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Editorial

Dear Colleagues,

We are happy to publish the second issue of CSMJ in 2024. We are getting more submissions every day and this makes us happy.

In this second issue of 2024, you can read the review article that gives important data about the role uf attachment in premature birth. The first research article establishes the role of maternal vitamin B12 deficiency and its association with infants' vitamin B12 and homocysteine levels. The second article in this issue evaluates the incidence and risk factors for RSV infections in infants. It may be interesting to read this article as we are in the start period of RSV infections in children nowadays. The third article evaluated older people that required general surgery clinic hospitalization from emergency medicine department. The last study in this issue aims to identify the role of keeping partial carbon dioxide levels in normal ranges for prevention of intraventricular hemorrhage in preterm infants.

I think that these articles will provide insights for your knowledge, clinical practice and further studies. Hoping to meet you with interesting articles in the third issue of CSMJ.

Best regards,

On Behalf of Deputy Editors, Associate Editors, and Editorial Secretary

Merih Çetinkaya

Editor-in-Chief

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Preterm Birth's Effects on Attachment

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ABSTRACT

The attachment established between the caregiver and the infant is a fundamental factor affecting mental health, starting from the prenatal period and developing during infancy. Prematurity is among the factors that influence the quality of attachment, making it difficult for healthy parent-child relationships to be established. Premature infants treated in intensive care units must separate emotionally and physically from their caregivers, putting them and their parents at risk of mental health problems and interrupting the attachment process. With the increase in premature birth rates, studies have investigated the relationship between attachment quality and premature birth, concluding that premature birth negatively affects secure attachment and that attachment quality decreases as gestational age decreases and neonatal intensive care time increases. Protective interventions and multidisciplinary approaches are recommended to reduce this negative effect, and long-term studies are needed to better understand the relationship.

Keywords: Attachment, neonatology, pediatric psychiatry, premature birth

Introduction

The perinatal period and the first years of childhood are critical for mental health throughout life. Brain development during the prenatal period and the first 3 years of life progresses at a unique pace, with over 1 million neural connections formed per second (1). Therefore, every positive or negative experience during this period has an impact on the infant's neural connections, shaping their future social, emotional, and cognitive functioning.

Physical health has direct and indirect effects on mental health. A comprehensive assessment includes not only a child's mental health but also physical, cognitive, and developmental evaluation. The "DC: 0-5 Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood" revised by Zero to Three in 2016 and translated into Turkish in 2020, addresses mental health in the first five years of childhood through a five-axis system. The third axis is dedicated to the child's physical health, with subcategories such as prematurity, prenatally detected medical conditions, acute-chronic medical conditions, history of procedures performed, and recurrent or chronic pain (2).

Biologically immature, preterm infants are at risk of developing motor, cognitive, and socioemotional complications. Physical health problems faced by preterm infants necessitate hospitalization in the neonatal intensive care unit, requiring separation from caregivers. Both caregivers and preterm infants may struggle to cope with this process, which can negatively impact their psychological health during the acute phase and subsequent years.

The literature contains numerous studies on the short- and long-term psychological problems caused by preterm birth, covering

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a wide range of topics, such as mothers' postpartum mental health issues, parent-infant attachment, and the potential psychiatric problems that preterm born children may face in the long term.

According to attachment theory, early relationships have significant effects on a child's development (3). Secure attachment is a protective factor for social and emotional development. It also plays a role in the acquisition of important mental health functions, such as self-esteem, coping skills, and resilience (4). On the other hand, insecure attachment can lead to problems, such as emotion regulation deficits, stress coping difficulties, and vulnerability, thereby creating a risk for psychiatric disorders (5). Secure attachment requires a caregiver who is continuously responsive, consistent, sensitive, and available (6). Preterm infants' families may have difficulty providing these conditions. Therefore, the effects of preterm birth on attachment have been a subject of interest in recent years.

This review examined the literature on the effects of preterm birth on attachment. The aim of this study is to provide useful information to clinicians and to provide ideas for future studies on this topic.

Preterm Birth: Definition, Risk Factors, and Epidemiology

The World Health Organization defines preterm birth as the onset of labor before the 37th week of pregnancy (7).

• Late preterm births: Births between 34 and 37 weeks of gestation.

• Moderately preterm births: Births between 32 and 34 weeks of gestation.

• Very preterm births: Births between 32 and 28 weeks of gestation.

• Extremely preterm births: Births before 28 gestational weeks (7).

Risk factors for preterm birth include maternal factors such as genetic predisposition, uterine anomalies, early (<18) or late (>40) maternity, and maternal infections, as well as psychosocial factors (8,9,10,11). Psychosocial risk factors include low socio-economic status, low education level, maternal anxiety/depression, divorce, separation or death, inadequate prenatal care, and maternal use of psychoactive substances (11).

Approximately 13.4 million babies (9.9% of all births) were born preterm worldwide in 2020. 15% of these births occurred before 32 weeks of gestation (12). According to data from the Turkish Ministry of Health, the preterm birth rate in Turkey was 12.9% in 2022, and the rate of births before 32 weeks of gestation was 10.8% (13). There has been a significant increase in preterm birth survival rates both globally and in Turkey over the last 20 years. Timely interventions for preterm births have led to an increase in the preterm birth rate and a decrease in mortality rates (14). Between 1990 and 2010, the preterm birth rate in developed countries increased from 2 million to 2.2 million. The increase in the number of preterm infants born between 32 and 37 gestational weeks was reported to increase the burden on countries. This increase has also led to increased morbidity rates in various fields for families and communities (15).

Preterm infants are born before they are fully developed in the womb and face serious health problems. The health problems of preterm infants vary according to gestational age and birth weight. Infants born earlier and with lower birth weights have a higher risk of experiencing health problems (16). In the United Kingdom, neonatal mortality rates increased between 2014-2021, and this increase was attributed to the increase in the number of preterm infants born before 24 weeks of gestation (17). Health problems such as respiratory distress syndrome, intraventricular hemorrhage, cardiac issues, infections, and feeding difficulties are common in preterm infants (16). Due to such health problems, it has been reported that approximately 900,000 preterm infants died worldwide in 2019 (12).

In recent years, especially with the rapid advancements in medicine, even much earlier born infants with lower weights can survive. For example, in Turkey in 2024, a "micro preemie" girl born at 24 weeks of gestation, weighing 370 grams, overcame the vital risk after a 155-day treatment process in the intensive care unit and was discharged (18). While these developments are encouraging, the long-term physical and mental developmental trajectories of children born at extreme prematurity who can be kept alive remain an area that requires further investigation.

Effects of Preterm Birth on Mental Health

Preterm infants having an immature neurobehavioral profile, being separated from their mothers early, receiving treatment in the neonatal intensive care unit, being perceived as a high-risk/special baby, and emerging perinatal complications all put them at risk for mental health problems (14,19). It has been reported that exposure to pain in the neonatal period leads to changes in stress regulation in the first few months of life, and in later developmental periods, it causes more behavioral and attention problems (19).

Studies are showing that individuals born prematurely have more growth and developmental disorders, attention deficit hyperactivity disorder, autism spectrum disorder,

learning difficulties, language development delays, emotional problems, and anxiety disorders in later life stages compared to those born at term (20,21,22). These studies have shown that preterm birth increases the risk of attention deficit hyperactivity disorder by 3 times and the risk of autism by 3.3 times compared to term births (23,24). According to a meta-analysis evaluating the cognitive functions of preterm infants born before 32 gestational weeks, preterm children have lower IQ scores compared to term infants, the presence of bronchopulmonary dysplasia is an important factor affecting long-term cognitive development, and each increase in the rate of bronchopulmonary dysplasia is associated with a decrease in IQ scores (25).

Studies examining the effects of preterm birth on language development have found that the preterm group scored significantly lower on language and speech assessment tests compared to the term group and had a higher risk of language development delays (21,26). A study that tracked very preterm and term individuals for 11 years found that very preterm infants who experienced high stress around the time of birth showed more internalizing symptoms at age 11. The study revealed that emotional skills acquired at 18 months were a significant predictor of these outcomes. Therefore, experiencing stress during infancy because of being born very preterm is a risk factor for emotional problems in pre-adolescents (27).

This meta-analysis compared the risk of mental illness in childhood, adolescence, and adulthood between individuals born with extremely low birth weight (<1000 grams) and normal birth weight. The study found that the extremely low birth weight group had more inattention, hyperactivity, internalizing, and externalizing problems in childhood, a higher risk of behavioral and oppositional problems, autism symptoms, and social difficulties in childhood, more hyperactivity, internalizing problems, and social difficulties in adolescence, and more depression, anxiety, and social difficulties in adulthood (20). A study examining the psychiatric symptoms of individuals born moderately preterm (24-32 gestational weeks) and at full term in adulthood discovered that the overall rates of mental health issues were higher in those born early compared to term-born individuals. The study also found that the risk of mental health problems was linked to low intelligence quotient, and the specific cluster of mental health issues was non-specific (28).

Attachment Theory and Attachment Disorders

Attachment is defined as the infant's tendency and desire to seek comfort, support, physical or emotional satiety, and protection from the caregiver (29). According to Bowlby's (30) attachment theory, infants can only sustain their lives in the presence of a primary caregiver who is willing to care for and protect them. It is stated that the attachment relationship begins in the first hours and days after birth, when excessive stimulation occurs in the infant's central nervous system. Infants initiate their first interaction with their mother through innate behaviors such as sucking, following, smiling, crying, and touching. Therefore, according to Bowlby (30), it is important for mothers to immediately hold and breastfeed the baby after birth.

Ainsworth and Bell (6) defined attachment as the emotional bond that an individual establishes with others and stated that for the development of a secure attachment, the infant must have a caregiver who responds consistently, sensitively, and is always available. According to Ainsworth and Bell (6), the attachment styles of children with their parents are shaped by the way parents care for and respond to their children. In the 1970s, Ainsworth's Strange Situation Test research observed how children aged 12 to 18 months reacted when they were separated from their mothers and reunited. As a result of this research, the defined attachment styles were categorized into three categories: "Secure Attachment, Avoidant Attachment, and Ambivalent/Resistant Attachment". Secure attachment is the most common and healthy form of attachment. Securely attached infants can use their mothers as a secure base to explore the environment. They may show various stress reactions when their mothers are absent, but they respond positively when they return home. Avoidant attachment is the second most common attachment style. These infants are not concerned with the whereabouts of their mothers and explore the environment, are minimally disturbed by their mother's absence, and appear to ignore their mothers when they return. Ambivalent/Resistant attached infants have difficulty separating from their mothers to explore, and although they try to make contact when their mothers return, they have difficulty calming down or returning to exploration. Ainsworth and Bell (6) emphasized in this study that the quality of attachment is determined more by the infant's response to the mother's return than by his/her response to his/her departure. For many years, attachment has been studied under these three categories. However, as the number of studies on attachment increased, the presence of a group that did not fit into these three categories became noticeable. Main and Solomon (31) worked on this unclassified group and defined a 4th category called "Disorganized Attachment". Disorganized attachment is the rarest but the most unhealthy form of attachment. Infants with this attachment style do not

exhibit an organized strategy. Even under intense stress, they may behave in ways such as staying away from the caregiver or clinging tightly to the caregiver (32).

The interaction between environmental (especially parental) and genetic factors in infancy and childhood leads to individual differences in attachment behaviors in later life (33). Attachment behaviors are interpersonal actions that aim to increase an individual's sense of security, especially during stressful times. These interpersonal patterns are quite stable and are known as "adult attachment styles" in adulthood. The impact of adult attachment styles on psychosocial factors, such as social functioning, coping, stress response, and psychological well-being is important (34).

Attachment disorders, which emerge before the age of 5 and are caused by extremely deprived and pathogenic caregiving conditions, are defined as "significantly impaired and developmentally inappropriate social relationships in most social contexts" (35). The official diagnostic classification of attachment disorders was first made in the Diagnostic and Statistical Manual of Mental Disorders: DSM-3, and the criteria were revised in DSM-3-TR and DSM-4. Currently, in the Trauma and Stressor-Related Disorders section of DSM-5, they are classified as "Disinhibited Social Engagement Disorder" and "reactive attachment disorder (RAD)" (36).

RAD is characterized by mixed feelings about seeking comfort from a caregiver, emotional withdrawal, lack of interest in socializing, reduced positive emotions, and unexplained fear or irritability. RAD may be observed in children who exhibit limited or no positive emotions. On the other hand, children with disinhibited attachment may display overly intrusive behavior, struggle to set appropriate social and emotional boundaries, and act overly friendly toward strangers. It is important to differentiate RAD from other psychological conditions that involve overly vigilant behavior and behaviors associated with autism spectrum disorders (36,37). Minnis et al. (38) conducted the first epidemiological study focusing on the prevalence of RAD in the general population. They found a prevalence of 1.4%. No studies on the prevalence of RAD have been found in our country. A study has reported that the risk factors for RAD include the presence of mental disorders in parents, in-utero smoking exposure, advanced paternal age, and being a single mother (39). It has been shown that the rates of receiving a RAD diagnosis are associated with induced birth, low birth weight, preterm birth, and staying in the intensive care unit (40).

Effects of Preterm Birth on Mother-infant Attachment

The impact of preterm birth on the mental health of both parents and infants has been evaluated. A key focus of these studies was the effect of preterm birth on the attachment process between the infant and caregiver, especially the mother.

