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INCIDENCE AND ETIOLOGY OF HYPOCALCEMIA IN INFANTS ADMITTED WITH SEIZURES AT TERTIARY CARE HOSPITAL

Original Research

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ABSTRACT

Background: Hypocalcemia is a significant metabolic disturbance in infants and a recognized cause of seizures. The condition often arises from vitamin D deficiency, hypoparathyroidism, or critical illnesses, disrupting calcium homeostasis. Understanding the clinical and biochemical contributors to hypocalcemia-related seizures is essential for timely diagnosis and management to prevent long-term neurological complications.

Objective: This study aimed to evaluate the clinical characteristics, biochemical parameters, and associated factors in infants presenting with hypocalcemia-related seizures, focusing on vitamin D status, parathyroid hormone (PTH) levels, and seizure characteristics.

Methods: A cross-sectional study was conducted at a tertiary care hospital over one year. Data were retrospectively collected for infants aged 1 month to 1 year diagnosed with hypocalcemia (serum calcium <8 mg/dL) and presenting with seizures. Exclusion criteria included seizures due to other metabolic disturbances, such as hyponatremia and hypoglycemia. Clinical data, including seizure type and duration, maternal vitamin D status, and feeding practices, were analyzed. Biochemical parameters such as serum calcium, phosphorus, magnesium, vitamin D, and PTH levels were evaluated. Associations were determined using chi-square tests, with $p<0.05$ considered statistically significant.

Results: Among 54 infants, 57.4% were male, and 94.4% were term. Vitamin D deficiency was identified in 38.9% of cases, significantly associated with hypocalcemia ($p=0.0001$). Hypoparathyroidism was present in 7.4% of infants ($p=0.004$). Most seizures (85.2%) lasted under five minutes, with prolonged seizures showing a significant association with hypocalcemia ($p=0.046$). Serum calcium levels ranged from 5–7 mg/dL in 66.7% of infants, and 37% exhibited low magnesium levels. Maternal vitamin D status was unknown in 53.7% of cases, with 24.1% being deficient.

Conclusion: Hypocalcemia-related seizures in infants are primarily associated with vitamin D deficiency and abnormal PTH levels. Early diagnosis and intervention targeting these factors are crucial to improving outcomes and preventing recurrent seizures.

Keywords: Calcium, Hypocalcemia, Infant, Magnesium, Parathyroid Hormone, Seizures, Vitamin D

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INTRODUCTION

Seizures affect approximately four to seven percent of newborns and toddlers at some point during early childhood, with a notable peak in incidence among infants under two years of age. In low-income countries, hypocalcemia represents a significant metabolic cause of infantile afebrile seizures, particularly during this vulnerable age. Early identification and treatment of hypocalcemia are crucial for mitigating unnecessary and costly interventions, such as lumbar punctures or the premature initiation of antiepileptic medications. Hypocalcemia, characterized by abnormally low levels of calcium in the blood, is a frequently underdiagnosed yet critical contributor to seizures in infants. Calcium plays a pivotal role in neuromuscular function, cellular activities, and blood coagulation, making its regulation especially vital during infancy—a period marked by rapid growth and neurological development (1, 2). Several maternal and neonatal factors influence calcium levels in newborns and young infants. Maternal health during pregnancy, complications during birth, and nutritional deficiencies have all been identified as key determinants. In Pakistan, where neonatal mortality rates remain alarmingly high at 49 per 1,000 live births, accounting for seven percent of global neonatal deaths, such underlying factors require urgent attention (4). The prevalence of hypocalcemia-related seizures has been reported to range from 20 to 35 percent in certain settings, with higher rates observed among preterm infants and those born to mothers with conditions such as diabetes or vitamin D deficiency (5). The etiological spectrum of hypocalcemia includes premature birth, birth asphyxia, inadequate calcium intake, vitamin D deficiency, and impaired parathyroid hormone (PTH) function. In some cases, genetic and metabolic disorders also contribute to reduced calcium levels, compounding the risk of seizures (6, 7, 8). The pathophysiology of hypocalcemia involves an imbalance in ion distribution across cell membranes, particularly in nerve and muscle cells, which heightens neuronal excitability and leads to seizures. Additionally, hypocalcemia can impair cardiac function and enzymatic processes dependent on calcium, further exacerbating the condition's clinical implications (9).

