MV duration	8	2-12	7	4-8	5	2-7	0.144
NIV	14	46.7	3	11.5	3	33.3	**0.017**
O2	28	93.2	25	96.2	9	100	0.685
O2 duration	4	2-6	3.5	2.5-5	3	2-5	0.603
iNO	3	10	0	0	1	11.1	0.24

RDS – respiratory distress syndrome; TTN - transient tachypnea of the newborn; MV – mechanical ventilation; NIV – noninvasive ventilation; O2 – oxygen; iNO – inhalational nitric oxide

Furthermore, the investigation of therapy modalities and their duration among different types of RD showed a statistically significant difference among groups for surfactant administration, with its most often use among newborns with RDS (p=0.002). The need for invasive mechanical ventilation and noninvasive ventilation support was significantly less frequent in newborns with TTN in comparison to other types of RD (p<0.001 and p=0.017, respectively) **(Table 4)**.

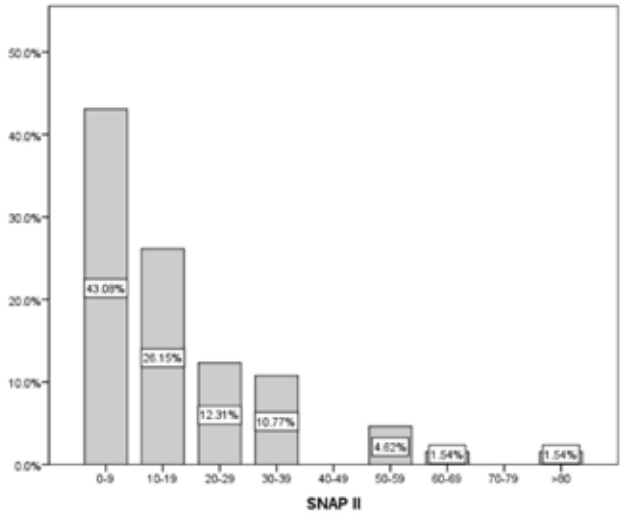

Figure 1. Distribution of investigated near-term newborns according to the SNAP II score.

Our results showed that 28 of our study patients (43,08%) had SNAP II score between 0 and 9, while 5 of them (7,7%) had a score with high mortality risk **(Figure 1)**. According to the SNAPPE II existing tables for calculating the mortality risk for the category of newborns with body weight > 1500g, 89,2% had risk below 5,2% (score between 0 and 39), while 10,8% had mortality risk between 15,4 and 66,7% (score 40 and higher) **(Figure 2)**.

Group I had the longest hospital stay, which was statistically significant (p=0.015). Of the late preterm infants, only one patient born between 35 and 35+6 gestational weeks experienced the fatal outcome. In terms of the SNAP II score, Group II had the highest score, although the differences between the groups were not statistically significant (p=0.055). The SNAPPE II scores did not show significant differences between the groups (p=0.121) **(Table 5)**.

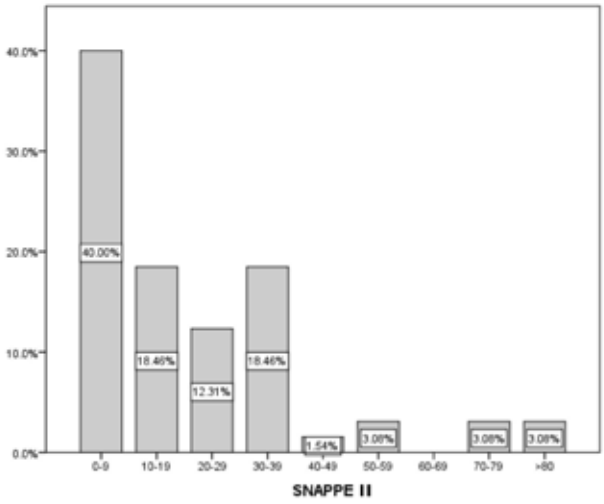

Figure 2. Distribution of investigated near-term newborns according to the SNAPPE II score

Regarding the type of RD, patients with RDS had the longest hospital stay , which was statistically significant (p=0.015). Additionally, SNAP II score was significantly higher in the group diagnosed with TTN compared to other types of RD (p=0.055) **(Table 6)**.

DISCUSSION

Prematurity represents a leading cause of morbidity and mortality in the neonatal period worldwide. The incidence of premature births shows an increasing trend despite the efforts made during past years (7). The rate of preterm birth increased between 1981. and 2003. by 31% (from 9,1% to 12,3%). It is largely influenced by an increased number of births in near-term gestation, which rose by 40% in the mentioned period (8). Data from the year 2010 showed that among live singleton births, late preterm births ranged from 3.0% to 6.0% and constituted between 65% and 75% of preterm births in high-income

Table 5. Length of hospital stay, fatal outcome, SNAP II and SNAPPE II scores in RD patients according to the gestational week.