Perinatal stress, which is a risk factor for preterm birth, also emerges as a consequence of preterm birth (41). It is thought that changes in uterine blood flow caused by maternal stress or cortisol passing from the mother to the fetus through the placenta may increase the risk of preterm birth (42,43). Parents of a preterm infant are at increased risk of depression and anxiety, and these emotional difficulties can stem from uncertainties about the infant's health and future (44). A systematic review discovered that 40% of mothers with preterm infants experienced postpartum depression. The review revealed that enduring depression was linked to earlier gestational age, lower birth weight, ongoing physical illness in the infant, and a perceived lack of social support (45). However, a prospective cohort study that followed mothers of preterm infants through pregnancy, delivery, and the postpartum period did not find a significant relationship between preterm birth and postpartum depression (46).

The presence of mental health issues in mothers can make it more difficult to establish a healthy mother-infant relationship, which is necessary for secure attachment. The results of studies on mother-preterm infant interactions are mixed. A meta-analysis found a negative relationship between maternal stress levels, the presence of depression, and secure attachment (47). Mothers of preterm infants have been observed to show less consistent, sensitive, and accepting behavior, and they may have unrealistic fears about their infant's safety. They also tend to engage in fewer emotional mirroring interactions. Although some studies found no differences in mother-infant interactions in the first 6 months between the preterm and full-term groups, others found that the interactions of preterm infants and their mothers were of higher quality than those of full-term infants. These studies concluded that mothers of preterm infants were more responsive, affectionate, and engaged in more direct, active, and controlled interactions with their infants, even if they smiled less and had less physical engagement (48,49). The interactions between preterm and term infants and their mothers showed the most differences in the first six months. By the corrected age of 12 months, the likelihood of developing secure attachment in preterm infants becomes similar to that in term infants (50).

Premature infants admitted to intensive care units for respiratory, nutritional, and other medical interventions are required to be separated from their caregivers emotionally and physically. Therefore, the attachment process of infants with limited social interaction may be disrupted (51). Increased length of stay in the intensive care unit, presence of respiratory problems, and significant neurological impairment have been associated with insecure attachment (50).

The findings of a study conducted in our country suggest that mothers who gave birth before the 32nd gestational age experienced higher anxiety levels at the 16th month after birth. Furthermore, infants with better mother-infant interaction exhibited higher cognitive development scores. The study also found that mother-infant interaction and secure attachment were similar in term and preterm healthy children. It was emphasized that it is not premature birth itself, but rather its medical, developmental, and/or neurological consequences that may affect mother-infant interaction and attachment (52).

A previous study found that premature infants born before 26 weeks of gestation had a 23% rate of secure attachment, whereas those born after 26 weeks had a 69% rate. The study emphasized that secure attachment is linked to better cognitive development, and the risk of insecure attachment increases as gestational age decreases (53).

In a study conducted in the Netherlands, researchers examined the attachment relationships between premature infants and term infants with their parents. The study found that the attachment scores of families with premature infants were higher than those of families with term infants. These findings suggest that in resource-rich developed countries, parents of premature infants may have higher levels of attachment compared with parents of infants born at term (54).

Multiple studies on maternal attachment have been conducted in our country. One such study was a descriptive and cross-sectional research involving 340 mothers in the maternity ward. The research revealed statistically significant maternal attachment in mothers aged 35 and older, those living in extended families, who described the birth process as very comfortable and easy, held their baby in the first 10 minutes, and had no concerns about the care of their baby (55). In another descriptive study involving 218 mothers with premature infants, it was found that there was a positive correlation between the gestational weeks of the babies and the scores on the Maternal Attachment Scale. Additionally, there was a negative correlation between the length of stay in the neonatal intensive care unit and the gestational age of the babies (56).

Temperament is a broad concept conceptualized as individual differences that emerge in infancy, remain relatively stable throughout life, and shape the foundation of the child's later personality. While studies have shown that preterm infants have less regulated and more active temperaments than full-term infants, some have not detected differences in temperament between the two groups. A meta-analysis on temperament characteristics in preterm infants found that preterm infants showed higher physical activity, less focus, and less sustained attention (19). Some studies have also shown that preterm infants are more passive, less alert in interactions, exhibit more compulsive adaptation behaviors, and have lower attention, play, and motor skills (50). No significant differences in emotional and behavioral development were found between preterm and full-term infants with adaptable temperament. However, preterm infants with a "compulsive" temperament showed more behavioral problems, eating problems, lower personal-social skills, and lower language-speech skills than full-term infants. However, the same study indicated that not only the temperament characteristics of the infants but also the behavioral patterns and sensitivity levels of the mothers shape the attachment through mutual interaction. It is stated that the combination of a sensitive mother and a preterm infant with an adaptable temperament is protective for secure attachment, whereas the combination of a controlling mother and a preterm infant with a compulsive-compliant temperament is risky for insecure attachment (57). The interactions between attachment, parenting styles, and temperament are complex and have been the subject of discussion in recent years. The consensus is that attachment and temperament influence each bidirectionally, and both are open to being affected by environmental factors such as parental sensitivity (58).

Effects of Premature Birth on Father-infant Attachment

Research on parents of premature infants has primarily focused on the mother-child relationship. Comparatively fewer studies have examined father-infant interactions. It has been reported that healthcare providers in neonatal intensive care units tend to assign a greater role to mothers in infant care, which can make mothers feel isolated and overburdened (59). Studies emphasize that fathers' involvement in the treatment of premature infants in neonatal intensive care units benefits the family (60).

A meta-synthesis study reported that fathers of premature infants go through 5 stages:

1) Unfamiliarity with the baby and lack of emotional bond,

2) Taking on the caregiver role and the role of the father,

3) Accepting the baby as their own,

4) Adopting the transition to having the baby at home,

5) Normalizing family life (61).

A study comparing the attachment of premature and full-term infants to their mothers and fathers found that full-term infants showed secure attachment to both parents, whereas premature infants, especially males, had lower attachment scores with both parents. The most important predictor of father-child attachment was the child's developmental status (62). Another cross-sectional study was conducted with 32 fathers of premature babies born before 37 weeks' gestation and hospitalized in a neonatal unit. The researchers used the paternal postnatal attachment scale and found that the infant's gender, father's age, and father's education level did not significantly affect the attachment of premature infants and their fathers. According to this study, the application of kangaroo care increased fathers' attachment scores (59).

Mothers of premature infants had higher postpartum depression scores than fathers in a study conducted in our country. The depressive process in fathers has negative effects on the cognitive development of premature infants (63). A systematic review investigating the effects of early interventions for fathers of premature infants in neonatal intensive care units noted that there are a limited number of studies in the literature, mostly focused on practices such as skin-to-skin contact. This review concluded that interventions aimed at increasing fathers' participation in the treatment process reduced fathers' anxiety and stress levels and increased their attachment scores (64).

Effects of Premature Birth on Adult Attachment Styles

Healthy early relationships formed in infancy contribute to a person's overall well-being, ability to form close relationships, and development of positive attachment styles in later life. Premature birth is a risk factor for the establishment of healthy early relationships. Although there are many studies on the parent-preterm infant attachment relationship, relatively few have examined the effect of premature birth on attachment organization during post-childhood. There are also relatively few studies on the long-term psychiatric consequences of premature birth, and only a small portion of these focus on attachment.

There is evidence that adults born prematurely have a lower quality of attachment to their mothers, lower self-esteem, and less emotional control. One study evaluated adults who were born prematurely and received kangaroo care in the intensive care unit and found that those who received this method were more accepted by their families and had a reduced indirect suicide risk compared with the group that did not receive it (65).

Individuals born prematurely tend to receive lower quality attachment scores as they get older and exhibit more dismissive attachment styles (66). A study on the attachment styles and romantic relationships of young adults born with very low birth weight found that the case group developed more avoidant attachment styles and had lower attachment scores associated with higher anxiety levels, compared to the control group (67). Another study concluded that while individuals born prematurely could form close relationships in young adulthood similar to their full-term counterparts, the premature group showed higher emotional reactivity and greater death anxiety (68).

Protective Interventions

Family-based, personalized interventions starting from the newborn's hospitalization period and covering the transition to home after discharge; reduce the mother's stress and depression, increase their self-confidence, and positively affect the mother-infant interaction. To foster a strong and healthy bond between a baby and its mother, it is essential to provide the mother with education on infant care and childrearing during the early years. This can have a lasting impact on the child's life. It is also important to teach mothers how to cope with stress, build their self-awareness and self-confidence, and offer supportive psychotherapy for expectant mothers (29). Parents of preterm infants report that they can cope with the situation more easily when they are present in the intensive care unit together with the baby and are informed about the baby's condition (60).

The kangaroo method is recommended to contribute to reducing infant mortality and morbidity and promote breastfeeding. The kangaroo method was first introduced in 1978 by Edgar Rey Sanabria in Colombia (69). The World Health Organization's four components of the kangaroo method are early, continuous, and prolonged skin-to-skin contact between the mother and the baby, breastfeeding, early discharge from the healthcare facility, and close follow-up at home (70). Meta-analyses are showing that this method reduces mortality and morbidity rates in preterm and low birth weight infants (71,72,73). It has been shown that breastfeeding is extended by about 4 months with the

kangaroo method, and thus, neonatal sepsis, hypothermia, hypoglycemia, and recurrent hospital visits are reduced, vital signs improve, head circumference increases, and pain scores decrease in infants who undergo this method (69). According to studies investigating the effects of the kangaroo method applied to preterm babies on attachment; this method stabilizes the physiological functions of the preterm baby, increases breastfeeding and weight gain, positively affects the mother-baby attachment, and reduces maternal stress (74,75,76,77).

Protective measures such as:

- Screening for preterm birth risk factors
- Monitoring high-risk pregnancies
- Support expectant mothers from the pre-pregnancy period to the postpartum period in terms of mental health
- Better and more comprehensive pain management in neonatal intensive care units
- Shorter hospital stay
- Supporting mother-father-infant interaction in intensive care units
- Continuing caregiver support after discharge
- Education about infant care
- Mental health screening for preterm infants

Conclusions and Recommendations

The perinatal period and the first years of childhood are critical for lifelong mental health. Preterm birth directly affects the physical health of infants and causes psychosocial stressors. Studies have shown that preterm birth is a risk factor that can negatively affect infant attachment, neurodevelopment, temperament, and mental health. Attention should also be drawn to the negative effects of preterm birth on parental mental health. Protective interventions and multidisciplinary follow-up are necessary for preterm infants aiming for healthy mental development. In the post-preterm birth process, factors such as attachment, mother-infant interaction, parental mental health, and infant mental health can vary from month to month. Short-term follow-up or cross-sectional studies may lead to conflicting results. Most of these studies have limited samples and relatively short observation periods. With increasing survival rates, preterm infants have been divided into more subgroups according to gestational age. Births at 24 weeks and 34 weeks differ in many ways. There are limited follow-up studies comparing subgroups defined by gestational age. In conclusion, long-term studies are needed to understand the effects of preterm birth on secure attachment.

Ethics

Authorship Contributions

Concept: E.Y.O., G.K., Design: E.Y.O., G.K., Data Collection or Processing: E.Y.O., Analysis or Interpretation: E.Y.O., Literature Search: E.Y.O., G.K., Writing: E.Y.O., G.K.

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Relationship of Vitamin B12 Level in Breastfeeding Mothers with Vitamin B12 and Homocysteine Levels of Infants

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What is known on this subject?

The vitamin B12 and homocysteine levels of breastfed infants were investigated. It was shown that these results were affected by the mother's vitamin B12 level. It was investigated what the mother's vitamin B12 level should be for infants to be healthier.

What this study adds?

It has been shown that maternal vitamin B12 levels affect infant B12 and homocystin levels. It has been shown that B12 deficiency is very common in mothers, and B12 deficiency and elevated homocysteine are very common in infants.

ABSTRACT

Objective: Vitamin B12 deficiency, an essential vitamin for the human body, is common in Turkey, and infants are at risk in this regard. This study was intended to investigate the effect of vitamin B12 levels of breastfeeding mothers with infant vitamin B12 and homocysteine levels.

Material and Methods: A total of 214 infants aged 1-6 months and their mothers who applied to the infancy outpatient clinic of İstanbul Medeniyet University Göztepe Training and Research Hospital were included in the study. In this study, vitamin B12 levels of the mothers, vitamin B12, folic acid, and homocysteine levels in the infants were primarily analyzed, and the associated risk factors were secondarily determined.

Results: The rate of adequate vitamin B12 levels in infants was 20.09% (n=43), and the rate of normal homocysteine levels in mothers of infants with sufficient vitamin B12 and normal homocysteine levels was 383.93 pg/mL and 379.07 pg/mL. 66.27% sensitivity and 75.56% specificity were calculated when 220 pg/mL was taken as the vitamin B12 cut-off value, which predicts homocysteine elevation.

Conclusion: This study predicted that only one in five infants had sufficient vitamin B12 levels, but if breastfeeding mothers had sufficient vitamin B12 levels, infants were much less likely to have vitamin B12 deficiency. Since adequate vitamin B12 levels are important for infants, especially in terms of neurodevelopment, we believe that it is necessary to evaluate pregnant women in our society in terms of vitamin B12 levels and to provide vitamin B12 support.

Keywords: Vitamin B12, homocysteine, pregnant, infant, lactation

Introduction

Vitamin B12, which is obtained from animal foods, is an essential vitamin for humans, and since it cannot be synthesized in the human body, it should be taken regularly in the diet. An adult human liver has an average of 2000 mcg of vitamin B12 storage, whereas a newborn's liver has 25-30 mcg of vitamin B12 storage (1). It has been shown that infants of pregnant women with low vitamin B12 levels do not have sufficient vitamin B12 levels (2).

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Vitamin B12 is involved in important reactions in the body, especially in cell division (3,4,5,6).

