

Acute kidney injury in a single neonatal intensive care unit in Turkey

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Background: Although advances in perinatal medicine have increased the survival rates of critically ill neonates, acute kidney injury (AKI) is still one of the major causes of mortality and morbidity in neonatal intensive care units. This study aimed to determine the prevalence of AKI and analyze demographic data and risk factors associated with the mortality or morbidity.

Methods: Of 1992 neonates hospitalized between January 2009 and January 2011, 168 with AKI were reviewed in the study. The diagnosis of AKI was based on plasma creatinine level >1.5 mg/dL, which persists for more than 24 hours or increases more than 0.3 mg/dL per day after the first 48 hours of birth while showing normal maternal renal function.

Results: The prevalence of AKI was 8.4%. The common cause of AKI was respiratory distress syndrome, followed by sepsis, asphyxia, dehydration, congenital anomalies of the urinary tract, congenital heart disease, and medication. The prevalence of AKI in neonates with birth weight lower than 1500 g was about three-fold higher than in those with birth weight higher than 1500 g ($P<0.05$). Pregnancy-induced hypertension, preterm prolonged rupture of membranes, and administration of antenatal corticosteroid were associated with increased risk of AKI ($P<0.05$). Umbilical vein catheterization, mechanical ventilation and ibuprofen therapy for patent ductus arteriosus closure were found to be associated

with AKI ($P<0.05$). The overall mortality rate was 23.8%. Multivariate analysis revealed that birth weight less than 1500 g, mechanical ventilation, bronchopulmonary dysplasia, anuria, and dialysis were the risk factors for the mortality of infants with AKI.

Conclusions: Prenatal factors and medical devices were significantly associated with AKI. Early detection of risk factors can reduce the mortality of AKI patients.

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Key words: acute kidney injury; mortality; neonatal intensive care unit; prevalence; risk factors

Introduction

Acute kidney injury (AKI) is a frequently encountered problem in tertiary level neonatal intensive care units (NICUs). It is usually a potentially reversible syndrome characterized by an abrupt reduction in glomerular filtration rate. AKI develops in approximately 8%-24% of all neonates admitted to NICUs, mostly secondary to hypovolemia, hypoxemia and hypotension.^[1,2] Over 70% of these cases represent prerenal AKI. Since AKI in newborns is usually asymptomatic, many such cases will be missed if relevant investigations are not conducted.^[3,4] Therefore, it is important to assess the predisposing factors and early subclinical findings of AKI to improve the treatment results of the disease.

Although several studies have shown that AKI is common in the NICUs, the precise prevalence of AKI are still unknown.^[5] Many studies have been carried out in adults and children, but only limited data are available on the etiology and prognosis of neonatal AKI in Turkish NICUs.

The aim of this study was to determine the prevalence AKI and to evaluate the risk factors in predicting mortality and short term outcome in our NICU.

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Methods

Study population

This retrospective study was conducted at the NICU of Sisli Etfal Education and Research Hospital between January 2009 and January 2011. All neonates admitted to the NICU during the period were included, but those who died in the first 48 hours after birth and those with a maternal history of renal failure were excluded. The study protocol was approved by the institutional ethics committee of the hospital.

Renal function

For the term and late preterm neonates, the diagnosis of AKI was made on the basis of serum creatinine levels >1.5 mg/dL at any time after first 48 hours of life with normal maternal serum creatinine levels, or creatinine level that increased at the rate of 0.3 mg/dL per day 48 hours after birth with oligo or anuria.^[4,6-10] Since the creatinine levels of preterm neonates (<34 weeks) were high in the first 3-5 days of life, serum levels were measured serially for 48 to 72 hours to diagnose AKI.^[11] The assessment of oliguria and anuria was based on urine flow of <1 mL/kg per hour and <0.5 mL/kg per hour 48 hours after birth.^[3,12] Urine output was measured every day by collecting urine in adhesive bags in an 8-hour interval.

