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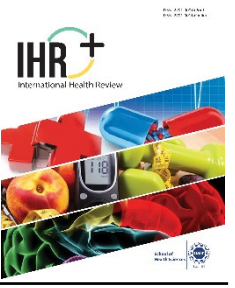

Title:	**Prevalence of Down Syndrome and its Relationship with Maternal Age in Tehsil Kabal, District Swat, Pakistan**
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Prevalence of Down Syndrome and its Relationship with Maternal Age in Tehsil Kabal, District Swat, Pakistan

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ABSTRACT

Down Syndrome (DS) is the most common chromosomal disorder, with a well-established link to advanced maternal age. However, robust epidemiological data on DS is lacking in many regions of Pakistan. This study aimed to determine the prevalence of DS and its association with maternal age in Tehsil Kabal, Pakistan. A community-based cross-sectional survey was conducted from December 2021 to May 2022 across all 14 wards in Tehsil Kabal. Data was collected via door-to-door visits using a structured questionnaire. Verbal informed consent was obtained from all participants. The informed consent was acquired orally since the research was based on a low-risk survey and most of the participants belonged to groups with low signature practices. The project was approved by the faculty and the department that supervised the research. Suspected cases were identified based on standard phenotypic features. Out of an estimated population of 390,000 (excluding children under 4), 114 individuals with DS were identified, yielding a prevalence of 0.03% (approximately 1 in 3,400 live births or 3 per 10,000). A strong association with maternal age was found: 56% of affected children were born to mothers aged 31-40, 29% to mothers aged 21-30, and 15% to mothers aged 41-50. A significant male predominance was observed (78% male vs. 22% female). Nearly, half (47%) of the identified individuals were aged 11-20 years. The prevalence of DS in Tehsil Kabal was observed to be lower than global averages but confirmed maternal age as a significant risk factor. The high male-to-female ratio and low survival into adulthood highlighted potential sociocultural and healthcare factors affecting the DS population in this region, warranting further study.

Keywords: chromosomal disorder, down syndrome (DS), epidemiology, maternal age, Pakistan, prevalence, public health, risk factors, Tehsil Kabal

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1. INTRODUCTION

Down Syndrome (DS) is a common multisystem genetic disorder caused by the presence of all or part of a third copy of chromosome 21 (trisomy 21). Down syndrome or Trisomy 21 is one of the most common chromosomal abnormalities. The majority of full trisomy 21 is caused by chromosomal non-disjunction occurring during maternal meiotic division (90%) [1]. This additional genetic material alters the course of development and results in the characteristic features associated with the syndrome. The condition is characterized by a constellation of clinical manifestations, including distinctive facial features (such as a flat nasal bridge, upward-slanting eyes, and a protruding tongue), intellectual disability of varying degrees, growth delays, and muscular hypotonia. DS is the most commonly identified genetic form of mental retardation as well as the leading cause of specific birth defects and medical conditions [2]. The Etiology of DS was identified in 1959 as the presence of entra-chromosome 2. DS was first described by British physician John Langdon Down in 1866 [3]. According to the World Health Organization (WHO), the global incidence of DS is estimated as 1 out of 600 – 1000 live births. Furthermore, individuals with DS are at a significantly higher risk for numerous congenital anomalies and medical conditions, most notably congenital heart defects, gastrointestinal abnormalities, hearing loss, and autoimmune disorders [4]. As the most prevalent chromosomal cause of intellectual disability, DS presents lifelong medical, developmental, and social challenges, impacting individuals, families, and healthcare systems globally [5].

Since many infectious diseases have been controlled by use of vaccines and antibiotics, congenital anomalies are increasingly playing a significant role in a neonatal mortality and morbidity [6]. The incidence of DS is profoundly influenced by maternal age, with a well-documented exponential increase in risk particularly after the age of 30 [7]. The majority of trisomy 21 cases (~90%) result from meiotic nondisjunction during oogenesis [8]. Consequently, the risk of having a child with DS rises from approximately 1 in 1,500 for a 20-year-old woman to about 1 in 100 by age 40. This relationship has significant implications for public health, especially in regions with shifting demographics in maternal age at conception. In many high-income countries, the trend towards later childbirth has been a key factor in the prevalence of DS, though this is often

moderated by the availability and uptake of prenatal screening and diagnosis [8]. Approximately, (40%) cases are due to chromosomal defects, drugs, chemotherapy, radiation exposure, and cousin marriage [9]. There are three types of DS:

- Trisomy 21: Trisomy 21 is usually caused by an error in cell division called "nondisjunction". Nondisjunction results in an embryo with three copies of chromosome 21 instead of the usual two. Prior to or at conception, a pair of 21st chromosomes in either the sperm or the egg fails to separate. As the embryo develops, the extra chromosome replicates in every cell of the body. This type of DS constitutes for 95% of cases [10].
- Mosaicism: Mosaicism or mosaic DS exists when there is a mixture of two types of cells, some containing the usual 46 chromosomes and some containing 47. Those cells with 47 chromosomes contain an extra chromosome 21. Mosaicism is the least common form of DS. It accounts for only about 1% of all cases of DS. Research indicates that individuals with mosaic DS may have fewer characteristics of DS than those with other types. However, broad generalizations are not possible due to the wide range of abilities that people with DS possess [10].
- Translocation: In translocation, which accounts for about 4% of cases of DS, the total number of chromosomes in the cells remain 46. However, an additional full or partial copy of chromosome 21 attaches to another chromosome, usually chromosome 14. The presence of the extra full or partial chromosome 21 causes the characteristics of DS [10].

Currently, there are more than 300,000 individuals with DS in the United States, up to 10,000 being born each year. DS is responsible for about one third of all cases of moderate to severe mental retardation. The worldwide incidence of DS is approximately 1 in 700 births. Affected males outnumber females at a ratio of 1.3 to 1.0. Approximately, 95% of cases are caused by trisomy 21, whereas the remainder are translocations (usually 14/21) or mosaics. The nondisjunction causing trisomy 21 originates in the egg 95% of the time and in the sperm 5% of the time. Approximately, half of embryos with DS spontaneously abort, a less common occurrence than in other

trisomic conditions. Since nondisjunction is heavily influenced by the effect of maternal age, the risk of a 35- to 39-year-old woman having a child with trisomy 21 is approximately 6.5 times that of a 20- to 24-year-old. This figure climbs to 20.5-fold for mothers between 40 and 44 years of age. Resultantly, whereas mothers in the over-35 age group account for only 7% of all pregnancies, they yield 20% to 25% of prenatal diagnoses of DS. With the increased use of prenatal diagnosis, approximately 40% of foetuses with DS in women aged 35 and older are now being terminated voluntarily. This results in a slightly decreased birth rate of children with DS [11]. Despite being a global health concern, epidemiological data on DS remains scarce in many developed and underdeveloped countries, including Pakistan. Available estimates, such as one from Karachi suggesting a rate of 0.2%, are often isolated and may not be representative of the diverse population across the country's urban and rural landscapes. Cultural factors, such as consanguineous marriages, are presumed to influence the prevalence of congenital disorders but remain under-investigated in the context of DS. Furthermore, a lack of nationwide registries, limited access to prenatal diagnostic services, and a scarcity of population-based studies have resulted in a critical knowledge gap. The specific prevalence and associated risk factors for DS in rural regions of Pakistan, such as Khyber Pakhtunkhwa (KPK), are virtually unknown. Therefore, to address this lack of localized data, the current study was conducted to determine the population-based prevalence of DS and to analyze its correlation with maternal age in Tehsil Kabal, District Swat, Pakistan. The study provided the first epidemiological snapshot of DS in this region, which is essential for informing public health strategies, guiding resource allocation for support services, and raising community awareness. While DS has received significant attention in developed nations, it remains a critically understudied public health issue in many developing economies of Asia. In Pakistan, structured efforts began with the establishment of the Pakistan Down Syndrome Association in 2009 and its subsequent recognition by Down Syndrome International. Despite this fundamental step towards awareness and advocacy, significant gaps persist in the healthcare infrastructure for individuals with DS. Access to specialized medical care, early intervention programs, and inclusive educational resources remains limited, underscoring a pressing need for enhanced public health initiatives and policy development [12].