In a few studies conducted in Turkey, vitamin B12 deficiency in the neonatal period was found to be 42% (7) and 74.2% (8), and this deficiency rate was 73% (9) in the geriatric age group, and data on the pediatric age group were insufficient. In Turkey, where vitamin B12 deficiency is common, infants who do not receive the necessary vitamin B12 support from their mother during the fetal period are expected to be born with low vitamin B12 storage. Therefore, pregnant women and mothers should have an extra well-being for their infants in addition to their own health. According to the recommendation of the United States National Institute of Health, the daily cobalamin requirement is 0.4 mg/day in early infancy, 2.4 mg/day in adulthood, and these requirements slightly increase during lactation and pregnancy. These recommendations are 2.6 mcg/day during pregnancy and 2.8 mcg/day during lactation (1,10). The World Health Organization routinely recommends iron and flaccid supplementation in pregnant women, but there is no routine recommendation for vitamin B12 supplementation (11).

Vitamin B12 deficiency can be clinically asymptomatic and can present as signs in many systems, especially hematological and neurological symptoms (12). Megaloblastic anemia, delayed neurological development in infants, delayed myelination and hypotonia, and peripheral sensory neuropathy are common signs (13,14).

Breastmilk is the only food source for infants in the first six months of life, and all micro- and macronutrients are transferred to the infant through breastmilk. It has been shown in studies that the mother's vitamin B12 level correlates with the vitamin B12 level in breastmilk and infant serum (6,7,8). In addition, there is a study showing that vitamin B12 and folic acid levels in pregnancy affect the homocysteine level of the infant at 2 years old. However, considering that infants up to the age of two will be severely affected by mixed nutrition, it should not be considered that the vitamin B12 and folic acids of the infants in this study should be affected only by the condition in pregnancy (15). Additionally, studies conducted in Turkey have been based on the relationship between pregnant women and newborn infants and have been conducted with working groups that are under the influence of fetal life (7,8), but there have been no studies on infants in the lactation period. In addition to detecting the vitamin B12 relationship between mothers and infants during lactation, one of the objectives of this study was to reveal the optimal vitamin B12 value for infants. The primary motivation of our study was that no study determining the optimal vitamin B12 level in infants was found in the literature at the time of the study.

Based on this information, this study aimed to determine the relationship between vitamin B12 levels in breastfeeding mothers and vitamin B12 and homocysteine levels in infants and the ideal vitamin B12 level of infants at 1-6 months of age and to determine the associated risk factors.

Material and Methods

This retrospective study was conducted between November 01, 2018 and November 21, 2019 at University of Health Sciences Turkey, İstanbul Medeniyet University Göztepe Training and Research Hospital by collecting data from 1-6-month-old infants with vitamin B12 and homocysteine values and their mothers whose vitamin B12 values were measured within 15 days. Infants who had a normal birth time and weight (>37 GW, >2500 gr), did not use vitamin B12 and folic acid, did not take formula or supplements, and donated human milk, did not have any additional disease (congenital heart disease, neurodevelopment retardation, chronical systemic disease, chronical respiratuar failure, metabolic disease, chronical renal disease, malnutrition, malabsorption) or clinical infections, and mothers who did not have malnutrition, intestinal malabsorption, or clinical infection, did not use metformin or proton pump inhibitors, had not undergone metabolic surgery, and did not use drugs containing vitamin B12 at that time were included in the study.

Study groups were formed with 214 infants and their mothers who met the inclusion criteria.

Mothers' vitamin B12 levels and infants' vitamin B12 and homocysteine levels simultaneously were compared, and their relationship was examined. Vitamin B12 level was defined as deficiency below 200 pg/mL, insufficiency in the range of 200-300 pg/mL, and adequacy above 300 pg/mL (12,16), while folic acid reference values below 3 ng/mL were defined as insufficiency, 3-5 ng/mL deficiency, 5-20 ng/mL adequacy (17). For infants, the age-appropriate homocysteine reference value of 3.3-8.3 µmol/L was defined as normal (18,19). The correlation of vitamin B12 level with birth weight, postnatal age at which the vitamin B12 test was performed, and whether mothers used vitamin B12 at the daily required dose (2.5-3 mcg) in the last 3 months of pregnancy were examined.

Prior to study commencement, permission was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Medeniyet University Göztepe Training and Research Hospital (decision no: 2019/0523, date: 25.12.2019).

Statistical Analysis

Statistical analysis was performed with the help of SPSS version 17.0. The normality of the variables to the normal distribution was examined using dusing histogram graphics and Kolmogorov-Smirnov test. Mean, standard deviation, and median values were used while presenting descriptive analysis. The Mann-Whitney U test was used to evaluate values that did not show normal distribution (non-parametric) between two groups, and the Kruskal-Wallis test was used to evaluate values between more than two groups. The Spearman correlation test was used to analyze the measurable data according to one another. Receiver operating characteristic curve analysis was used to find a cut-off value for vitamin B12 in infants that can predict high homocysteine levels. Cases with a p value 0.05 were considered statistically significant.

Results

Two hundred and fourteen infants were included in the study. 45.33% (n=97) of the infants were born with normal spontaneous vaginal delivery, and 54.67% (n=117) were born with cesarean section. It was detected that the B12 deficiency in 50.47% (n=108) of infants, B12 insufficiency in 29.44% (n=63) of infants, B12 deficiency in 14.95% (n=32) of mothers, B12 insufficiency in 31.78% (n=68) of mothers. Homocysteine elevation was found in 78.97% (n=169) of infants, whereas the folate value was 100% (n=122) of infants whose folate was measured as normal (Table 1).

The correlation between maternal vitamin B12 levels and infant vitamin B12, infant homocysteine, and the number of meals consumed in meat per week was analyzed. Accordingly, a statistically significant positive correlation was observed between maternal vitamin B12 level and infant B12 level; there was a significant negative correlation between maternal vitamin B12 level and infant homocysteine level ($p<0.001$, Table 2). No significant correlation was found between the vitamin B12 level of mother and the number of meals consumed in meat weekly ($p=0.475$, Table 2).

The rate of vitamin B12 supplementation in the last 3 months of pregnancy was 72.43% (n=155) (Table 1). Compared with the B12 and homocysteine levels of the infants of mothers who used B12-containing vitamins for the last 3 months during pregnancy and the infants whose mothers did not use it; the vitamin B12 levels of the infants of mothers who used vitamin B12-containing vitamins in the last 3 months of pregnancy were statistically significantly higher than the others ($p=0.003$, Table 3). However, no significant relationship was found between the homocysteine levels of infants whose mothers used B12-containing vitamins for the last 3 months during pregnancy and those who did not ($p=0.063$, Table 3).

The study also examined the correlation between birth weight and B12 levels of infants, but no significant relationship was found ($p=0.412$, data is not shown). According to postnatal age, there was also no significant relationship between

Table 1. Demographic characteristics and vitamin levels of the study groups

Parameters		n	%
Postnatal age (days)	30-60 days	80	37.38
	61-120 days	93	43.46
	121-180 days	41	19.16
Form of delivery	Vaginal	97	45.33
	C/S	117	54.67
B12 supplementation during the last 3 months after birth	Yes	155	72.43
	No	59	27.57
Mothers' vitamin B12 level status	Deficiency	32	14.95
	Insufficiency	68	31.78
	Adequacy	114	53.27
Infant vitamin B12 level status	Deficiency	108	50.47
	Insufficiency	63	29.44
	Adequacy	43	20.09
Infant homocysteine level status	Normal	45	21.03
	High	169	78.97
Infant folic acid level status	Normal	122	100.00

C/S: Cesarean section

Table 2. Correlation between maternal vitamin B12 level and maternal age

Parameters		Mothers' vitamin B12
Infants' vitamin B12 levels	R	0.372
	P	<0.001
Infants' homocysteine	R	-0.376
	P	<0.001
Amount of meat meals the mother consumes per week	R	0.049
	P	0.475

Spearman correlation test

Table 3. Effect of using B12 vitamin in pregnancy on infants'

	B12 supplementation during the last 3 months after birth		p
	Yes	No	
*Infants' vitamin B12 level (pg/mL)	247.43±131.81	193.24±89.73	0.003
*Infants' homocysteine level (mcd/dL)	12.08±5.30	13.89±6.55	0.063

*Mann-Whitney U test, *Mean ± SD*
SD: Standard deviation

vitamin B12 level was compared between infant and mother (data is not shown).

Mother's vitamin B12 levels were examined according to the infants with vitamin B12 >300 pg/mL and normal homocysteine level. Mothers with infants with vitamin B12 levels >300 pg/mL were found to be significantly higher than those without vitamin B12 value (p<0.001, Table 4). Similarly, mothers with normal infant homocysteine levels were significantly more likely to have high vitamin B12 levels than those with high vitamin B12 levels (p<0.001 Table 4).

Infants with normal homocysteine had an average vitamin B12 level of 301.31±119.01 pg/mL, whereas infants with high homocysteine had 214.16±118.90 pg/mL, and there was a statistically significant difference between them (p<0.001, data is not shown).

The presence of a cut-off value was examined using receiver operating characteristic analysis of the vitamin B12 level to predict the normal level of homocysteine. When determining this value, it was noted that the percentage of both sensitivity and specificity was high, and 220 pg/L was selected as the value that met the criteria. According to this, 66.27% sensitivity, 75.56% specificity, 91.06% positive predictive value, and 37.36% negative predictive value were calculated when the cut-off value was 220 pg/mL (Figure 1, table data is not shown).

When mothers' vitamin B12 levels were examined as groups; vitamin B12 levels of infants with maternal B12 levels >385 pg/mL were higher than those with maternal B12 levels between 300-384 pg/mL and those with <300 pg/mL (p<0.001, Table 5). The homocysteine levels of infants with maternal B12 levels >385 pg/mL were lower than those with maternal B12 levels between 300-384 pg/mL and those with <300 pg/mL (p<0.001, Table 5).

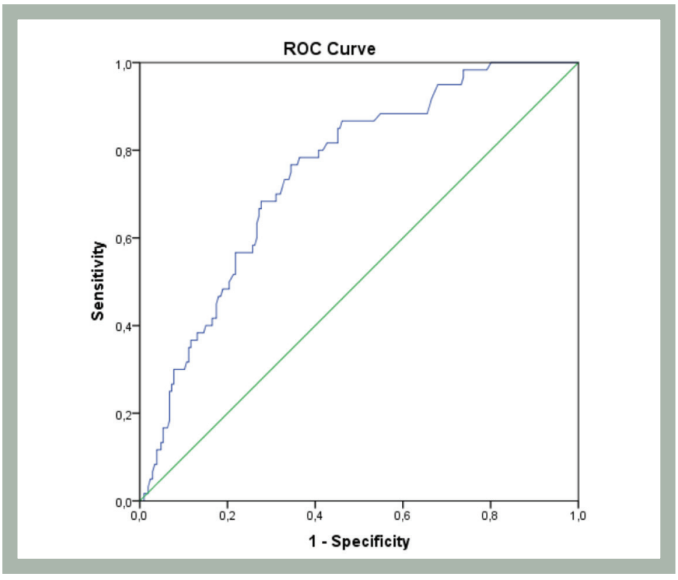

Figure 1. Receiver operating characteristic analysis of vitamin B12 value to predict the normal homocysteine level

ROC: Receiver operating characteristic

Table 4. Mothers' vitamin B12 levels according to the B12 vitamin and homocysteine status of infants

Parameters		Mothers' B12 vitamin level	p
*Infants' B12 vitamin level (pg/mL)	<300	300.25±104.48	<0.001
	>300	383.93±135.90	
*Infants' homocysteine level (mcg/dL)	Normal	379.07±123.89	<0.001
	High	300.55±108.50	

*Mann-Whitney U test, *Mean ± SD*
SD: Standard deviation

Table 5. Infant B12 vitamin and homocysteine levels according to the mother's vitamin B12 level

	Mothers' B12 vitamin level (pg/mL)			
	<300	300-385	>385	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Infant B12 vitamin level (pg/mL)	196.01±110.28	236.03±113.04	293.95±134.20	<0.001
*Infants' homocysteine level (mcg/dL)	14.41±6.54	12.06±4.72	9.86±3.55	<0.001

**Kruskal-Wallis test, SD: Standard deviation*

Discussion

When the results of 214 infants and their mothers were evaluated in our study, the rate of infants with vitamin B12 levels below 200 pg/mL was 50.4%, and the rate of infants with vitamin B12 levels of 200-300 pg/mL, which is known as insufficient, was 29.4%. When the set two results were evaluated together, the rate of infants with a vitamin B12 value below 300 pg/mL was found to be 79.8%, and this value is higher than 61%, which was determined by Yetim et al. (20) from cord blood in the neonatal period. However, it could not be compared because there were no studies conducted on infants in Turkey.

It has been proven that there is a strong correlation between serum vitamin B12 levels in pregnant women and vitamin B12 levels in cord blood. In a study of Yetim et al. (20) on newborns' cord blood, vitamin B12 levels were found below 300 pg/mL in 93% of pregnant women's serum and 61% of cord blood, and folic acid deficiency was not detected in any of the mothers or infants. Folic acid deficiency, which is another cause of homocysteine height, was not detected in any of the 122 infants whose folic acid levels were measured in our study. This result proves that the homocysteine elevation in our patients was caused by vitamin B12 deficiency. The most important reason for the absence of folic acid deficiency was the use of 400 g of folic acid support given during pregnancy except 8 patients. Although the vitamin B12 level of newborns in the proposal study was 42%, with a rate of infants with a level below 200 pg/mL, in our study, 50.4% was found in infants who are 1-6 months of age, and although the differences in the study groups were considered, infants experienced severe vitamin B12 deficiency from the neonatal period (7). Önal et al. (7) also stated in this study that the vitamin B12 level of infants decreased after the postnatal 15th day; in our study, infants in the 1-6 month period had more vitamin B12 deficiency than in the newborn period, but in our study, no significant differences were found between them selves when infants aged 1-6 months were divided into 3 age groups.