Glomerular filtration rate was estimated using Schwartz formula ($k \times \text{height [cm]}/\text{plasma creatinine [mg/dL]}$). The constant k was 0.33 for infants born after gestation for less than 38 weeks and 0.45 for those born after gestation for more than or equal to 38 weeks.^[13,14] Renal impairment was grouped into three categories based on the site involved: pre-renal, renal and post-renal AKI. Differentiation of pre-renal and renal failure was based on urine sodium and creatinine levels and fractional excretion of sodium (FENa).^[9,10] Fractional excretion of sodium more than 2.5%-3.0% was considered as intrinsic AKI at a gestational age of less than or equal to 32 weeks. FENa less than 6% was used to define intrinsic AKI in babies born after less than 32 weeks of gestation.^[15,16] Renal failure index (RFI) may sometimes be used as an alternative to FENa. However, there is no good reason to prefer one over the other since both provide the same information.^[9] We did not calculate RFI in all of the infants. Those who had urinary tract obstruction diagnosed with ultrasonography, or renal scintigraphy were considered as having postrenal failure.^[9,10]

Definition of variables

Gestational age of the infants was determined by early fetal ultrasound and new Ballard score after birth. Prematurity was defined as birth at less than 37 weeks of gestation. Premature rupture of membranes

was defined as membrane rupture before the onset of labor.^[17] Asphyxia was diagnosed when patients met the following criteria: (1) metabolic or severe, combined acidemia (pH less than 7.0) in arterial umbilical cord blood; (2) Apgar score of 0-3 for more than 5 minutes; (3) neonatal neurological manifestations (seizures, coma or hypotonia); (4) multisystemic dysfunction of organs, i.e. cardiovascular, gastrointestinal, hematological, pulmonary or renal systems).^[18] All neonates with clinical features of asphyxia were staged by the Sarnat and Sarnat scoring system.^[19] Dehydration was defined as a weight loss of more than 10% of the birth weight at the end of the 1st week of life or clinical findings of dehydration with hypernatremia.^[20] Respiratory distress syndrome was defined on the basis of clinical, laboratory and radiological findings and respiratory support for ≥ 6 hours within the first 24 hours after birth. Sepsis was defined as a positive blood culture or urine culture along with clinical signs of infection.^[21,22] Metabolic acidosis was diagnosed if blood pH <7.20 and $\text{HCO}_3 \leq 12$ mmol/L or base excess ≤ -6 . Hypernatremia and hyponatremia were defined as serum sodium concentration >150 mmol/L and <130 mmol/L, respectively.^[20] Hyperkalemia was defined as serum potassium level >7.5 mmol/L in the first day of life and >6.5 mmol/L in the remaining days.^[23] Hypertension was diagnosed with systolic and diastolic blood pressures curves described by Zubrow et al.^[24] Liver failure was defined by the elevated levels of aspartate aminotransferase and alanine aminotransferase that were three times higher than the upper limit of normal values.^[8]

Management

The infants who developed AKI were treated according to the standard protocol: ensuring adequate hydration [insensible loss (mL) + urine (mL)], maintaining optimal fluid-electrolyte balance (serial measurement of electrolytes), normalizing arterial blood pressure, and minimizing nephrotoxin exposure. As the levels of nephrotoxic agents were not routinely monitored, we adjusted the doses of the agents and dosing intervals according to the calculated glomerular filtration rate so as to minimize the exposure of nephrotoxin or withdraw the agents if possible. We checked fluid/electrolyte requirement every 8 hours. Infants with AKI are not treated routinely with a low dose of dopamine at our unit.

In patients with no response to treatment (severe metabolic acidosis, persistent hyperkalemia, fluid overload with evidence of hypertension and/or pulmonary edema refractory to diuretic therapy, neurologic symptoms and calcium/phosphate imbalance with hypocalcemic tetany), peritoneal dialysis was performed. Hemodialysis facility was not available in our center.

Data collection

Detailed maternal and neonatal information about age, gender, gestational age, prenatal history, maternal and neonatal medical diseases, Apgar score at five minutes, use of medical devices (central venous catheter, umbilical catheter, percutaneous catheter, mechanical ventilation), other relevant medical conditions and laboratory results, treatment modality and outcomes were collected for each infant.

Statistical analysis

Statistical analyses were performed by SPSS version 15 (SSPS Inc, Chicago, USA). Univariate analysis was performed to identify differences between infants with and without AKI; the Chi-square test and Fisher's exact test were used to compare categorical variables and Student's *t* test was used to analyze continuous variables. Significant variables were identified by univariate analysis and entered into a stepwise logistic regression analysis. A *P* value less than 0.05 was considered statistically significant.