2. MATERIALS AND METHODS

2.1. Study Area

The current study was conducted in Tehsil Kabal of District Swat from December 2021 to May 2022**.** The study area of this research is illustrated in Figure 1.

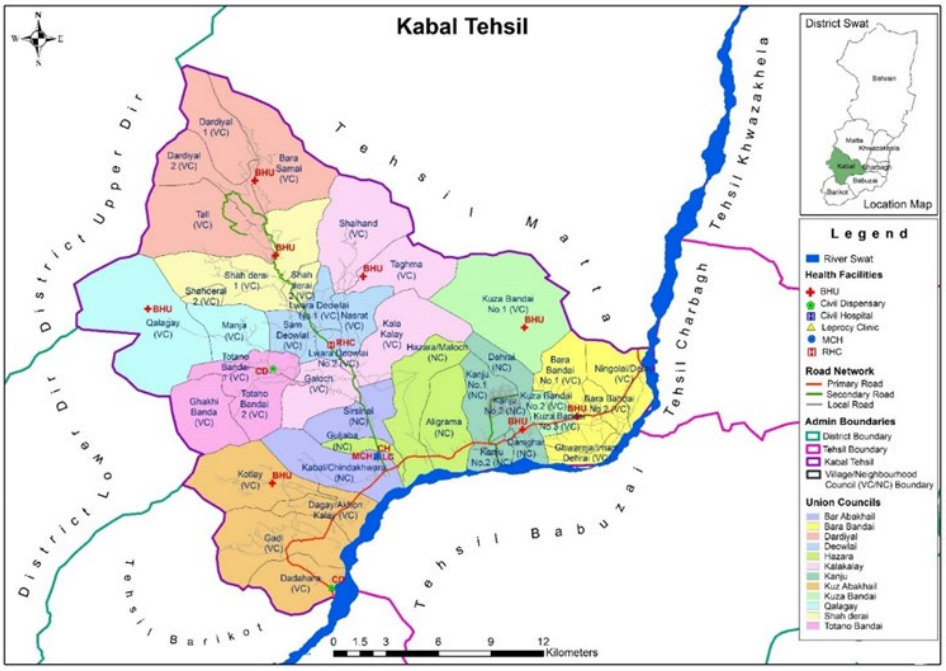

Figure 1. Tehsil Kabal Map (Study Area) Retrieved from DC Office Swat

2.2. Selection Criteria

Data was collected by extensive door to door surveys in all villages of the study area to document actual number of individuals affected with DS. All children above age 4 were included in the study.

2.3. Data Collection

The survey was conducted in Tehsil Kabal so as to identify people with DS. Demographic and clinical data of caregivers was collected with the help of a structured questionnaire. A group of six trained field workers who were already familiar with community surveys, and experts in local language took part in data collection. They were given a short training on the

interview methods and identification of important physical characteristics that relate to DS. The field workers participated voluntarily and were not paid to participate. Since only a questionnaire was used in the study, and no intervention or biological sampling was conducted, it was minimal-risk research. This project was discussed and approved by the supervisory faculty and the Department of Biotechnology, University of Swat. Each caregiver was provided with informed consent verbally before the interview. Questionnaire consisted of four sections:

- The first section dealt with the respondents' demographic data, which included their age, sex, height, and patient address.
- Second section was about family history, parents' age, number of normal and abnormal siblings, blood relation of parents before marriage, and health-related issues of mother.
- Third section was about physical features of the patients. Physical features included short height, round face, almond-shaped eyes, iris spots, small ears, small flat nose, short neck, small hands, small fingers, loose joints, and large sticky tongue.
- Fourth section dealt with mental condition of the patients, such as depression, social withdrawal, dementia, and anxiety.

2.4. Data Analysis

Data was entered and analyzed in the Microsoft Excel [13]. Key variables were summarized using descriptive statistics (counts, percentages, means, standard deviations, and standard errors). Cross tabulations and percentage distributions were used to analyze relationships between variables (e.g., age category of the mother versus age category of number of affected children, sex distribution across age groups, etc.). The results are presented in Tables 1-6 and Figures 2-6. No inferential hypothesis tests were conducted.

3. RESULTS

The findings provided a demographic overview of DS in Tehsil Kabal, Pakistan.