According to the data obtained in our study, the vitamin B12 level was 200 pg/mL in 14.9% of breastfeeding mothers, and the rate of mothers with sufficient B12 vitamin levels at 200-300 pg/mL was 31.7%. According to the statistics, vitamin B12 deficiency, which is common in our society, was significantly higher in breastfeeding mothers, and the vitamin B12 level of infants fed by these mothers was also low in correlation with the mother (Table 2).

When the relationship between vitamin B12 obtained from animal foods and the nutrition of the mother was examined, a limited history was taken regarding how many meals of meat they consumed weekly, as the nutritional anamnesis of the mothers could not be assessed in detail, and this anamnesis was not significantly associated with her vitamin B12 level ($p>0.05$). The probable cause of this situation was the incomplete declaration of the families.

In our study, it was found that mother's vitamin B12 level and infants' vitamin B12 level showed a positive correlation, whereas the infants' homocysteine level showed a negative correlation, as expected. In a study by Siddiqua et al. (21) in Bangladesh, a negative correlation was found between maternal vitamin B12 levels and infant homocysteine level,

however, no studies involving homocysteine levels were found in Turkey or other European countries. A retrospective study conducted by Akcaboy et al. (22) in Turkey in 2014 on infants with vitamin B12 deficiency found vitamin B12 deficiency in all their mothers.

In addition, we found that the average vitamin B12 level of infants whose mothers used supplements containing vitamin B12 in the last 3 months of pregnancy was significantly higher than that of infants who did not use it (p=0.003, Table 3). It was found that a difference of 54 pg/mL occurred when the values of the two groups of infants were compared. For this reason, we believe that it is important that pregnant women are evaluated for vitamin B12 levels when initiating iron and folic acid replacement during their follow-up programs.

In another study, a multicenter study conducted by Chebaya et al. (6) examined the relationship between maternal serum, breastmilk, and infant serum B12 levels in Canadian and Cambodians during lactation. It was reported that Canadian mothers took vitamin B12 supplements during pregnancy and lactation, but Cambodian mothers did not, and the vitamin B12 levels of Canadian mothers were found to be statistically significantly higher due to their better socio-economic status and their use of vitamin B12 supplements. In Canada, maternal serum, breast milk, and infant serum vitamin B12 levels were significantly correlated, and in Cambodian mothers, a correlation was found between maternal and infant serum vitamin B12 levels. Vitamin supplement use has positive effects on infant and mother's vitamin B12 values, but mother and infant B12 vitamin levels are directly related regardless of supplement use. In our study, a strong correlation between maternal and infant vitamin B12 levels was observed, which supports this study.

In our study, infants were divided into 3 groups as 31-60 days old, 61-120 days old, 121-180 days old according to postnatal age after the neonatal period, and no significant differences were found between age groups when values in terms of vitamin B12 levels were taken. In the study conducted on Cambodian and Canadian mothers, infants were divided into two groups according to postnatal age, as before and after 8 weeks of pregnancy, and it was shown that they had lower vitamin B12 levels as postnatal age progressed, but no statistically significant difference was found (6). Compared with studies on vitamin B12 deficiency during the neonatal period in Turkey (7,8,20). Infants in our study had a higher rate of vitamin B12 deficiency, which supports the study conducted by Chebaya et al. (6) from Canada. Although the level of vitamin B12 decreases in 1-6 months period, there is no statistically significant difference (Table 4).

A statistically significant difference was found between the vitamin B12 levels of the mothers when the infants had adequate vitamin B12 and normal homocysteine levels compared with those who did not. In this study, it should be considered that the vitamin B12 level of mothers should be kept above 385 pg/mL in order for infants to have sufficient vitamin B12 and normal homocysteine levels. For mothers, this review was first introduced in our study.

In the adult age group, the normal vitamin B12 level is 300 pg/mL, and insufficiency is indicated as 200-300 pg/mL (16). A 90% sensitivity to normal vitamin B12 levels has been reported. Currently, we know that a level of 300 pg/mL does not show 100% sensitivity, and according to the results of our study, we believe that a level of 300 pg/mL of vitamin B12 in mothers is insufficient for infants fed to breastfeeding mothers. It is one of the results of our study that if breastfeeding mother's vitamin B12 level can be maintained above 385 pg/mL, the infant can have vitamin B12 levels above 300 pg/mL and homocysteine levels below 8.3 µmol/L.

Clinical findings of vitamin B12 deficiency were not evaluated in our study, in a study by Lai et al. (23); when the cognitive scores of 2-year-old children of pregnant women who were followed up in 2 groups as those with and without vitamin B12 deficiency during pregnancy were compared, the cognitive score of the group with vitamin B12 deficiency was found to be significantly lower. But in this study, while the presence of many environmental, familial, and genetic factors that can affect the cognitive functions of infants restricts reliability, vitamin B12 deficiency can also be considered as a risk factor for neurodevelopmental retardation.

The effects of persistent hyperhomocysteinemia on cerebrovascular events, diabetes development, and cardiovascular events in adults are known (24,25). Vitamin B12 deficiency in infancy, childhood, and old age is one of the leading causes of hyperhomocysteinemia (18). One of the most common causes of vitamin B12 deficiency in the infant group is low vitamin B12 storage and insufficient intake due to maternal vitamin B12 deficiency (26).

In Turkey, there are valuable studies on pregnant women and newborns regarding vitamin B12 levels, but there is not enough data on the relationship between vitamin B12 and homocysteine levels during the infant period (6,9).

In our study, the cut-off vitamin B12 level was found for the first time in order to predict the elevation of homocysteine in the infant period and was found to be 220 pg/mL, and the values detected for 220 pg/mL are as indicated: sensitivity, 66.2%; specificity, 75.5%; negative predictive value: 37.3%; and positive predictive value, 91.0%. Accordingly, the homocysteine

elevation rate of those with vitamin B12 levels below 220 pg/mL was 91%, whereas the homocysteine normality rate of those above 220 pg/mL was 37.3%. The reason for this is that a majority of our infant patients had vitamin B12 levels below 300 pg/mL. We can say that the average vitamin B12 level of infants with normal homocysteine levels is 301.3 pg/mL and that is the normal cut-off value of 300 pg/mL and its above can also be used as a safe range for infants.

In a study conducted in Turkey, the B12 vitamin cut-off value of newborns was 232.5 pg/mL with 70% specificity and sensitivity, and the homocysteine value of 4.7 µmol/L was determined as the cut-off value for 58% specificity and 68% sensitivity (20). It has been shown in these two studies that infant and neonatal homocysteine levels are significantly lower than adult homocysteine levels.

Conclusion

In addition, as detected in our study, vitamin B12 deficiency is common among infants and breastfeeding mothers. Since vitamin B12 deficiency is common in developing countries such as Turkey, infants can be protected from vitamin B12 deficiency, especially by preventing mothers' vitamin B12 deficiency. Our recommendation is to check the vitamin B12 level in the early period of pregnancy follow-up, since vitamin B12 deficiency is very common in Turkey, to start daily maintenance B12 at a dose of 2-5 mcg if there is a deficiency, to start preparations containing vitamin B12 in a maintenance dose, and continue during lactation. In this way, fetal vitamin B12 stores can be sufficiently formed during pregnancy, and during lactation, infants can receive sufficient levels of maintenance B12 vitamins through the mother.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Medeniyet University Göztepe Training and Research Hospital (decision no: 2019/0523, date: 25.12.2019).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.P., Concept: S.P., Design: S.P., Data Collection or Processing: S.P., Analysis or Interpretation: S.P., A.K., Literature Search: S.P., A.K., Writing: S.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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Incidence and Clinical Profile of Respiratory Syncytial Virus Infection in Infants Admitted with Diagnosis of Lower Respiratory Tract Infection

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What is known on this subject?

Respiratory syncytial virus (RSV) infection exhibits a higher prevalence among males, and a notable association was identified between RSV infection and patients younger than 6 months. Seasonal variations in RSV incidence were evident, with peak infections observed in December, January, and March. Statistically, a negative association was found between the duration of breastfeeding and RSV infection. RSV positivity was significantly correlated with meteorological parameters such as temperature and relative humidity. A significant association was noted between clinically diagnosed otitis media and chest retraction due to RSV infection.

What this study adds?

The study highlights that the age of patients younger than 6 months, breastfeeding practices, and environmental factors such as air temperature and humidity appear to have a significant impact on the development of RSV infection.

ABSTRACT

Objective: Lower respiratory tract infections of predominantly viral origin disproportionately affect infants and children, and respiratory syncytial virus (RSV) is a primary pathogen in this age group. This study employed rapid testing methodologies to detect RSV infection among hospitalized pediatric patients, providing insights into its prevalence, epidemiological, and clinical characteristics, and impact on mortality and morbidity.

Material and Methods: This study, conducted between September 1, 2009 and April 30, 2011, targeted infants aged 0-24 months who were hospitalized with lower respiratory infections at the Pediatric Clinic of University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Hospital. Upon admission, each patient underwent a comprehensive medical history evaluation, which included assessments for prematurity, congenital heart disease, recurrent infectious diseases, reactive respiratory system disease, and immune system disorders. Additionally, physical examination, routine tests, and nasopharyngeal swab samples were collected. RSV detection was performed using the Respi-Strip kit.

Results: Among the 311 patients included in the study, 182 (58%) were male, and RSV was detected in 110 (35%) patients. Of those who tested positive for RSV, 72 (65%) were male. A significant prevalence of RSV infection was observed among patients aged 6 months. The incidence of RSV was notably higher in December, January, and March. A statistically significant negative correlation was found between the duration of breastfeeding and the likelihood of RSV infection. RSV positivity was significantly associated

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ABSTRACT

with temperatures below 10 °C and relative humidity levels exceeding 60%. Additionally, a significant association was noted between RSV infection, the presence of clinically diagnosed otitis media, and chest retraction.

Conclusion: Regular screening for RSV is essential for early diagnosis, enabling targeted therapy, and improving patient outcomes. This proactive strategy may reduce morbidity, mortality, and economic impacts. Further epidemiological and clinical research on RSV transmission is crucial for protecting populations at risk, enhancing disease prevention measures, optimizing isolation protocols, and developing novel treatment options.

Keywords: Lower respiratory tract infection, infant period, respiratory syncytial virus

Introduction

According to the World Health Organization's 2020 data, lower respiratory infections (LRIs) are the fourth leading cause of death globally and a major contributor to child mortality among infectious diseases. It is estimated that one in seven deaths in children under the age of 5 is attributed to LRIs (1,2).

The predominant cause of LRIs are viruses, with infants and young children particularly being susceptible. Key viral pathogens responsible for lower respiratory tract infections in the pediatric population include respiratory syncytial virus (RSV), human rhinovirus, human metapneumovirus, parainfluenza viruses, influenza A-B and adenoviruses (3). According to 2022 data from the Turkish Statistical Institute, LRIs accounted for 8.2% of deaths in children aged 1-4 years in Turkey. The Turkey Burden of Disease Study reported that respiratory infections were the second cause of death in the 0-4 age group, representing 13.4% and 6.5% in the 5-14 age group. These infections account for 14% of all deaths in the 0-14 age group (4,5). This data highlights that LRIs pose a significant public health concern in children under 2 years old in the country.

RSV is a common cause of bronchiolitis and pneumonia during infancy. Although RSV typically causes flu-like symptoms in adults, it can cause severe lower respiratory tract infections in approximately 40% of infected infants and young children within 2 to 5 days. Approximately 50-70% of infants are infected with RSV in the first year and 95% by the age of 2 despite the presence of serum antibodies. Re-infections with RSV can occur even with existing antibodies in subsequent years. Primary RSV infection can have a severe course in infants aged 2 months with high levels of maternal antibodies. Severe primary RSV infections are particularly problematic in infants aged 2 months with high maternal antibody levels and in those with chronic lung or congenital heart disease, leading to frequent severe respiratory infections and increased mortality. Rapid and accurate diagnosis of the viruses responsible for LRI is critical for initiating timely and appropriate treatment, avoiding unnecessary antibiotic use, implementing appropriate isolation measures, and preventing hospital-acquired infections caused by these viruses. Methods such as viral isolation via cell culture and serological assays are expensive and may take weeks to yield results from the onset of viral infection. To facilitate an early diagnosis, tests such as electron microscopy, enzyme immunoassay, radioimmunoassay, and latex agglutination have been developed. Additionally, using nasopharyngeal swab samples, the RSV Respi-Strip kit, which employs the strip method with monoclonal antibodies to determine the RSV F protein, enables rapid bedside diagnosis (6,7).

The aim of this study was to determine the role of RSV as a causative agent of lower respiratory tract infections in children aged 0-24 months. The study was conducted on patients admitted to the Pediatric Clinic of University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital within the specified age range.

In particular, during winter months, a significant proportion of children admitted to our clinic present with LRIs. The purpose of this study was to detect RSV infection using a rapid testing method among children aged 0-24 months admitted to our hospital due to LRI. The objectives of this study were to determine the prevalence of RSV infection, analyze its epidemiological and clinical characteristics, and evaluate its impact on mortality and morbidity.