Results

In 2028 infants hospitalized during the study period, 36 were excluded. In the remaining 1992 infants, 168 (133 pre-term, 35 term infants) developed AKI, with a prevalence of 8.4%. In these infants with AKI, 88.2% were inborns, 11.8% outborns (born at other hospitals). The mean gestational age and birth weight of infants with AKI were 32±2.1 weeks and 1350±450 g, respectively. Very low birth weight (VLBW) infants (<1500 g) accounted for 34.5% (58/168) of the infants with AKI. Their prevalence of AKI was three times higher than that of those infants with birth weight lower than 1500 g (20% vs. 7%, *P*<0.05). The prevalence of AKI according to birth weight was 6% in infants of 1500-2500 g and 8% in infants more than 2500 g. Seventy-three infants (43.5%) developed AKI within the first week of life, 52 (31.0%) within 8-14 days and 43 (25.5%) after two weeks. Demographic characteristics of the infants are shown in Table 1. Univariate analysis showed that pregnancy-induced hypertension, preterm prolonged rupture of membrane (PPROM), administration of antenatal corticosteroid, small gestational age and birth weight less than 1500 g were associated with the increased risk of AKI (*P*<0.05). Unfortunately, we could not collect information about intrauterine exposure to nonsteroidal anti-inflammatory agents during the prenatal period in this study. Therefore, we were unable to determine their relationship with the disease or other causes.

Endotracheal intubation at birth, umbilical vein

catheterization, mechanical ventilation and ibuprofen therapy for patent ductus arteriosus closure were found to be significantly associated with AKI (*P*<0.05) (Table 2). The duration of mechanical ventilation was longer in the infants with AKI (12±4.8 vs. 5.2±2.1 days, *P*=0.001). Also, the duration of nephrotoxic antibiotic exposure was found to be longer in infants with AKI (13.4±2.5 vs. 6.4±2.1 days, *P*=0.001) despite there was no difference in the types of nephrotoxins exposed.

According to the primary site of the disease, 82 (48.8%) of the infants had prerenal failure, 78 (46.4%) had renal failure, and 8 (4.8%) had postrenal failure. The etiologic factors and site of occurrence of AKI are shown in Table 3. The most common causes of AKI were respiratory distress syndrome and neonatal sepsis. The most frequently isolated organism was *Klebsiella*

Table 1. Baseline characteristics of the study population

Variables	AKI (-) (n=1824)	AKI (+) (n=168)	<i>P</i>
Pregnancy-induced hypertension	164 (9.0)	33 (19.6)	0.02
Preterm prolonged rupture of membranes	218 (12.0)	40 (23.8)	0.03
Antenatal steroid	192 (10.5)	49 (29.2)	0.01
Female	890 (48.8)	78 (46.4)	0.76
Cesarean section	1057 (57.9)	128 (76.2)	0.06
Birth weight			
<1000 g	75 (4.1)	25 (14.9)	0.001
1000-1500 g	215 (11.8)	33 (19.6)	0.04
1501-2500 g	730 (40.0)	45 (26.8)	0.06
>2500 g	804 (44.1)	65 (38.7)	0.92
SGA	273 (15.0)	56 (33.3)	0.04
Apgar score at 5 min*	8 (4-10)	7 (4-10)	0.84

Figures in parentheses indicate percentages. *: data are given as median (range). AKI: acute kidney injury; SGA: small for gestational age.

Table 2. Therapeutic intervention and drug treatment before the onset of AKI

Variables	AKI (-) (n=1824)	AKI (+) (n=168)	<i>P</i>
Intubation at birth	220 (12.1)	45 (26.8)	0.04
Mechanical ventilation	420 (23.0)	90 (53.6)	0.03
Catheterization			
Umbilical vein	420 (23.0)	85 (50.6)	0.04
Umbilical artery	10 (0.5)	5 (3.0)	0.71
Percutaneously inserted central catheter	185 (10.1)	32 (19.0)	0.43
Persistent ductus arteriosus treated with ibuprofen	10 (0.5)	15 (8.9)	0.02
Respiratory distress syndrome treated with surfactant	375 (20.6)	64 (38.1)	0.07
Use of nephrotoxic antibiotics			
Aminoglycosides	890 (48.8)	104 (61.9)	0.19
Loop diuretics	33 (1.8)	12 (7.1)	0.08
Vancomycin	125 (6.9)	14 (8.3)	0.73
Amphotericin B	5 (0.3)	1 (0.6)	0.91

Figures in parentheses indicate percentages. AKI: acute kidney injury.