	All N=65 N (%)	Group I 34–34+6 GW N=16 N (%)	Group II 35–35+6 GW N=14 N (%)	Group III 36–36+6 GW N=35 N (%)	p
Length of hospital stay	15 (10-22)	21.5 (13-35)	17 (11-24)	12 (9-18)	0.015
Fatal outcome	1(1.5)	0(0)	1(1.5)	0(0)	NA
SNAP II	12 (5-24)	16 (8.5-26)	19.5 (5-32)	5 (5-16)	0.055
SNAPPE II	16 (5-30)	20 (8.5-35.5)	23 (5-34)	10 (5-26)	0.121

GW – gestational week; SNAP II - Score for Neonatal Acute Physiology II; SNAPPE II - Score for Neonatal Acute Physiology Perinatal Extension II

countries (9, 10). In Serbia, the frequency of preterm newborns increased from 5.7% to 6.7% between 2009 and 2014, along with an increase in near-term births from 3,9% to 4,7 % (17% increase) (11).

In our study, the majority of the included newborns were male (67.7%), which is in correlation with the findings of a higher morbidity and mortality rate among late preterm males in comparison to females (12). BW was significantly different between the groups according to gestational age, with the lowest BW in the group born between 34 and 34+6 weeks. BW below 10 percentiles was found in only 2 out of 65 patients. Low BW as a consequence of intrauterine growth restriction (IUGR) might represent an indication for delivery between 34 and 36+6 weeks (13). Gilbert et al. described lower RDS incidence in infants with IUGR born before 30 gestational weeks, while in late preterm gestation this incidence was significantly higher (14). Our results showed most frequent use of antenatal corticosteroids in the group born between 34 and 34+6 weeks. Only 9.2% of all the mothers got this therapy. Such low incidence of mothers prenatally treated with corticosteroids might reflect its insufficient protective effect for severe RDS development. Antenatal administration of corticosteroids in mothers with expected preterm birth has been reported to increase the survival rate, decrease the risk of RDS and the use of mechanical ventilation, necrotizing enterocolitis, and intraventricular hemorrhage (15). Prenatal corticosteroid therapy is recommended in all pregnant women with the risk of birth before 34 weeks (16). Furthermore, corticosteroid administration between 34 and 36 weeks lowers the risk of respiratory morbidity, but not the risk of mortality (15). AS lower than 7 in the 5th minute was found in 21,5% of included newborns, while 10,8% showed the need for resuscitation. AS in the 1st and the 5th minute were lowest in the group born between 34 and 34+6 gestational weeks. Low AS increases the frequency of respiratory disorders in late preterm newborns. The incidence of perinatal asphyxia characterized as AS lower than 7 in the 5th minute is 3-fold higher in late preterm neonates than in term neonates (17).

Most frequent causes of RD in near-term infants included in this study were RDS and TTN. Other less common causes were also recorded, such as amniotic fluid aspiration, PPHN, MAS, and pneumothorax. The most common type of RD in the group born between 34 and 34+6 weeks was RDS, and in the group born between 35 and 35+6 weeks was TTN. According to the results of univariate logistic regression, newborns below 35 gestational weeks had an 8,15-fold increased risk of RDS occurrence. Additionally, near-term infants with low BW (below 2500 g) had a 3,47 times higher risk of developing RDS. In a study conducted by Rubaltelli et al. (18), the incidence of RD in late preterm infants was reported to be approximately 30%, while in term newborns the incidence was only 1%. Another study demonstrated that RDS was the most common type of RD in newborns between 34 and 34+6 weeks, with the occurrence rate of around 10% (17). A study from 2018 showed that approximately 9% of late preterm infants developed RDS or TTN (19). This frequency decreases with gestation, showing the rate of 0.3% in term newborns at 40 weeks (17). One large observational study of 19000 preterm and 166000 term newborns showed a decrease in the TTN incidence with an increasing gestational age, resulting in

Table 6. Length of hospital stay, fatal outcome, SNAP II and SNAPPE II scores in different types of RD.

	RDS N=30		TTN N=29		Others N=9		p
	N	%	N	%	N	%	
Fatal outcome	1	3.3	0	0	0	0	NA
Length of hospital stay	21.5	13-35	17	11-24	12	9-18	**0.015**
SNAP II	16	8.5-26	19.5	5-32	5	5-16	**0.055**
SNAPPE II	20	8.5-35.5	23	5-34	10	5-26	0.121

RDS – respiratory distress syndrome; TTN – transient tachypnea of the newborn; SNAP II - Score for Neonatal Acute Physiology II; SNAPPE II - Score for Neonatal Acute Physiology Perinatal Extension II

its frequency of 6,4% in neonates born at 34 weeks, 2,5% in those born at 36 weeks, and only 0,3% in term infants (17). This could be due to impairment of hormonal stimuli that accompany a normal term delivery, and which is responsible for establishing successful pulmonary transition by activating biochemical processes responsible for absorption of lung fluid from the alveoli.

In our research, we observed that among the complications of RD treatment, PPHN occurred in 16.9% of cases, while pneumothorax was present in 20% of cases.