Material and Methods

This study was conducted from September 1, 2009, to April 30, 2011, and included patients aged 0-24 months who presented to the General Pediatric Outpatient Clinic and Pediatric Emergency Department of University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital with a diagnosis of LRI and were deemed suitable for hospitalization. Only patients who could not be managed on an outpatient basis and were eligible for admission to the pediatric clinic were selected for the study. Prior to inclusion, parents were notified about the study, and informed consent was obtained before the inclusion of any children. The

study protocol was approved by the Ethics Committee of the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital (no: 78113307/1005/168, decision no: 7, date: 23.09.2009). Upon admission, patients' medical histories, physical examinations, and diagnostic tests, such as chest X-ray, complete blood count, biochemistry, blood gas analysis, and C-reactive protein levels, were evaluated. Comprehensive data were recorded, including patient age, sex, admission month, admission season, parental educational level, family income level, maternal age, family smoking habits, exposure to air pollution, number of rooms in the household, household size, birth order, duration of hospitalization, history of previous infections, gestational age by weeks, mode of delivery, and duration of breastfeeding.

The clinical findings at admission included fever, cough, runny nose, tachypnea, dyspnea, stridor, wheezing, apnea, acute otitis media (AOM), chest retraction, and pulse oximetry values.

Patients included in the study underwent routine tests upon admission, which included the collection of nasopharyngeal swab samples. The collection procedure involved positioning the patient's neck appropriately and using a sterile cotton swab to obtain the sample. The samples were tested with the Abbott RSV Respi-Strip (Rapid Diagnostic Test for Syncytial Virus Detection in nasopharyngeal Specimens, Gembloux-Belgium). The procedure involved placing the swabs in tubes containing approximately 0.5 cc of test matrix, transferring them into a liquid medium, and inserting a strip into the prepared sample. After a 15 min incubation period, the results were interpreted. The appearance of a double red line in the indicator carrying monoclonal antibodies against the fusion (F) protein of RSV was considered positive, whereas a single red line was considered negative. The absence of a line was considered an invalid sample. The entire evaluation process (from sample collection to interpretation) took approximately 20 minutes.

On the same day that RSV nasopharyngeal swabs were collected, meteorological data on temperature, humidity, and atmospheric pressure were obtained from daily records of the General Directorate of Meteorology.

Data regarding supportive respiratory care interventions administered to patients included the use of bronchodilators, duration and types of use, oxygen inhalation (duration and dosage),and antibiotic use.

For patients requiring intensive care, information was documented on the use of mechanical ventilators, duration of intensive care admission, and clinical course of the patients during the intensive care monitoring period.

Statistical Analysis

Statistical analysis of the study data was performed using the SPSS (Statistical Package for the Social Sciences) for Windows. Descriptive statistical methods, including mean, standard deviation, and frequency distributions, were employed to evaluate the study data. To compare quantitative variables between groups, the Student's t-test was used for normally distributed data, whereas the Mann-Whitney U test was applied for non-normally distributed data. For the comparison of qualitative data, the Pearson chi-squared test and Fisher's exact test were used. Statistical significance was determined at a threshold of $p<0.05$, with a confidence interval of 95%.

Results

Between September 1, 2009, and April 30, 2011, a total of 311 patients aged 0-24 months who presented with LRIs at the Pediatric Clinic of University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital were included in the study. Patients who were deemed suitable for hospitalization after failure of outpatient treatment provided informed consent prior to participation.

Of 1.809 patients admitted to the 1st pediatric clinic during the study period, 311 (17.2%) were enrolled in this study. The cohort comprised 129 (41.5%) women and 182 (58.5%) men. RSV was detected in 110 (35.4%) patients, whereas 201 (64.6%) tested negative for RSV. Among the RSV-positive patients in our study, 72 (65.5%) were male, and 38 (34.5%) were female, resulting in a male-to-female ratio of 1.89 (Figure 1).

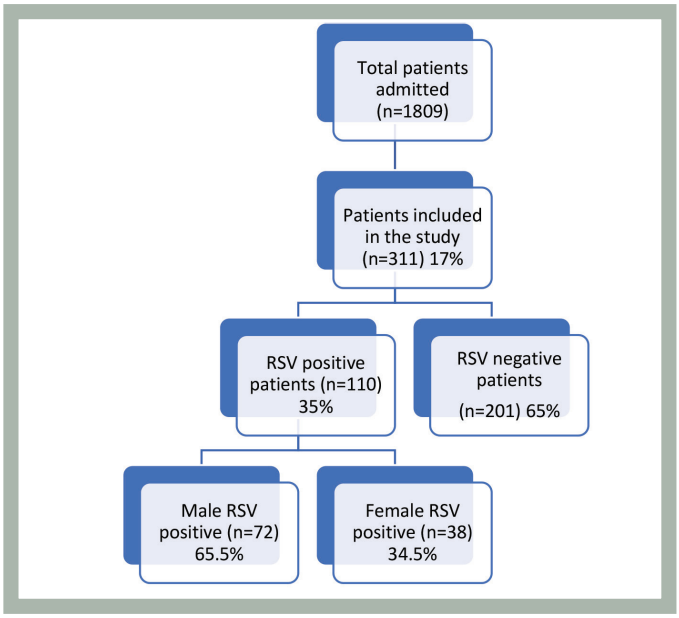

Figure 1. General characteristics of patients
RSV: Respiratory syncytial virus

Patients were categorized by age into the following groups 0-1 months, 1-6 months, 6-12 months and 12-24 months. RSV positivity was significantly higher in patients aged 6 months (p=0.01), with a mean age of this group was 5.8±5.2 months in this group. The mean ages were 3.5±3.2 months for RSV (+) patients and 6.8±5.6 months for RSV (-) patients (Table 1). The median length of hospitalization was similar between RSV-positive and -negative patients at 7 days. Seasonal analysis of RSV-positive cases among the 110 patients identified as RSV-positive revealed that 64 (58%) were admitted during winter months (December, January, February), 36 (33%) during spring months (March, April, May), and 10 (9%) during autumn months (September, October, November). The incidence of RSV was significantly higher in December, January, and March (Table 2). Breastfeeding duration was classified as 3 months, 4-6 months, 7-9 months, 10-12 months, and >12 months. It was observed that 76 (69%) of the patients with RSV infection had been breastfed for less than 3 months, and none of the 5 patients who had been breastfed for more than 12 months had RSV infection (Table 3). Analysis of meteorological data indicated a significant relationship between RSV infection rates and temperatures below 10 °C as well as relative humidity levels above 60% (Table 4). Clinical findings at admission showed that patients with chest retraction and AOM had a significantly higher incidence of RSV infection. The severity of

Table 1. Demographic characteristics and risk factors of children with RSV-positive and RSV-negative LRTI

Variables	RSV (-) (n=201)	RSV(+) (n=110)
Male	110 (61%)	72 (65%)
Female	91 (39%)	38 (35%)
Age (months)	6.8±5.6	3.5±3.2
Age groups		
0-1 months	13 (6%)	22 (20%)
>1-6 months	117 (58%)	70 (64%)
>6-12 months	46 (23%)	16 (14%)
>12-24 months	26 (13%)	2 (2%)
Birth characteristics		
Preterm	28	14
Term	173	96
Delivery method		
Spontaneous vaginal	96	59
Cesarean section	105	51
Socio-economic status		
Low	63 (31%)	54 (49%)
Middle	125 (62%)	51 (47%)
High	13 (6%)	5 (4%)
Smoking exposure		
Yes	107 (53%)	64 (58%)
No	94 (47%)	46 (42%)
Maternal education		
No education	56 (28%)	29 (27%)
Primary education	131 (65%)	71 (64%)
High school and university courses	14 (7%)	10 (9%)
Paternal education		
No education	12 (6%)	5 (4%)
Primary education	120 (60%)	62 (56%)
High school and university courses	69 (34%)	43 (40%)

RSV: Respiratory syncytial virus, LRTI: Lower respiratory tract infection

Table 2. Significant associations between RSV infection and months

Conditions	n	p value
Months		
December	28 (25%)	**0.001**
January	24 (22%)	**0.001**
March	20 (18%)	**0.001**
Seasons		
December, January, and February	64 (58%)	
March-May	36 (33%)	
September-November	10 (9%)	

RSV: Respiratory syncytial virus

Table 3. Relationship between breastfeeding and RSV infection

Condition	n	p value
Breastfeeding for 3 months (positive correlation with RSV infection)	76 (69%)	**0.016**
Breastfeeding 4-6 months	20	
Breastfeeding 7-9 months	10	
Breastfeeding 10-12 months	4	
Breastfeeding for more than 12 months	0	
Breastfeeding >12 months (no RSV infection in any of them)	5 (4.5%)	**0.016**

RSV: Respiratory syncytial virus

Table 4. RSV infection and meteorological conditions

Conditions	p value
Temperature below 10 °C	**0.019**
Humidity ≥60%	**0.013**
Air pressure	0.717

RSV: Respiratory syncytial virus

Table 5. Significant associations between RSV infection and patient age and clinic experience

Conditions	p value
<6 months of age	**0.001**
Otitis media	**0.023**
Chest retraction detection	**0.030**
Worsening in the LRI clinic	**0.008**

RSV: Respiratory syncytial virus, LRI: Lower respiratory infection

LRI symptoms was classified as mild, moderate, and severe , with RSV-positive patients exhibiting more severe symptoms (Table 5).

No significant findings were observed in the other statistical evaluations (Table 6).

Discussion

LRIs are primarily caused by bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, as well as viruses such as influenza and RSV. Globally, LRIs are the leading cause of death, accounting for over 2 million deaths annually. They are particularly deadly for children under 5 years old, with approximately 0.67 million deaths recorded in this age group worldwide in 2019 (8).

Acute viral pneumonia is a recurring problem throughout childhood. Although RSV becomes less prominent as an etiologic agent after the first year , it still plays a causative role in approximately 40%-75% of hospitalized cases of bronchiolitis, 15%-40% of childhood pneumonia, and 6%-15% of croup. Bronchiolitis and pneumonia caused by RSV are more common in males than in females, with a ratio of approximately 1.5:1. In the United States, additional risk factors include having one or more siblings in the home, being of white race, residing in rural areas, maternal smoking, and maternal education < of less than 12 years. Medical factors in infants associated with the highest risk are prematurity chronic lung disease, congenital heart disease, immunodeficiency, and prematurity itself. However, approximately 80% of children under 2 years hospitalized for RSV infection do not have easily identifiable risk factors (9).

The prevalence of RSV infection, its rapid transmissibility, and potential to cause severe clinical manifestations in high-risk cases have been the subjects of numerous studies. For instance, Hacımustafaoğlu et al. (10), reported the rate of RSV in patients under 2 years of age admitted to the hospital due to LRI as 37.9%. Similarly, study conducted by Tayachew et al. (11) in Ethiopia between 2021-2022 , found that among 1.174 children under 2 years of age with diagnosis of LRI,

Table 6. Conditions not significantly associated with RSV infection

Conditions	p value
Maternal age	0.559
Method of birth	0.090
Birth order	0.598
Presence of sick siblings	0.657
Daycare attendance	0.442
Smoking in the family	0.644
Exposure to environmental smoke	0.499
Number of family members	0.995
Number of rooms in the house	0.136
Parental education level	0.315
Family income	0.103
Pulse oxygen saturation	0.210
Fever	0.855
Cough	0.510
Runny nose	0.705
Tachypnea	0.294
Nasal flaring	0.649
Stridor	0.115
Apnea	0.889
Shortness of breath	0.285
Bronchodilator use	0.405
Duration of bronchodilator use	0.202
The type of bronchodilator used	0.933
Oxygen intake times	0.520
Need for mechanical ventilation	0.420
Length of hospital stay	0.078
Need for intensive care	0.854
Length of stay in intensive care	0.469
Infiltration before and after lung X-rays	0.584
Exacerbations of LRI	0.232
Liver function impairment	0.057
Kidney function impairment	0.672
Blood gas analysis	0.382
Leukocytosis	0.059
Lymphocytosis	0.057
Anemia	0.157
Elevated CRP levels	0.605
Thrombocytopenia	0.231

LRI: Lower respiratory infection, CRP: C-reactive protein

278 (23.7%) tested positive for RSV. In the study of Di Carlo et al. (12) between November 2005 and May 2006, among 645 children under 2 years of age admitted to the hospital with LRI diagnosis, 335 were considered to have a viral disease, among these 178 (27.6% of all patients) were identified as RSV positive in the tests. Hatipoğlu et al. (13) found that, out of 80 patients under 2 years of age admitted to the hospital, 28 (35%) were identified as RSV positive. Pale et al. (14) detected RSV infection rate as 26.7% (113/424) of the participants with LRI in Mozambique. In our study, we focused on 311 patients aged 0-24 months diagnosed with LRI and admitted to the hospital and determined the frequency of RSV as 35.4%. Our findings are consistent with those of the existing literature. We also obtained results similar to those from studies conducted in our country.

A notable correlation exists between RSV hospitalizations and patient age, with younger patients experiencing higher hospitalization rates. Stein et al. (15) conducted a systematic literature review and meta-analysis involving 34 studies from 26 countries. The current study indicated that RSV infections are particularly severe in patients aged 1 year and those with a history of premature birth. According to the same study, the hospitalization rate for RSV patients in the under 5 years category was 4.37%, for those 1 year of age 19.19%, for those under 6 months 20.01%, and for premature infants under 1 year, it was 63.85% (15). According to our study, the mean age was 3.6±3.2 months for RSV (+) LRI and 6.8±5.6 months for RSV (-) LRI group (p=0.002). RSV positivity was significantly higher in patients aged 6 months (p=0.01).