Table 3. Causes of AKI according to kidney involvement

Causes	Prerenal (n=82)			Renal (n=78)			Postrenal (n=8)		
	≤1500 g	1501-2500 g	>2500 g	≤1500 g	1501-2500 g	>2500 g	≤1500 g	1501-2500 g	>2500 g
Respiratory distress syndrome	21 (25.6)	15 (18.3)	4 (4.9)	14 (17.9)	7 (9.0)	3 (3.8)	-	-	-
Sepsis	8 (9.8)	2 (2.4)	6 (7.3)	8 (10.3)	4 (5.1)	4 (5.1)	-	-	-
Asphyxia	-	-	6 (7.3)	-	4 (5.1)	16 (20.5)	-	-	-
Dehydration	1 (1.2)	4 (4.9)	5 (6.1)	-	2 (2.6)	4 (5.1)	-	-	-
Congenital anomalies of urinary system	-	-	-	-	-	4 (5.1)	-	-	8 (100)
Congenital heart disease	-	5 (6.1)	5 (6.1)	-	-	-	-	-	-
Medications	-	-	-	6 (7.7)	2 (2.6)	-	-	-	-

Figures in parentheses indicate percentages. AKI: acute kidney injury.

pneumonia (n=24). Of 26 asphyxiated babies, 16 had mild-moderate asphyxia and 10 had severe asphyxia.

In 48 infants (28.6%) with hypotension receiving inotropic support, 36 were given dopamine, and 12 received dopamine and dobutamine in combination. Only two infants had systemic hypertension, none of the 48 infants received antihypertensive agents.

In 115 infants with metabolic acidosis, 25 were treated by infusion of 8.4% sodium bicarbonate. In 20 infants with hyperkalemia (two infants with acute cardiac arrhythmias), 12 were treated with calcium gluconate, sodium bicarbonate and insulin infusion. Thirty-six infants developed hyponatremia, and 8 hypernatremia. Hyponatremia or hypernatremia was managed according to the underlying conditions. Ten infants were treated by peritoneal dialysis.

The overall mortality rate was 23.8% in infants with AKI during their hospitalization. The most common cause of death was multiple-organ failure secondary to the underlying diseases rather than renal failure. The proportion of infants with hyponatremia was higher in non-survivors (70% vs. 12.5%, $P=0.001$). The presence of respiratory problem requiring mechanical ventilation is a risk factor for mortality, the duration of which was significantly longer in the non-survivors (7 ± 2.1 vs. 3 ± 1.2 days, $P<0.05$). The duration of dialysis was also longer in the non-survivors [5 (3-9) vs. 3 (2-5) days, $P=0.001$].

We found that VLBW, bronchopulmonary dysplasia, antenatal steroid, high creatinine level, blood urea nitrogen and potassium, low serum sodium level, anuria, dialysis and mechanical ventilation, hypotension requiring inotropic support were significantly associated with the mortality of the infants ($P<0.05$) (Table 4).

All factors associated with the mortality of the infants were assessed by stepwise logistic regression analysis. VLBW, bronchopulmonary dysplasia, mechanical ventilation, anuria and dialysis were the important determinants of mortality in neonates with renal failure ($P<0.05$) (Table 5).

In this study, the infants with AKI were hospitalized for a longer duration (32 ± 8.4 vs. 20 ± 10.2 days, $P<0.05$). Unfortunately, follow-up information about