Management of hypocalcemia in infants presenting with seizures requires the rapid correction of calcium levels, often through intravenous calcium gluconate in acute cases. Addressing underlying deficiencies, such as those of vitamin D and magnesium, is equally critical to preventing recurrent episodes. Breastfeeding, while the optimal nutrition source for infants, may pose additional risks if mothers are deficient in vitamin D, as breast milk alone often lacks sufficient levels of this vital nutrient (10, 11). Despite the recognition of hypocalcemia as a seizure risk factor, data regarding its specific incidence and etiological contributors in various populations remain inconsistent and underreported. Regional variability, differences in healthcare settings, and population characteristics contribute to this knowledge gap. The current study seeks to address these limitations by providing a localized understanding of the incidence and etiology of hypocalcemia in infants admitted with seizures at a tertiary care hospital. By identifying the prevalence and underlying causes, the study aims to refine screening protocols and enhance management strategies, ultimately improving outcomes for high-risk infants and reducing preventable complications related to hypocalcemia.

METHODS

A cross-sectional study was carried out at Aga Khan University in collaboration between the Department of Pediatric Endocrinology, Department of Pediatrics and Child Health, Department of Chemical Pathology, and the Department of Pathology and Laboratory Medicine. The study included retrospective data collected over a one-year period, from December 2021 to November 2022, through the integrated laboratory management system (ILMS) and patient medical records. The population studied consisted of infants aged between one month and one year who were admitted with seizures and diagnosed with hypocalcemia, defined as serum calcium levels below 8 mg/dL (reference range: 8–10.2 mg/dL). Total serum calcium was utilized as the primary marker of physiological calcium status. However, limitations of total calcium measurements in certain conditions, such as hypoalbuminemia, nephrotic syndrome, liver disease, capillary leak syndrome, and protein-losing enteropathies, were acknowledged. Seizures caused by other metabolic derangements, including hyponatremia (serum sodium <135 meq/L) and hypoglycemia (blood glucose <60 mg/dL), were excluded from the study to maintain specificity. Biochemical parameters analyzed included serum calcium, phosphorus, magnesium, alkaline phosphatase, parathyroid hormone (PTH), and vitamin D levels. Normal reference ranges for infants were defined as serum phosphorus between 4–7 mg/dL, serum magnesium between 1.6–2.6 mg/dL, alkaline phosphatase levels of 54–369 IU/L, and PTH levels of 16–87 pg/mL. Vitamin D status was categorized as deficient (<20 ng/mL), insufficient (21–29 ng/mL), sufficient (≥30 ng/mL), or toxic (>150 ng/mL).

Clinical data were reviewed from both electronic and paper-based medical records, encompassing demographic and clinical characteristics such as age, sex, birth order, weight, length-for-age, dietary history (including exclusive breastfeeding, formula feeding, mixed feeding, and milk dilution), sunlight exposure, maternal vitamin D levels, gestational age, and detailed seizure characteristics (type, duration, and frequency). Infants with a history of epilepsy, cerebral palsy, brain tumors or malformations, head trauma, or prior calcium treatment were excluded to avoid confounding factors. The study design adhered to strict ethical guidelines, and approval was granted by the Ethics Review Committee (ERC) of Aga Khan University (approval reference number 2021-5410-14050, dated 07-Nov-2021). Data analysis was performed using SPSS version 26. Descriptive statistics were used to calculate frequencies and percentages