RSV, a major cause of infant hospitalization. RSV is an enveloped negative-stranded RNA virus that has recently been reclassified in the Pneumoviridae family. Infection of respiratory cells occurs when two major surface glycoproteins (G and F) get into contact with the cell receptor CX3CR1 and mediate entry by F, respectively. Viral mRNA transcription, genomic RNA synthesis, and nucleocapsid formation occur in large cytoplasmic inclusion bodies to avoid recognition by the host innate immune response. Most progeny virions remain attached to the infected cell surface; and the F of infected cells with adjacent cells results in the formation of large multinucleated syncytes that eventually undergo apoptosis. Desquamated epithelial cells can form plugs, which, when combined with mucus and fibrin, may lead to obstructions in the lower airways (16). Severe RSV infections during infancy also increase the risk of asthma in children, which continues into adolescence (17). We noted more severe clinical symptoms in children with RSV, particularly an increased incidence of chest retractions, consistent with the literature.

Numerous studies have observed a positive correlation between RSV infection and male gender. Bourdeau et al. (18) found that of the 11,014 RSV-related hospitalized patients, 54.8% (5.488) were male. Biggs et al. (19), of the 1.129 RSV-positive cases, 665 (59%) were male. Our study is consistent with the literature, identifying 72 (65%) of the 110 RSV-positive cases as male.

RSV infections often present with both upper and lower respiratory symptoms, including coryza, fever, pharyngitis, and otitis media (AOM) (9). AOM is a known complication of RSV infection affecting as many as 50% of children under 5 years old with RSV. The incidence of RSV-associated AOM is significantly higher in children under 2 years of age than in older children. Sagai et al. (20) examined 230 children diagnosed with RSV infection using enzyme immunoassay. Among these children, 120 (52.2%) developed AOM. RSV antigen was detected in the middle ear fluid of 36 out of 52 patients with AOM (69.2%). Additionally, this study identified a significantly higher incidence rate of AOM amongst children under 2 years of age (73.1%) than among older children (29.7%) (20). In our study, we observed an increased frequency of otitis media in cases with RSV infection (p=0.023), consistent with the literature.

Globally, RSV follows a seasonal pattern. In temperate climates, RSV circulates throughout the winter season and peaks between December and January. In tropical regions, RSV outbreaks still occur during hot, humid, and rainy days in the summer season (21). In their study, Miyama et al. (22) described the RSV outbreaks in Japan between the years 2012 and 2019 and identified that during the 2012-2016 seasons, epidemic clusters were detected between September and December, whereas during 2017-2019, they were between July and October seasons. Constantopoulos et al. (23) found increased RSV infection in November, peaking in February. These cases decreased gradually until May in Greece. Rossi et al. (24) concluded that the frequency of RSV infection increased in February and March in Italy. In our study, we found that 58.2% of RSV-positive cases were observed in the winter months (December, January, February), 32.7% in the spring months (March, April, May), and 9.1% in the fall months (September, October, November). We identified that outbreaks peaked in December, January, and March. Our research yielded results similar to those reported in the literature. Some studies have described the epidemiological changes in RSV outbreaks following the coronavirus disease-2019 (COVID-19) pandemic. Ren et al. (25) demonstrated that, in 2020-2021, the RSV positivity rate in children hospitalized with LRI remained high, in all groups of patients <5 years

as compared to patients from 2018-2019 in central China. In contrast, Stamm et al. (26) described a parallel decline in RSV incidence in Germany in 2020. Mondal et al. (27) described that RSV activity had significantly declined since the pandemic outbreak and remained low until October 2021 in the USA. These studies indicated that the decrease in RSV frequency during the COVID-19 pandemic was influenced by isolation and contact restriction measures. Ren et al. (25) noted an increase in RSV cases, which was attributed to the virus's high resilience in external environments and ease of transmission. Although the frequency and outbreaks of RSV showed variance during and after the COVID-19 pandemic, a study conducted by Çağlar et al. (28) in our country covering the period from April 2018 to March 2023 demonstrated that RSV infection returned to its usual seasonality, beginning in the fall, peaking in winter, and ending in spring. There is a need for studies in our country to analyze the epidemiological changes in RSV following the COVID-19 pandemic.

The mechanism by which breastfeeding reduces the risk of infection is not entirely clear although the immunomodulatory content is known. In the early months of life, it is believed to be effective against respiratory infections through both mucosal and systemic protective mechanisms (29). In the systematic review by Mineva et al. (30), we found that non-breast feeding practices pose a significant risk of severe RSV-associated acute LRI and hospitalization. Exclusive breastfeeding for more than 4-6 months significantly reduced the rates of hospitalization, length of hospital stay, demand for supplemental oxygen, and admission to intensive care units (ICU) (30). In our study, we similarly observed a significant inverse correlation between the duration of breastfeeding and the incidence of RSV infection. This indicates that longer breastfeeding durations are associated with lower frequencies of RSV infection.

Numerous studies have been conducted to determine the relationship between RSV infection and meteorological conditions. Linssen et al. (31) conducted a 13-year study on pediatric intensive care unit (PICU) admissions for RSV bronchiolitis in the Netherlands. They identified maximum temperature and global radiation as weather variables with the strongest predictive effect on RSV-related PICU admission burden. Decreases in temperature and global radiation are directly proportional to RSV infection rates. Additionally, increases in relative humidity and cloud coverage contribute to higher infection rates (31). Wagatsuma et al. (32) demonstrated that low mean temperature and high relative humidity are positively correlated with RSV infection in Japan. In the data we obtained, we found a significant relationship between RSV infection and meteorological conditions. We observed a significant increase in RSV infections when air temperatures were below 10 °C. Additionally, relative humidity levels of 60% or higher were found to be a significant facilitating factor for the occurrence of RSV infection.

Conclusion

Based on the results of our study, proper isolation, prevention of infection spread, patient monitoring, and appropriate treatment planning can be more accurately implemented when RSV is detected in nasopharyngeal swab samples from patients. Among infectious diseases, respiratory tract infections rank first among serious problems, especially in developing countries. Periodic screening and detection of the causative microorganism in cases of lower respiratory tract infections will significantly reduce morbidity, mortality, and financial burden through patient isolation, implementation of appropriate treatment regimens, and follow-up. Societal risk can be reduced through socio-economic support and education programs for families with patient cases. Considering the transmission periods and clinical features of RSV infection identified in our study, more comprehensive research should prioritize preventive medicine practices for individuals at risk for RSV, followed by the identification of the causative agent, isolation, and use of newly developed treatment methods, to yield beneficial results in controlling the disease.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital (no: 78113307/1005/168, decision no: 7, date: 23.09.2009).

Informed Consent: Parents were informed of the study and provided informed consent before inclusion of any cases.

Authorship Contributions

Surgical and Medical Practices: P.A., Y.A., T.A., Concept: P.A., Y.A., T.A., Design: P.A., Y.A., H.Ç., Data Collection or Processing: P.A., H.Ç., Analysis or Interpretation: P.A., Y.A., T.A., Literature Search: P.A., T.A., H.Ç., Writing: P.A.

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Retrospective Analysis of Patients Aged 65 and Over who were Admitted to the General Surgery Clinic from the Emergency Department

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What is known on this subject?

Patients aged over 65 years are a population that increasingly utilizes healthcare services due to the progression of aging, which is associated with a rise in chronic diseases and a decline in physical function. This age group is particularly vulnerable to multiple chronic conditions, such as heart failure, hypertension, diabetes mellitus, and chronic obstructive pulmonary disease, and is also at high risk of acute medical conditions and trauma. Consequently, emergency departments are frequently utilized by the elderly population, leading to a significant increase in the number of elderly patients visiting these facilities. Frequent visits to emergency services by patients aged over 65 years are driven by factors such as the potential for rapid deterioration of acute illnesses, age-related immune system deterioration, and challenges in managing existing chronic conditions.

What this study adds?

This study aimed to analyze the conditions that necessitate general surgery admission among patients aged >65 years who presented to the emergency department and identify the factors affecting the management and prognosis of these patients.

ABSTRACT

Objective: This study aimed to retrospectively analyze the surgical intervention needs and outcomes of patients aged >65 years who were admitted from the emergency department to the general surgery ward due to gastrointestinal complaints. This study further explores the impact of age and comorbidities on surgical outcomes in this population.

Material and Methods: A total of 525 patients aged 65 years and older who presented with gastrointestinal symptoms were included in this retrospective observational study conducted at İzmir Katip Çelebi University Atatürk Training and Research Hospital. Data on demographic characteristics, presenting complaints, diagnoses, surgical interventions, and outcomes were collected and analyzed using IBM SPSS Statistics 26.0.

Results: The mean age of the study population was 79.72±9.25 years, and 45.1% were female. The most common presenting complaint was abdominal pain (54.7%), and the most frequent diagnoses were ileus (25.0%), acute cholecystitis (21.9%), and perforation (10.1%). Emergency surgery was required in 35.6% of the patients. The present study found a statistically significant association between higher mortality rates and diagnoses such as perforation, mesenteric ischemia, and trauma. Mortality was also significantly higher among patients with severe comorbidities.

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ABSTRACT

Conclusion: Elderly patients requiring emergency surgical intervention are at high risk of mortality, particularly in the presence of specific diagnoses and comorbidities. These findings highlight the need for careful surgical decision-making and the adoption of multidisciplinary approaches in the management of elderly patients to improve outcomes. Further research is recommended to optimize perioperative care in this vulnerable population.

Keywords: Geriatrics, emergency department, general surgery

Introduction

Patients aged >65 years represent a population that increasingly utilizes healthcare services due to the progression of aging, which is associated with a rise in chronic diseases and a decline in physical function (1,2,3). This age group is particularly vulnerable to multiple chronic conditions, such as heart failure, hypertension, diabetes mellitus, and chronic obstructive pulmonary disease (COPD), and is also at high risk of acute medical conditions and trauma (4,5,6). Consequently, emergency departments are frequently utilized by the elderly population, leading to a significant increase in the number of elderly patients visiting these facilities. Frequent visits to emergency services by patients aged over 65 years are driven by factors such as the potential for rapid deterioration of acute illnesses, age-related immune system deterioration, and challenges in managing existing chronic conditions.

In the general population presenting to emergency departments, acute conditions requiring general surgical constitute a significant healthcare burden (6). Conditions such as acute abdomen, appendicitis, bowel obstruction, gastrointestinal perforation, acute cholecystitis, and trauma are common general surgical issues encountered in the emergency department that require prompt intervention (7). These conditions increase the need for surgical evaluation and intervention, and delays in surgical management can lead to severe complications. These acute conditions directly impact the treatment process and prognosis of patients.

Common general surgical pathologies in the elderly include gallbladder diseases, gastrointestinal obstruction, diverticulitis, and hernia complications (8). These patients are more susceptible to surgical intervention because of age-related physiological changes and comorbidities, and they also carry a higher risk of postoperative complications. This study aimed to analyze the conditions that necessitate general surgery admission among patients aged >65 years who presented to the emergency department and identify the factors affecting the management and prognosis of these patients.

Material and Methods

Study Design

This retrospective observational study was conducted in the Emergency Department of İzmir Katip Çelebi University Atatürk Training and Research Hospital. The İzmir Katip Çelebi University Ethics Committee approved the study prior to its commencement (decision no: 0634, date: 17.10.2022). The study was conducted by including the patient population between 13.04.2021 and 05.06.2023.

Study Population

This study included all adult patients aged over 18 years who presented to the emergency department with complaints of abdominal pain, nausea, vomiting, and other gastrointestinal symptoms. Patients who were referred from other centers, were brought to the emergency department intubated or in cardiac arrest/exitus, pregnant, or with incomplete data were excluded from the study (Figure 1).

Study Protocol

The age, sex, presenting complaint, diagnosis, need for surgery, admission location, and outcome information of all

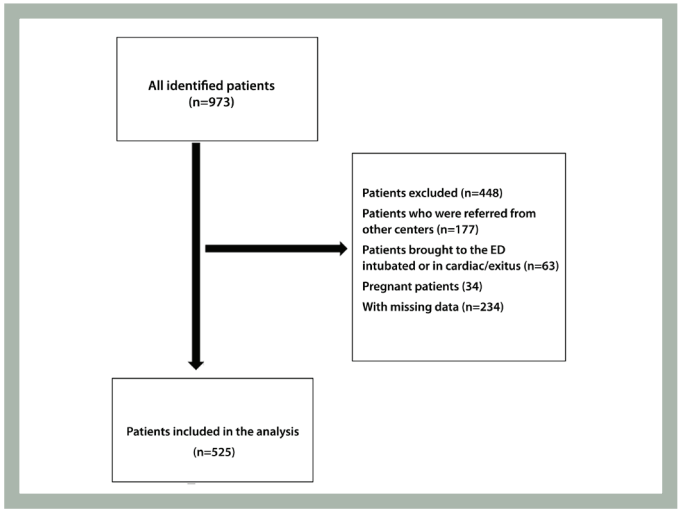

Figure 1. Flow-chart
ED: Emergency department

included patients were obtained from the hospital's electronic medical records and recorded on the study form. Statistical analyses were conducted based on these data.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, New York, USA). Descriptive statistics were presented as n and % for categorical variables and as mean ± standard deviation (minimum-maximum) or median, 25th and 75th percentiles (Q1-Q3) for continuous variables, depending on the normality assumption. The Shapiro-Wilk test was used to assess the normality of the assumption of continuous variables; when the p value was less than 0.05, the data were considered not normally distributed. Levene's test was applied to evaluate the homogeneity of variances; in cases in which the assumption of homogeneity was not met, alternative non-parametric tests were used.