Table 4. Univariate analysis of risk factors for mortality of patients with AKI

Variables	Non-survivors (n=40)	Survivors (n=128)	P
Respiratory distress syndrome	16 (40.0)	48 (37.5)	0.40
Bronchopulmonary dysplasia	18 (45.0)	20 (15.6)	0.001
Necrotizing enterocolitis	14 (35.0)	33 (25.8)	0.72
Antenatal steroid	19 (47.5)	30 (23.4)	0.04
Intraventricular hemorrhage	9 (22.5)	23 (18.0)	0.68
VLBW	36 (90.0)	22 (17.2)	<0.001
At onset of AKI			
Age (d)*	3 (3-22)	3 (3-34)	0.45
Creatinine (mg/dL)	3.2±0.7	1.9±0.2	<0.001
Blood urea nitrogen (mg/dL)	119±51	96±37	0.01
Serum sodium level (mmol/L)	125.3±3.4	136.9±5.2	<0.001
Serum potassium level (mmol/L)	7.5±1.2	6.1±0.5	0.04
Metabolic acidosis	28 (70.0)	87 (68.0)	0.91
Oliguria	18 (45.0)	45 (35.2)	0.25
Anuria	22 (55.0)	7 (5.5)	<0.001
Peritoneal dialysis	8 (20.0)	2 (1.6)	<0.001
Mechanical ventilation	34 (85.0)	56 (43.8)	0.03
Inotropic support	38 (95.0)	10 (7.8)	<0.001

Figures in parentheses indicate percentages; *: data are given as median (range). VLBW: very low birth weight; AKI: acute kidney injury.

Table 5. Multivariate analysis of risk factors for mortality in patients with AKI

Predictive factors	OR	95% confidence interval	P
Anuria	12.1	3.2-24.1	0.001
Dialysis	8.5	4.5-11.2	0.001
Mechanical ventilation	6.5	2.7-12.1	0.01
Bronchopulmonary dysplasia	4.2	1.8-6.3	0.03
VLBW	2.8	1.4-4.4	0.02
Antenatal steroid	1.3	0.6-1.9	0.42
Inotropic support	1.2	0.2-2.1	0.65

AKI: acute kidney injury; VLBW: very low birth weight; OR: odds ratio.

renal outcome could not be collected from most of the infants possibly because of low socioeconomic status or illiteracy of their parents. The infants mostly came from families of low socioeconomic status in economically deprived parts of Istanbul. This may explain why they were lost to follow up. Only 20 infants were followed up until their age of one year. Of 8 infants with postrenal AKI, 3 were diagnosed with chronic renal

failure at the time of discharge. Serum creatinine levels of 5 infants normalized and remained in the normal range within a year. Three infants with chronic renal failure were referred to and followed up by the pediatric nephrology department of the hospital. None of 17 infants showed deterioration of renal function at the end of the first year.

Discussion

Despite recent advances in neonatology, mortality and morbidity related to AKI pose a significant problem. This study provided a descriptive overview of AKI in newborns who had been admitted to our NICU. We found that the prevalence of AKI in newborn infants was 8.4% during the study period. Since the prevalence depends on the populations studied, literature searching reveals a wide range from 2.5% to 82%.^[6,25,26] But it is reported to be as high as 75% in VLBW infants and is strongly significant in smaller and sicker infants.^[8,27] In contrast to some studies, we found that the rate of AKI in newborns with VLBW was much lower than that previously reported.^[6] However, it was higher than we reported as some neonates were underestimated because of nonoliguric renal failure.^[28] Obviously, gestational age and birth weight are the most important factors determining the prevalence of AKI.

There are several reasons for the high risk of renal failure in premature infants. First, these infants may suffer from insults during intrauterine life because of infections, intrauterine growth retardation, placental insufficiency or maternal medication. Second, the postnatal course of premature infants is often complicated by hypovolemia, sepsis, hypotension and ischemia.^[1,2,12] These factors would make preterm infants more vulnerable to renal failure. Fetal programming hypothesis suggests that an adverse intrauterine milieu causes structural, hormonal and metabolic adaptations in the fetus.^[29] In the present study, we observed that pregnancy-induced hypertension, preterm prolonged rupture of membranes, antenatal steroid, and birth weight <1500 g were significantly correlated with AKI development. Adverse intrauterine environment may produce renal damage in the neonatal period. Antibiotic use during pregnancy was reported to have adverse effects on neonatal renal function.^[27] The present study revealed that PPRM treatment with antibiotics during pregnancy may contribute to exposure of newborns to nephrotoxic agents. Also, PPRM itself is an intrauterine insult.