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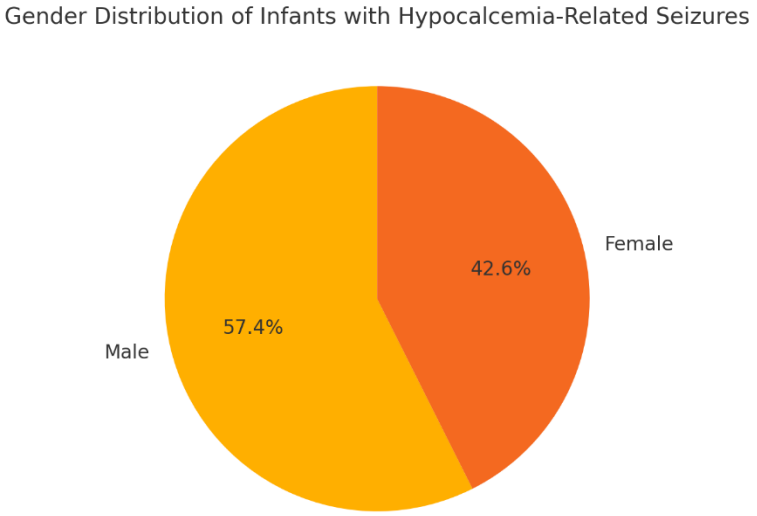
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for categorical variables, while means and standard deviations were computed for continuous variables. Relationships between hypocalcemia and clinical factors, including vitamin D deficiency, hypoparathyroidism, seizure types, and duration, were examined using chi-square tests, with statistical significance set at a p-value of less than 0.05.

RESULTS

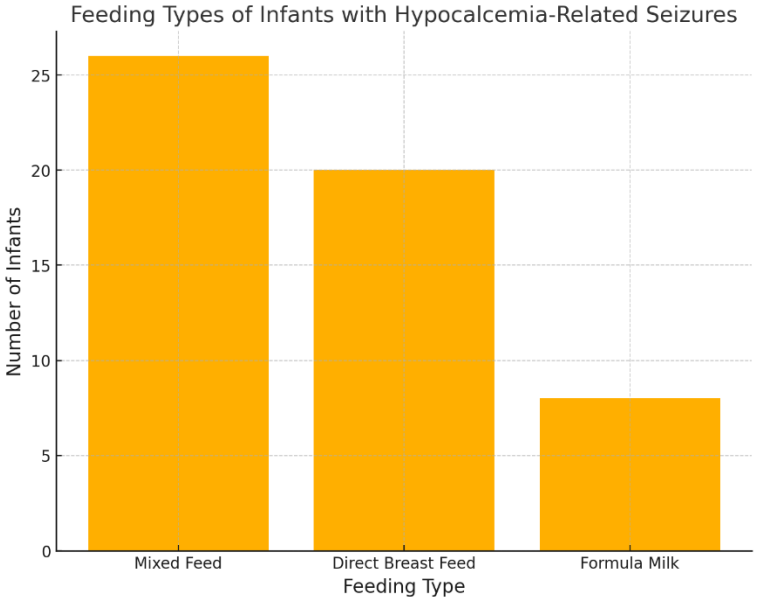
The study analyzed the demographic, clinical, and biochemical characteristics of infants with hypocalcemia-related seizures. Among the 54 infants included, 57.4% were male, and 42.6% were female. The majority of the infants were term (94.4%), with only 5.6% born preterm. Birth order analysis revealed that 50% were second-born, followed by 27.8% third-born and 16.7% fourth-born. Most cases (92.6%) were admitted through the emergency room, with feeding patterns showing mixed feeding (breastfeeding and formula milk) as the most common type (48.1%), followed by exclusive breastfeeding (37%) and formula feeding (14.8%).

Clinical assessment revealed that 51.9% of the infants experienced more than two seizure episodes, with generalized seizures being the most frequent type, accounting for 57.4% of cases. Focal seizures were observed in 25.9%, while 16.7% presented with a combination of generalized and focal seizures. Hypocalcemia was identified as the leading cause of seizures, responsible for 74.1% of cases. Other causes included meningitis or sepsis (13.0%), febrile seizures (11.1%), and inborn metabolic disorders (1.9%). The most common underlying cause of hypocalcemia was vitamin D deficiency (38.9%), followed by sepsis or multisystem failure (37%), malabsorption syndromes (7.4%), hypoparathyroidism (7.4%), and renal tubulopathy (3.7%). Notably, 85.2% of seizures lasted less than five minutes, and maternal vitamin D deficiency was documented in 24.1% of cases, with 53.7% of maternal vitamin D statuses remaining unknown.