The Mann-Whitney U test was used to compare age distributions by gender and discharge/exit status between the two independent groups. For comparisons involving more than two groups, the Kruskal-Wallis test was used to analyze variables such as presenting complaint, diagnosis, the necessity of surgery, discharge from the emergency department, and admission to the ward or intensive care unit (ICU). The continuity correction test and Pearson's chi-square test were used to analyze the distributions of gender according to presenting complaint, diagnosis, surgery, ward admission, and discharge or exit status, as well as the distribution of discharge/exit status according to gender, presenting complaint, diagnosis, surgery, and ward admission. A p value of <0.05 was considered statistically significant in all statistical analyses.

Results

A total of 525 patients were included in the study, of which 237 were women. The mean age of female patients was 80.73±9.50 years (range: 65-101), whereas the mean age of male patients was 78.89±8.97 years (range: 65-98). This indicates that female patients were, on average, older than male patients. The overall mean age was 79.72±9.25 years, reflecting a wide age range among the patients (65-101 years). The most common presenting complaint was abdominal pain [54.7% of cases, followed by nausea and vomiting (13.3%), constipation (6.9%), and other complaints]. The most common diagnosis was ileus (25.0%), followed by acute cholecystitis (21.9%) and perforation (10.1%). In total, 35.6% of patients underwent emergency surgery. Most patients (93.0%) were discharged, whereas 7.0% were exitus. The mean age of exitus patients (87 years) was significantly higher than that of those who were discharged (p<0.001). The demographic characteristics of the patients are presented in Table 1.

Comparison of presenting complaints, diagnosis, surgical need, ward admission, and exitus status by sex was

Table 1. Descriptive statistics (n=525)

Variable	Descriptive statistics
Age	
Mean ± SD	79.72±9.25
Min-max	65-101
Sex (n, %)	
Female	237 (45.1%)
Male	288 (54.9%)
Presenting complaint (n, %)	
Abdominal pain	287 (54.7%)
Nausea, vomiting	70 (13.3%)
Constipation	36 (6.9%)
Bloody stool	6 (1.1%)
Diarrhea	4 (0.8%)
Other	122 (23.2%)
Diagnosis (n, %)	
Ileus	131 (25.0%)
Acute cholecystitis	115 (21.9%)
Perforation	53 (10.1%)
Hernia	46 (8.8%)
Diverticulitis	24 (4.6%)
Gastrointestinal bleeding	11 (2.1%)
Acute appendicitis	30 (5.7%)
Mesenteric ischemia	15 (2.9%)
Trauma	30 (5.7%)
Other	70 (13.3%)
Surgery (n, %)	
No surgery	248 (47.2%)
Emergency surgery	187 (35.6%)
Elective surgery	90 (17.1%)
Ward/ICU (n, %)	
Discharge from the ED	3 (0.6%)
Ward admission	469 (89.3%)
ICU admission	53 (10.1%)
Exitus/discharge (n, %)	
Discharged	488 (93.0%)
Exitus	37 (7.0%)

SD: Standard deviation, Min-max: Minimum-maximum, ICU: Intensive care unit, ED: Emergency department

performed. A statistically significant difference was found in the diagnostic category between the two genders, whereas no significant differences were observed in other variables. Specifically, the diagnosis of hernia was significantly more common in males than in females, and the difference was statistically significant. The comparison results are presented in Table 2.

Table 2. Distribution analysis of presenting complaint, diagnosis, surgery, ward admission, and discharge or exit status by gender (n=525)

Variables	Gender		p value
	Female (n, %)	Male (n, %)	
Presenting complaint			
Abdominal pain	133 (56.1)	154 (53.5)	0.112++
Nausea, vomiting	36 (15.2)	34 (11.8)	
Constipation	14 (5.9)	22 (7.6)	
Blood stool	0 (0.0)	6 (2.1)	
Diarrhea	3 (1.3)	1 (0.3)	
Other	51 (21.5)	71 (24.7)	
Diagnosis			
Ileus	61 (25.7)[a]	70 (24.3)[a]	0.033++
Acute cholecystitis	51 (21.5)[a]	64 (22.2)[a]	
Perforation	26 (11.0)[a]	27 (9.4)[a]	
Hernia	11 (4.6)[a]	35 (12.2)[b]	
Diverticulitis	14 (5.9)[a]	10 (3.5)[a]	
Gastrointestinal bleeding	3 (1.3)[a]	8 (2.8)[a]	
Acute appendicitis	13 (5.5)[a]	17 (5.9)[a]	
Mesenteric ischemia	9 (3.8)[a]	6 (2.1)[a]	
Trauma	10 (4.2)[a]	20 (6.9)[a]	
Other	39 (16.5)[a]	31 (10.8)[a]	
Operation			
No operation	114 (48.1)	134 (46.5)	0.713++
Emergency operation	86 (36.3)	101 (35.1)	
Elective operation	37 (15.6)	53 (18.4)	
Clinic/ICU			
Discharged from an emergency	1 (0.4)	2 (0.7)	0.461++
Directorate admission	208 (87.8)	261 (90.6)	
Intensive care admission	28 (11.8)	25 (8.7)	
Ex/discharged			
Discharged	218 (92.0)	270 (93.8)	0.538+
Ex	19 (8.0)	18 (6.3)	

+Continuity correction test, ++Pearson's chi-square test, Here, a and b as superscripts represent statistically similarity and difference groups, ICU: Intensive care unit

The comparison of other variables according to in-hospital mortality status is presented in Table 3. There is a statistically significant differences between the discharge and exitus groups in the diagnosis and ward-ICU categories. The exitus rates are higher in the perforation, mesenteric ischemia, and trauma groups, and this increase is statistically significant. The results are detailed in Table 3.

Table 3. Distribution analysis of exitus/discharge status by sex, presenting complaint, diagnosis, surgery, and ward admission (n=525)

Variables	Discharge/ex status		p value
	Discharge (n, %)	Ex (n, %)	
Gender			
Female	218 (44.7)	19 (51.4)	0.538+
Male	270 (55.3)	18 (48.6)	
Presenting complaint			
Abdominal pain	265 (54.3)	22 (59.5)	0.213++
Nausea, vomiting	69 (14.1)	1 (2.7)	
Constipation	34 (7.0)	2 (5.4)	
Bloody stool	6 (1.2)	0 (0.0)	
Diarrhea	3 (0.6)	1 (2.7)	
Other	111 (22.7)	11 (29.7)	
Diagnosis			
Ileus	126 (25.8)[a]	5 (13.5)[a]	**<0.001++**
Acute cholecystitis	111 (22.7)[a]	4 (10.8)[a]	
Perforation	44 (9.0)[a]	9 (24.3)[b]	
Hernia	43 (8.8)[a]	3 (8.1)[a]	
Diverticulitis	24 (4.9)[a]	0 (0.0)[a]	
Gastrointestinal bleeding	11 (2.3)[a]	0 (0.0)[a]	
Acute appendicitis	28 (5.7)[a]	2 (5.4)[a]	
Mesenteric ischemia	11 (2.3)[a]	4 (10.8)[b]	
Trauma	23 (4.7)[a]	7 (18.9)[b]	
Other	67 (13.7)[a]	3 (8.1)[a]	
Operation			
No operation	235 (48.2)	13 (35.1)	0.116++
Emergency operation	168 (34.4)	19 (51.4)	
Elective operation	85 (17.4)	5 (13.5)	
Clinic/ICU			
Discharged from an emergency	3 (0.6)[a]	0 (0.0)[a]	**<0.001++**
Ward admission	444 (91.0)[a]	25 (67.6)[b]	
Intensive care admission	41 (8.4)[a]	12 (32.4)[b]	

+Continuity correction test; ++Pearson's chi-square test, Here, a and b as superscripts represent statistically similarity and difference groups, ICU: Intensive care unit

Discussion

This study examined the surgical intervention needs and outcomes of patients over 65 years old who presented to the emergency department with gastrointestinal complaints. The findings show significant parallels with similar studies in the literature, highlighting the high risk associated with surgical interventions in the elderly population and the need for careful management of these cases. Consistent with the literature, perforation, mesenteric ischemia, and trauma were found to be more fatal in patients over 65. In these patient groups, quicker decision-making and more aggressive treatment are necessary.

Our study found that the need for surgical intervention increases with advancing age, and the postoperative prognosis of these patients is generally poorer. These findings align with numerous studies that examine the outcomes of surgical interventions in elderly patients, with the literature frequently noting that patients over 80 years old have a higher risk of surgical complications and mortality. For example, emergency surgical interventions in patients over 80 years old are associated with mortality, particularly due to surgical complications, sepsis, and pneumonia (9,10). Additionally, it is emphasized that long-term survival rates after surgical interventions are generally low in elderly patients and that postoperative care is critically important for this group (11).

In the literature, comorbidities are identified as one of the main factors affecting postoperative mortality in elderly patients. Our study also examined the impact of comorbidities on surgical outcomes in elderly patients. Many studies have shown that advanced age and associated chronic diseases negatively impact surgical outcomes, with these patients being at higher risk for complications and mortality after surgery (12). Specifically, comorbidities such as hypertension, chronic heart disease, and chronic obstructive pulmonary disease (COPD) increase the risk of mortality following surgical intervention in elderly patients. However, some studies suggest that this relationship is not always clear, and that surgical outcomes in elderly patients cannot be solely explained by comorbidities (9). In this context, our study observed a similar trend, where chronological age alone did not have a significant impact on postoperative mortality, but severe comorbidities emerged as important risk factors.

Our finding that perforation, mesenteric ischemia, and trauma are more closely associated with mortality in elderly patients is widely supported by the literature. Perforation cases, particularly gastrointestinal perforations, are associated with high mortality rates in elderly patients; this is further exacerbated by weakened immune systems, reduced physiological reserves, and comorbidities (13). In such cases, delayed diagnosis and treatment significantly reduce the chances of survival, leading to rapid progression of sepsis (14). Similarly, mesenteric ischemia is a serious cause of death among elderly patients, often linked to atherosclerosis and other vascular diseases, leading to rapid necrosis and sepsis, which increases mortality (15). The literature indicates that elderly patients have a reduced ability to tolerate mesenteric ischemia due to circulatory issues, which is why surgical intervention is often insufficient (16). Trauma also carries a high risk of mortality in the elderly population, particularly when complicated by osteoporosis and general frailty (11). This significantly increases the likelihood of fatal outcomes from traumatic injuries; particularly head traumas and long bone fractures are associated with serious outcomes in elderly patients (13). Studies examining the impact of trauma in the elderly population have found significantly higher mortality rates compared to younger populations (15). Additionally, each of these diagnoses carries significantly increased risks of morbidity and mortality in the postoperative period in elderly patients (14). Elderly patients, with their declining physiological reserves and increasing burden of comorbidities, are more vulnerable to these types of surgical interventions, leading to significantly higher mortality rates (11).

These results clearly indicate that surgical intervention decisions in the elderly population must be carefully evaluated and that a multidisciplinary approach should be adopted for these patients. Particularly in cases of perforation, mesenteric ischemia, and trauma requiring surgical intervention, early diagnosis and treatment strategies can improve survival rates, but these cases generally carry high risks, as frequently emphasized in the literature (11,16).

Surgical intervention decisions in the elderly should be made carefully, considering the patient's overall health status, comorbidities, and the potential benefits of surgery. The literature often discusses the impact of advanced age and comorbidities on surgical outcomes, but it is also noted that these factors alone should not determine surgical decisions (10,12). Our study also emphasizes the need for careful evaluation of the surgical needs of elderly patients and the optimization of postoperative care.

The long-term outcomes of surgical interventions in elderly patients are important in terms of the overall health status and quality of life of this population. Studies have shown that long-term survival rates are low after surgical interventions in elderly patients, and that these patients have greater postoperative care needs (9,10). Additionally, managing postoperative complications in elderly patients is

critically important to improve their quality of life and reduce mortality rates. In this context, multidisciplinary approaches can contribute to optimizing postoperative care following surgical interventions.

Study Limitations

This study is based on a retrospective design and is subject to the inherent limitations of retrospective data collection, such as data loss and recording errors. The study used data obtained from a single center, which may limit the generalizability of the results. Additionally, the inability to fully control for potential confounding variables, such as comorbidities and other clinical factors, may create limitations in the interpretation of the findings. Finally, the study focused on cases requiring surgical intervention and may have overlooked other clinically significant conditions that did not require surgery.

Conclusion

In conclusion, this study highlights the high risk associated with emergency surgical interventions in elderly individuals and underscores the importance of multidisciplinary approaches in managing such patients. It is also important to note that diagnoses such as perforation, mesenteric ischemia, and trauma are associated with higher mortality rates in patients aged >65 years. Future studies should focus on what can be done more quickly in cases of mortal diagnoses among older people.

Ethics

Ethics Committee Approval: The İzmir Katip Çelebi University Ethics Committee approved the study prior to its commencement (decision no: 0634, date: 17.10.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: T.D.Ş., E.E.G., Concept: S.K., Design: M.G.E., U.P., Data Collection or Processing: S.K., T.D.Ş., Analysis or Interpretation: U.P., E.E.G., Literature Search: M.G.E., T.D.Ş., Writing: M.G.E., S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Is There a Relationship Between Carbon Dioxide Fluctuations and Intraventricular Hemorrhage in Preterm Infants?

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What is known on this subject?

Previous studies on premature babies have revealed different relationships between carbon dioxide (CO_2) levels and cranial pathologies. An association between periventricular leukomalacia and hypocarbia was reported in older articles. Although a more recent study found no association between changes in blood gases and cranial hemorrhages in the neonatal intensive care unit, the same data found a correlation between end-tidal CO_2 levels in the delivery room and intraventricular hemorrhages.