It is well known that prenatal steroids may lead to low birth weight and compromise organogenesis, but its effects on nephrogenesis have not yet been investigated

extensively.^[30,31] Finken et al^[32] found that the subjects who were exposed antenatally to betamethasone had a lower glomerular filtration rate. An animal study^[33] suggested that pups whose mothers were treated with dexamethasone had a lower kidney weight and a lower number of glomeruli. The results of investigations indicated that measures should be taken to prevent AKI and promote the development of renal tissue in the early fetal life.

AKI is often difficult to diagnose clinically because there is no consensus on what caused AKI. So far, few prospective epidemiological studies have been reported to profile the occurrence and outcome of AKI.^[3,34] Studies^[35,36] found the relationship of high levels of serum creatinine with neonatal AKI, which leads to misdiagnosis of a significant number of infants according to the current definitions in adults and pediatric populations. In our study, biochemical indices (blood urea nitrogen, creatinine level), urine output, and underlying etiology before the diagnosis of AKI were evaluated. In the diagnosis of AKI in VLBW neonates, we should be aware of the fact that serum creatinine level may increase and be stable during the early neonatal period in infants of less than 1000 g compared with those of 1000 to 1500 g. VLBW neonates have high FENa even without any sign of AKI.^[11] This is a challenge of the diagnosis of AKI.

Mechanical ventilation is a life-saving method for patients with acute respiratory failure. In the present study, AKI was found to be associated with mechanical ventilation after birth. Evidence has shown that mechanical ventilation may contribute to the pathogenesis of AKI. AKI is caused by several mechanisms rather than by a single one.^[37,38] One possible mechanism is the compromise of renal blood flow by hypercapnia or hypoxemia, which may affect vascular dynamics via activation or inactivation of vasoactive factors such as nitric oxide, angiotensin II, endothelin, and bradykinin. Another possibility is a pulmonary inflammatory reaction in response to barotrauma, with the release of inflammatory mediators and the induction of a systemic inflammatory reaction.^[39-41]

AKI in NICUs mostly occurs as a result of perinatal conditions such as placental insufficiency, congenital anomalies etc. A few of infants have primary renal disease. Studies^[6,9,10,23,27,42] found that the predisposing causes of AKI vary widely. Asphyxia is the most common cause of AKI^[6,43] followed by sepsis.^[44] Predisposing factors of AKI in our patients, according to the order of frequency, were respiratory distress syndrome, sepsis and asphyxia. Other factors such as drugs and patent ductus arteriosus may also contribute to the development of AKI.

To date, various prognostic factors have been used

in predicting mortality in cases of neonatal AKI. Risk factors, including birth weight, extrarenal diseases, sepsis, septic shock, multiorgan failure, oligo-anuria, hypotension, vasopressors and mechanical ventilation, have also been used in detecting mortality of AKI cases in the NICU.^[8,23] Gupta et al^[28] observed that abnormal renal sonographic scan and hyponatremia were associated with poor prognosis in newborns with AKI who had asphyxia. A national study^[23] conducted in Turkey showed that hypoxia, metabolic acidosis, hypervolemia and dialysis were significantly associated with the mortality of children with AKI. In our study, multivariate analysis demonstrated that VLBW, mechanical ventilation, anuria, bronchopulmonary dysplasia, and dialysis were significantly associated with the mortality of infants. Critically ill infants are more likely to die from multi-organ failure rather than from renal failure.

There are some limitations in this study. First, our study is a retrospective one based on chart review which did not contain all the information we needed. Second, long-term outcomes and delayed renal sequel in survivors could not be assessed because their families could not be followed up. Third, we measured serum creatinine levels at intervals of 48-72 hours, which may be related to the high prevalence of AKI in neonates, especially in those with VLBW.

In conclusion, this study demonstrates that AKI is still an important problem despite advances in neonatal intensive care. Prenatal factors include pregnancy-induced hypertension, preterm prolonged rupture of membranes, and antenatal steroid are significantly associated with AKI after birth of infants. VLBW, mechanical ventilation, anuria, bronchopulmonary dysplasia and dialysis are risk factors for the mortality of newborns with AKI. Further studies are required to develop preventive strategies for AKI in high-risk neonates.

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Contributors: Bolat F, Comert S, Bolat G were responsible for study idea, design, data collection and analysis. Kucuk O, Can E, and Bulbul A performed data collection and analysis.

Bolat F, Uslu HS edited the manuscript. Bolat F and Nuhoglu A supervised, reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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