Biochemical evaluation showed that 66.7% of infants had serum calcium levels between 5–7 mg/dL at presentation, while 13% had levels below 5 mg/dL. Magnesium levels were within the normal range (1.6–2.6 mg/dL) for 63% of the infants, with the remaining 37% exhibiting low magnesium levels. Phosphorus levels were normal (4–7 mg/dL) in 53.7%, while 37% had low levels, and 9.3% had elevated levels. Sodium levels were normal (>135 meq/L) in 94.4% of the infants, and all had glucose levels above 60 mg/dL, excluding hypoglycemia as a contributing factor.

Parathyroid hormone (PTH) levels showed that 42.6% of infants did not have PTH measured, while 24.1% had inappropriately normal levels, 24.1% had appropriately raised levels, and 9.3% exhibited low levels, consistent with hypoparathyroidism. Vitamin D deficiency (<20 ng/mL) was prevalent in 50% of the infants, and 29.6% lacked vitamin D measurement altogether. The mean serum calcium level was 6.03 ± 1.07 mg/dL, phosphorus was 4.45 ± 1.81 mg/dL, and magnesium was 1.63 ± 0.49 mg/dL. Vitamin D levels averaged 2.57 ± 1.04 ng/mL, and mean PTH levels were 3.02 ± 1.02 pg/mL.



Statistical analysis revealed significant associations between hypocalcemia and vitamin D deficiency (p=0.0001), hypoparathyroidism (p=0.004), seizure duration (p=0.046), maternal vitamin D deficiency (p=0.003), and elevated alkaline phosphatase levels (p=0.005). However, no statistically significant associations were observed for seizure type (p=0.123), feeding type (p=0.210), or PTH levels (p=0.619).

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Table 1: Demographic profile of infants with hypocalcemia-related seizures

Parameter	**Type**	**Frequency (%)**
Gender	Male	**31 (57.4%)**
	Female	**23 (42.6%)**
Gestational Age	Preterm (<37 weeks)	**3 (5.6%)**
	Term (>37 weeks)	**51 (94.4%)**
Birth Order	First born	**2 (3.7%)**
	Second born	**27 (50.0%)**
	Third born	**15 (27.8%)**
	Fourth born	**9 (16.7%)**
	Fifth born	**1 (1.9%)**
Visit Type	ER	**50 (92.6%)**
	Clinic	**4 (7.4%)**
Feeding Type	Direct breast feed	**20 (37.0%)**
	Formula milk	**8 (14.8%)**
	Mixed feed	**26 (48.1%)**

Table 2: Seizure Characteristics and Etiology of Hypocalcemia in Infants

Parameter	**Type**	**Frequency (%)**
Number of Seizure Episodes	<2	**26 (48.1%)**
	>2	**28 (51.9%)**
Seizure types	Generalized	**31 (57.4%)**
	Focal	**14 (25.9%)**
	Both Generalized & Focal	**9 (16.7%)**
Cause of Seizure	Hypocalcemic seizures	**40 (74.1%)**
	Febrile seizures	**6 (11.1%)**
	Meningitis/sepsis	**7 (13.0%)**
	Inborn metabolic disorder	**1(1.9%)**
Cause of Hypocalcemia	Vitamin D deficiency	**21 (38.9%)**
	Hypoparathyroidism	**4 (7.4%)**
	Malabsorption	**4 (7.4%)**
	Sepsis/Multisystem failure/critical illness	**20 (37.0%)**
	Others	**3 (5.6%)**
	Renal tubulopathy	**2 (3.7%)**
Seizure Duration	<5 min	**46 (85.2%)**
	>5 min	**8 (14.8%)**

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Mother's Vitamin D Status	Deficient	**13 (24.1%)**
	Insufficient	**12 (22.2%)**
	Unknown	**29 (53.7%)**

Table 3: Biochemical Parameters of Infants with Hypocalcemia-related Seizures

Parameter	**Type**	**Frequency (%)**
Magnesium Level	<1.6 mg/dl	**20 (37.0%)**
	1.6-2.6 mg/dl	**34 (63.0%)**
Initial Calcium Level	<5 mg/dl	**7 (13.0%)**
	5-7 mg/dl	**36 (66.7%)**
	7-8 mg/dl	**11 (20.4%)**
Sodium	<135 meq/L (Hyponatremia)	**3 (5.6%)**
	>135 meq/L (Normal)	**51 (94.4%)**
Glucose	>60 mg/dl (Normal)	**54 (100%)**
PTH Level	<3 pg/ml	**5 (9.3%)**
	16-87 pg/ml	**12 (22.2%)**
	>87 pg/ml	**14 (25.9%)**
	Not done	**23 (42.6%)**
Phosphorus	<4 mg/dl	**20 (37.0%)**
	4-7 mg/dl	**29 (53.7%)**
	>7 mg/dl	**5 (9.3%)**