What this study adds?

According to the results of this study, keeping CO_2 levels within the normal range is extremely important for controlling intracranial hemorrhage in preterm infants.

ABSTRACT

Objective: This study aimed to examine the association between hypo/hypercapnia and fluctuations in carbon dioxide (CO_2) levels and severe intraventricular hemorrhage (IVH) during the initial 72 hours of life among preterm infants.

Material and Methods: A retrospective study of premature infants with birth weights between 750 and 1.250 g and gestational ages of 30 weeks who required respiratory support. Blood gas measurements were collected during the first 3 days of life. Multivariate analyses were performed to assess the association between hypercapnia and carbon dioxide pressure (pCO_2) fluctuations and IVH.

Results: Our cohort included 376 patients with a median gestational age of 28 weeks and a median birth weight of 920 g. After controlling for gestational age and birth weight, histologic chorioamnionitis and pCO_2 fluctuations remained significantly associated with severe IVH.

Conclusion: Fluctuations in pCO_2 over a short period may have a stronger association with severe IVH than the mere occurrence of hypo- or hypercapnia.

Keywords: Hypercapnia, hypocapnia, preterm infant, intraventricular hemorrhage

Introduction

It is known that there is a relationship between carbon dioxide (CO_2) levels and intracranial hemorrhage in premature babies (1). In particular, previous studies have supported a link between low CO_2 levels and periventricular leukomalacia and that excessive ventilation increases neurodevelopmental problems in premature babies (2). While some studies suggest that this relationship is related to CO_2 fluctuations

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rather than CO_2 levels, others argue that acidosis is a more valuable predictor of cranial hemorrhage than gas pressure in blood gases (2,3). Premature babies cannot maintain the intracranial vascular circulation balance. In these babies, the response of the vascular bed to the amount of blood CO_2 is inadequate (4). As a result of this physiological deficiency, blood gas fluctuations result in severe neurological morbidity. Given these different results in the literature (5,6), we wondered whether this relationship existed in our patient population. In this study, we aimed to investigate the potential relationship between CO_2 levels during the first 3 days and severe intraventricular hemorrhage (IVH) in preterm infants.

Material and Methods

All babies born at less than 30 weeks of gestation, with a birth weight between 750 and 1.250 g, who required respiratory support in the first hours of life and were admitted to the Neonatal Intensive Care Unit at Ankara Bilkent City Hospital between January 2020 and December 2022, were included in the study. Respiratory support was defined as the need for continuous positive airway pressure (CPAP) or mechanical ventilation. Early death, defined as death occurring within the first 3 days of life, congenital anomalies, or missing data were excluded from the analysis. The resuscitation history of the babies in the delivery room, birth weight, gestational age, whether they received surfactants, type of respiratory support, and the results of the first transfontanel ultrasonography were recorded.

We divided and compared the infants into two groups based on cranial ultrasound findings: the first group consisted of infants with grade 3 or 4 cranial bleeding, while the remaining infants formed the second group. Blood gas parameters, data on the first admission to the ward, and other blood gas values within the first 3 days were included in the study data. At least two different blood gas results were recorded per day. Because most of our patients had venous blood gas samples, partial venous carbon dioxide pressure (pCO_2) data in this study were generated by comparing only venous blood gases to avoid confusion. A small number of patients with only arterial and no venous blood gas samples were not included in the study.

Considering that >90% of intracranial hemorrhages in premature babies occur within the first 72 hours of life and that early CO_2 changes are also associated with this problem, we evaluated the relationship between the values in the first 72 hours and early ultrasonography results specifically for this study.

Data analyzed included the main prenatal and neonatal characteristics that have previously been shown to be associated with severe IVH (7), including birth weight, gestational age, preeclampsia, hypertension, premature prolonged rupture of membranes, antenatal steroid (ANS) use, histologic chorioamnionitis (8), 1- and 5-minute Apgar scores, use of nasal CPAP or nasal intermittent positive pressure ventilation, and use of invasive intermittent mechanical ventilation. In addition, data were collected on severe IVH [grades 3 and 4 parenchymal bleeding according to the classification described by Papile et al. (9)], and the infants were divided into two groups according to ultrasound findings. The highest and lowest pCO_2 values were determined from blood gas results obtained during the first 72 hours of life. Measures of pCO_2 dispersion for each patient, including the maximum to minimum range (difference in pCO_2), were calculated. Hypercapnia was defined as any pCO_2 level >65 mmHg within the first 3 days of life. Hypocapnia was defined as any pCO_2 35 mmHg. Normocapnia was defined as maintaining all pCO_2 levels between 35 and 64 mmHg during the first 3 days of life. pCO_2 fluctuation was defined as the difference between two consecutive pCO_2 measurements 6-h apart for each infant. The 6-h interval was selected empirically to assess relatively rapid changes in pCO_2 levels among patients. A difference of more than 20 mmHg between two consecutive pCO_2 levels was considered a prominent fluctuation.

Our hospital is one of the largest healthcare centers in Turkey, with a birth rate of over 15,000 deliveries per year. Our department has 150 neonatal intensive care unit (NICU) beds with all the facilities needed for preterm infant care, including cardiac surgery, extracorporeal membrane oxygenation, a cardiac angiography laboratory, laser intervention for prematurity retinopathy, and hemodialysis. At our facility, preterm infants are initially resuscitated in the delivery room with blended oxygen, commencing at a concentration of 30%, and adjusted according to pulse oximetry measurements. A T-piece resuscitator is used to administer CPAP or positive pressure ventilation. For surfactant use and indications, our department follows and complies with national guidelines (10). Subsequent doses of surfactant are administered based on the need for supplemental oxygen and high mean airway pressure on the ventilator. We use less-invasive surfactant applications when the infant is on non-invasive respiratory support and requires surfactant. Ventilator adjustments are based on blood gas measurements, which are typically performed every 6-12 hours unless there is an additional need for closer monitoring.

This retrospective study was approved by the Ethics Committee and Institutional Review Board no. 2 of Ankara Bilkent City Hospital, (decision number: E2-21-553, date: 02.06.2021).

Statistical Analysis

Descriptive statistics were computed using SPSS for Windows® version 22.0 (SPSS Inc., Chicago, IL). The data were presented as mean (± standard deviation), median (range), or frequency (percentage) as applicable. Continuous variables were analyzed using the t-test, non-parametric data were analyzed using the Mann-Whitney U test, and categorical variables were analyzed using the chi-square test for bivariate analysis of hypercapnia levels and fluctuations. A logistic regression model was used to investigate the relationship between pCO_2 fluctuations and the occurrence of severe IVH, adjusting for potential confounders such as gestational age, ANS administration, gender, 5-min Apgar score, and hypercapnia. Previous studies have identified higher gestational age and ANS use as factors linked to decreased risk of IVH (11). Additionally, the regression model accounted for the 5-min Apgar score and hypercapnia as an indicator of respiratory compromise. Statistical significance was determined using a p value threshold of <0.05.

Results

During the study period, a total of 483 babies were born in our hospital with a birth weight between 750 and 1.250 g and a gestational age of 30 weeks. Data for 427 babies were accessed, of which 22 died in the early period; data for 29 patients could not be accessed. The study data were created using the results and information from 376 patients. The median gestational age was 28 weeks (range 25-30), and the median birth weight was 910 g (range 750-1250). The baseline characteristics of the study population are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the study population

Total number of infants	376
Gestational age, (weeks)*	28 (25-30)
Birthweight (grams)*	910 (750-1250)
Gender, male	191 (50)
Complete course of antenatal steroids	236 (62)
Cesarean section	244 (65)
Histologic chorioamnionitis	157 (42)
Apgar score of 5 min <5	75 (20)
Delivery room intubation	168 (44)
Number of blood gas samples during the first 72 h	10 (8-14)
Hypocapnia	169 (45)
Hypercapnia	86 (23)
Both hypocapnia and hypercapnia	56 (15)
pCO_2 fluctuation	105 (28)

**Median (minimum maximum) or n (%), pCO_2: Carbon dioxide pressure*

When we divided and compared the infants into two groups based on cranial ultrasound findings, one group comprised infants with grade 3 or 4 cranial bleeding, while the remaining infants comprised the control group. Significant differences were observed between these groups in terms of gestational age, ANS use, histologic chorioamnionitis, 5th-min Apgar score, hypocapnia, and CO_2 fluctuations (Table 2). After adjusting for gestational age and birth weight, logistic regression analysis revealed that ANS use, histologic chorioamnionitis, and CO_2 fluctuations were independent factors associated with intracranial hemorrhage (Table 3).

Discussion

Our study data supported the existence of a relationship between early fluctuations in CO_2 levels in blood gas and intracranial hemorrhage in premature infants. This study showed that very low and very high CO_2 levels were independently correlated with the severity of cranial hemorrhage, and fluctuations in CO_2 levels were associated with IVH.

Table 2. Factors associated with intracranial hemorrhage

Variable	Grade 3-4 IVH (n=58)	No and grade 1-2 (n=318)	p value
Gestational age in weeks*	27±1.5	28.2±2	<0.01
Birth weight, grams*	872±190	890±210	0.32
Antenatal steroids	23 (40)	213 (66)	<0.01
Histologic chorioamnionitis	34 (60)	123 (38)	<0.01
Apgar score @5 min <5	26 (45)	49 (15)	<0.01
Hypercapnia	18 (31)	68 (21)	0.107
Hypocapnia	39 (67)	130 (40)	<0.01
pCO_2 fluctuation	38 (65)	67 (21)	<0.01

**Mean ± SD, others n (%), IVH: Intraventricular hemorrhage, pCO_2: Carbon dioxide pressure, SD: Standard deviation*

Table 3. Logistic regression results of intracranial hemorrhage

Variable	Odds ratio	95% confidence interval	p value
Gestational age	0.8	0.62-1.02	0.06
Antenatal steroids	0.3	0.2-0.52	<0.01
Histologic chorioamnionitis	1.4	1.05-1.9	0.02
Apgar score @5 min <5	1.2	0.56-2.34	0.7
Hypocapnia	1.15	0.43-3.03	0.65
pCO_2 fluctuations	2.5	1.2-5.4	0.014

pCO_2: Carbon dioxide pressure

Previous studies on premature babies have revealed varying relationships between CO_2 levels and cranial pathologies. An association between periventricular leukomalacia and hypocarbia was previously demonstrated (12). Subsequent publications have emphasized the relationship between CO_2 fluctuations and IVH, highlighting the need to closely monitor blood CO_2 levels in preterm infants (13). Although a more recent study found no association between changes in blood gases and cranial hemorrhages in the NICU, the same data revealed a correlation between end-tidal CO_2 levels in the delivery room and IVHs (3).

Our team conducted a retrospective neurodevelopmental study on 230 premature babies, which revealed a relationship between very low and very high CO_2 levels in blood gases taken in the first days of life and neurodevelopmental disorders. A difference of >20 mmHg in pCO_2 measured in blood gases was also associated with abnormal motor skills in premature babies. In the multinomial logistic regression analysis of the same study's data, which included birth weight, gestational age, and duration of ventilator use, the risk of a ≥20 mmHg difference in pCO_2 values between the two blood gas samples and the risk of any developmental index being below 75 was found to be statistically significant [odds ratio: 4.64 (1.58-13.6 95% confidence interval), p=0.005] (14).

In the most comprehensive multicenter randomized controlled study conducted on this subject, targeting high CO_2 levels and maintaining them within normal limits were compared, and it was revealed that these two targets did not affect neurodevelopmental outcomes in premature babies (15).

In a study conducted by Altaany et al. (7), which is very similar to our research, it was concluded that there may be a relationship between fluctuations in CO_2 levels and cranial hemorrhages.

Study Limitations

Our study has some limitations. The first of these is that it was conducted retrospectively, and we do not yet have the long-term results of the patients. We could not determine the independent effects of early ventilation methods/modes applied to premature babies on blood gases. Additionally, we may not have included all factors that could contribute to cranial hemorrhage in the analysis. However, our patient sample size is sufficient, and the data we collected and accessed are reliable.

Conclusion

In conclusion, according to the results of this study, maintaining CO_2 levels within the normal range is extremely important for controlling intracranial hemorrhage in preterm infants. Planned prospective studies to examine the effects of different ventilation methods on CO_2 levels in premature babies will provide new insights into this subject.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Ethics Committee and Institutional Review Board no. 2 of Ankara Bilkent City Hospital, (decision number: E2-21-553, date: 02.06.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: H.G.K.K., Concept: H.G.K.K., Data Collection or Processing: Ş.B.T., N.T., Analysis or Interpretation: F.E.C., Literature Search: G.K.Ş., Writing: B.S.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Yıldızgören MT, Dede BT. The role of fascia in myofascial pain syndrome: a look at cinderella tissue. Cam Sakura Med J. 2024;4:1-8.

The authors inadvertently published the article without adding the references to Figure 2. Reference has been added to the sentence on page 3.

Incorrect sentence: A schematic representation of the fascia from the skin to the muscle is shown in Figure 2.

Correct sentence: A schematic representation of the fascia from the skin to the muscle is shown in Figure 2 (**12,38**).

The caption for Figure 2 on page 3 has been changed:

Incorrect sentence: Schematic representation of the fascia from skin to muscle

Correct sentence: Schematic representation of the fascia from skin to muscle (**12,38**)

Reference **38** have been added under the "References" section on page 8.

38. Ryskalin L, Morucci G, Natale G, Soldani P, Gesi M. Molecular mechanisms underlying the pain-relieving effects of extracorporeal shock wave therapy: a focus on fascia nociceptors. Life. 2022;12:743.

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