Patients included in this study had severe types of RD and needed hospitalization in tertiary center, which accounts for a high incidence of complications. More than half of the study patients had a need for mechanical ventilation, with a mean duration of 7 days, 30% were on noninvasive ventilation, 18,5% of newborns received surfactant, and 6.2% were treated with iNO. Other studies showed inconsistent results regarding therapy use in near-term newborns with RD (20). One investigation showed an incidence of ventilatory support of 6.6% in 34 weeks and 3% in 36 weeks, and surfactant administration depended of gestational age (2,2 – 7,4%) (17). Oppositely, Shaikh et al. (21) described the need for MV in 78,5% of infants born at 34 weeks, while it decreased to 15% at 36 weeks.

The average duration of hospital stay in our study was 15 days. Comorbidities of our patients, such as jaundice, feeding difficulties, infections, could have been the reason for a longer hospital stay. The frequency of readmission is significantly higher in late preterm than in term infants, showing an incidence of 6,3% in newborns between 35 and 36 gestational weeks and 2,4% after 40 weeks (22). An earlier study showed that mean hospital length stay for infants in NICU with RD was 12 days for those born at 34 weeks, 8 days for 35 weeks and 6 days for neonates born at 36 weeks (17).

Only one patient had the lethal outcome, which resulted in mortality rate of 1,5% for our study group. Mortality is found to be 4,6-fold higher in near-term than in term neonates (23). The analysis of late preterm infants with RD found the mortality rate of 0,8% at 34 weeks, 0,4% at 35 weeks, and only 0,1% at 40 gestational weeks (17).

We observed disease severity through the calculation of SNAP II and SNAPPE II scores. More than 40% of our study patients had SNAP II score between 0 and 9, and less than 8% had a score with high mortality risk. According to the SNAPPE II existing tables for calculating the mortality risk for the category of newborns with body weight > 1500g, 89,2% of our patients had a risk below 5,2% (score between 0 and 39), while 10,8% had mortality risk between 15,4 and 66,7% (score 40 and higher).

Our study results showed the highest frequency of pneumothorax in the group born between 35 and 35+6 gestational weeks. Regardless RD type, one research found pneumothorax to be one of the most frequent complications of both the disease and its treatment (24). Oppositely, some earlier investigations failed to detect an increased incidence of pneumothorax in newborns aged 34 to 36+6 weeks (17).

CONCLUSIONS

Based on the results presented in this study, we can draw certain conclusions.

The most common types of RD in late preterm infants are RDS and TTN. Among the infants included in our study, the mortality rate was 1,5%. However, mortality risk in infants with high SNAPPE scores exceeded 15%.

RDS is most frequently observed in infants born before 35 weeks of gestation and with low BW. Late preterm infants with RDS often require surfactant administration and experience longer hospital stays compared to other types of RD.

TTN typically requires less frequent use of invasive and noninvasive mechanical ventilation. It also carries a lower risk of complications and comorbidities.

Late preterm newborns with the highest incidence of TTN are born between 36 and 36+6 weeks of gestation. Furthermore, their likelihood of experiencing complications and comorbidities decreases as their gestational age increases.

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UZROCI I ISHODI LEČENJA RESPIRATORNOG DISTRESA KOD NOVOROĐENČADI KASNE PRETERMINSKE GESTACIJE - ISKUSTVO TERCIJARNOG NEONATALNOG CENTRA

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Sažetak

Uvod/Cilj: Respiratorni distres (RD) je najčešći uzročnik morbiditeta kod preterminske novorođenčadi. Cilj ove studije je utvrđivanje najčešćih uzroka RD-a kod kasne preterminske novorođenčadi, analiza karakteristika RD-a u odnosu na nedelju gestacije i utvrđivanje faktora koji utiču na nepovoljan ishod kasne preterminske novorođenčadi sa RD-om.

Metode: Ovom studijom su obuhvaćena novorođenčad gestacijske starosti 34 0/7 do 36 6/7 nedelja sa RD-om, hospitalizovana u Institutu za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić". Analizirane su demografske i kliničke karakteristike, klinički znaci i tok bolesti, pojava komplikacija, kao i kvantifikovanje težine bolesti pomoću neonatalnih skorova. Ishod lečenja je praćen kroz preživljavanje, trajanje mehaničke ventilacije i dužinu hospitalizacije. Pacijenti su poređeni prema gestaciji, kao i prema vrsti oboljenja. Za obradu podataka korišćene su metode deskripitivne i analitičke statistike.

Rezultati: Studijom je obuhvaćeno 65 ispitanika, od kojih je većina muškog pola. Najčešći uzroci RD-a bili su respiratorni distres sindrom (RDS) (46,2%) i tranzitorna tahipneja novorođenčeta (TTN) (40%). TTN je bila najzastupljenija kod novorođenčadi u 36. nedelji gestacije, a RDS ispod 35. nedelje gestacije. Novorođančad su prosečno bila hospitalizovana 15 dana, a mortalitet je iznosio 1,5%.

Zaključak: Najčešći uzroci RD-a kod kasne preterminske novorođenčadi su RDS i TTN. Ovo je osetljiva kategorija novorođenčadi sa visokim rizikom za teške komplikacije, udruženi morbiditet i smrtni ishod.

Ključne reči: respiratorni distres, predterminsko novorođenče, tranzitorna tahipneja, respiratorni distres sindrom

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