Table 4: Parathyroid Hormone (PTH) and Vitamin D Status in Infants with Hypocalcemia- related Seizures

Parameter	**Type**	**Frequency (%)**
PTH	Inappropriately Normal	**13 (24.1%)**
	Appropriately Raised	**13 (24.1%)**
	Low	**5 (9.3%)**
	Not Done	**23 (42.6%)**
Vitamin D Level	Normal	**6 (11.1%)**
	Deficient	**27 (50.0%)**
	Insufficient	**5 (9.3%)**
	Not Done	**16 (29.6%)**
Magnesium	Normal	**34 (63.0%)**
	Low	**20 (37.0%)**

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Table 5: Parameter of electrolytes

Parameter	Mean ± SD
Calcium Level	**6.03 ± 1.07**
Phosphorus Level	**4.45 ± 1.81**
Magnesium Level	**1.63 ± 0.49**
Vitamin D Level	**2.57 ± 1.04**
PTH Level	**3.02 ± 1.02**
Alkaline Phosphatase	**400.0 ± 100.0**
Initial Calcium Level	**2.07 ± 0.58**

Table 6: Association between Clinical and Biochemical Parameters with Hypocalcemia

Parameter	Category	Frequency (%)	p-value
Vitamin D Status	Deficient	19 (38.9%)	**0.0001**
	Insufficient	5 (10.4%)	
	Normal	0 (0%)	
	Not Done	13 (25.9%)	
Hypoparathyroidism	Present	4 (7.4%)	**0.004**
	Absent	33 (61.1%)	
Seizure Type	Generalized	31 (57.4%)	**0.123**
	Focal	14 (25.9%)	
	Both Generalized & Focal	9 (16.7%)	
Seizure Duration	< 5 minutes	46 (85.2%)	**0.046**
	> 5 minutes	8 (14.8%)	
Feeding Type	Direct Breast Feed	20 (37.0%)	**0.210**
	Formula Milk	8 (14.8%)	
	Mixed Feed	26 (48.1%)	
Seizure Episodes	< 2	26 (48.1%)	**0.558**
	> 2	28 (51.9%)	
PTH Level	Inappropriately Normal	13 (24.1%)	**0.619**
	Appropriately Raised	13 (24.1%)	
	Low	5 (9.3%)	
Mother's Vitamin D Status	Deficient	13 (24.1%)	**0.003**
	Insufficient	12 (22.2%)	
	Unknown	29 (53.7%)	
Phosphorus Level	< 4 mg/dl	20 (37.0%)	**0.312**
	4-7 mg/dl	29 (53.7%)	

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	> 7 mg/dl	5 (9.3%)	
Alkaline Phosphatase (ALP)	Elevated	24 (44.4%)	**0.005**
	Normal	10 (18.5%)	
	Low	**20 (37.0%)**	

DISCUSSION

Hypocalcemia-related seizures in infants represent a critical clinical issue with potential long-term neurological and developmental consequences. The underlying etiologies, including vitamin D deficiency, hypoparathyroidism, and critical illnesses such as sepsis, highlight the multifactorial nature of this condition. Biochemical imbalances, particularly low calcium and phosphorus levels, are central to the pathophysiology of hypocalcemic seizures. The findings of this study underscore the necessity for early identification and targeted management of these underlying factors to prevent significant morbidity. The study revealed a higher prevalence of hypocalcemia-related seizures in male infants (57.4%), consistent with findings from previous studies, such as those by Naz et al. and Verma et al., which also reported a predominance of male infants with hypocalcemic seizures. This gender disparity may be attributed to genetic and hormonal factors predisposing male infants to altered calcium homeostasis (12,13). The predominance of term infants (94.4%) in the cohort aligns with observations by Kamat et al., who noted that hypocalcemia frequently affects term infants, particularly those exclusively breastfed. However, contrasting evidence from Rahman et al. highlighted a higher risk of hypocalcemia in preterm infants in other settings, suggesting that the interplay of gestational age, feeding practices, and regional factors warrants further exploration (15,17). Vitamin D deficiency emerged as the most prevalent cause of hypocalcemia in this study (38.9%), reinforcing findings by Kamat et al. and Kumar et al., who also emphasized the critical role of vitamin D in calcium homeostasis among infants (18,19). The association between exclusive breastfeeding and vitamin D deficiency was evident, as most infants in this cohort were either exclusively breastfed or received mixed feeding. This aligns with evidence suggesting that inadequate maternal vitamin D intake or supplementation contributes to infantile hypocalcemia. Maternal vitamin D status was unknown for 53.7% of the cases in this study, reflecting a significant gap in routine screening practices. These findings further underline the need for proactive maternal and infant vitamin D monitoring and supplementation.

Seizure characteristics in this study revealed that generalized seizures were more common (57.4%) than focal seizures (25.9%), with over half of the infants experiencing more than two seizure episodes. These results corroborate findings by Kumar et al., who reported a high frequency of generalized seizures among infants with hypocalcemia. Hypocalcemia was identified as the leading cause of seizures in the cohort (74.1%), followed by conditions such as sepsis and febrile seizures. This aligns with observations by Bande et al., who identified hypocalcemia as a predominant cause of seizures, particularly in infants with vitamin D deficiency (18). Biochemical findings showed that 66.7% of infants had serum calcium levels between 5–7 mg/dL, and 63% had normal magnesium levels, with 37% exhibiting hypomagnesemia. Although the correlation between magnesium levels and hypocalcemia was less pronounced in this study, earlier research by Kamat et al. suggested that magnesium deficiency can exacerbate hypocalcemia in certain clinical contexts. The role of phosphorus levels was notable, with hypophosphatemia observed in 37% of cases, which aligns with findings by Amare et al. on the relationship between phosphorus disturbances and neonatal seizures (15,20). Significant associations between vitamin D deficiency and hypocalcemia ($p=0.0001$) and between hypoparathyroidism and hypocalcemia ($p=0.004$) further validated the biochemical complexity underlying hypocalcemic seizures. The study has several strengths, including a comprehensive assessment of biochemical markers, a well-defined inclusion criterion, and the identification of maternal and infant risk factors. These strengths enhance the reliability of the findings and provide valuable insights for clinical practice. However, the study's limitations include its cross-sectional design, which restricts the ability to infer causality. The reliance on retrospective data from a single tertiary care hospital may limit the generalizability of the results. Furthermore, incomplete documentation of maternal health parameters, particularly vitamin D status, represents a notable limitation that may have introduced bias. This study contributes to the growing body of evidence on the importance of addressing vitamin D deficiency, exclusive breastfeeding without supplementation, and maternal health in preventing hypocalcemia-related seizures. While the findings align with existing literature, further research with larger, multicentric cohorts and prospective designs is needed to address gaps and provide more robust evidence for preventive and therapeutic strategies.

CONCLUSION

This study emphasizes the critical role of hypocalcemia in seizures among infants, highlighting key contributors such as vitamin D deficiency and hypoparathyroidism. The findings underscore the importance of early recognition, targeted nutritional interventions, and routine monitoring of calcium metabolism to mitigate the risk of long-term complications. By identifying underlying factors and addressing maternal and infant nutritional gaps, the study provides a foundation for refining preventive strategies and improving clinical outcomes. These insights contribute to a more comprehensive understanding of hypocalcemia-related seizures, reinforcing the need for further research to optimize care for this vulnerable population.

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Author	Contribution
Muzna Arif	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision Methodology, Investigation, Data Curation, Writing - Review & Editing
Hafsa Majid	Investigation, Data Curation, Formal Analysis, Software Software, Validation, Writing - Original Draft
Khadija Nuzhat Humayun	Formal Analysis, Writing - Review & Editing Writing - Review & Editing, Assistance with Data Curation

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