Table 1. Maternal Age and Sex-specific Distribution of Down Syndrome Cases and their Siblings

Mother Age	Sex		Siblings	
	Males	Females	Normal	Abnormal
21-30	28	5	30	3
31-40	47	17	59	5
41-50	14	3	15	2
Mean	29.6	8.33	34.67	3.33
SE	5.52	2.53	7.46	0.51

Among the 114 identified cases, maternal age distribution revealed that most affected children were born to mothers aged 31–40 (n = 64, 56.1%), followed by mothers aged 21–30 (n = 33, 28.9%), and 41–50 (n = 17, 14.9%). A significant male predominance was observed across all maternal age groups, with an overall male-to-female ratio of 3.56:1 (89 males vs. 25 females). Regarding sibling history, most siblings were reported as unaffected, with only 10 siblings across all maternal age groups reported with abnormalities (Table 1).

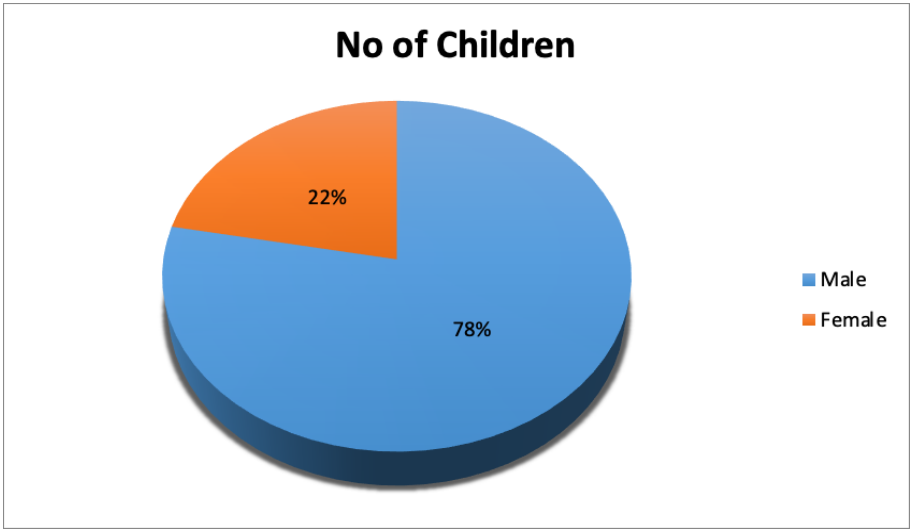

Figure 2. Percentage of Affected Children by Gender

Figure 2 Showing affected male and female children. Total affected male children are 78% and affected female children are 22%.

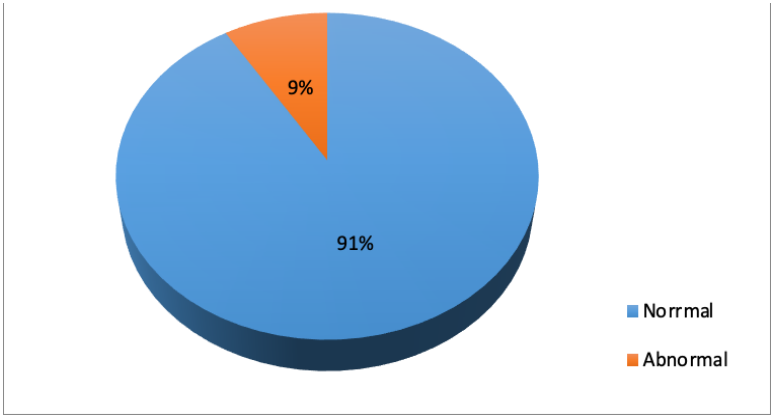

Figure 3. Percentage of Normal and Abnormal Siblings

Percentage of total normal and abnormal siblings of the affected children. 91% siblings were normal and 9% siblings were abnormal.

During the survey, affected children were found in all 14 wards (Ningolai, Kabal, Bara Bandai, Kuza Bandai, Kanju, Hazara, Bar Abakhel, Kuz Abakhel, Kalakalay, Deowlai, Shah Dherai, Dardiyal, Qalagay, Totano Bandai). In 7 wards as shown in Table 2, most of the affected children were found in Kuza Bandai 15 and Kanju 13 due to the reason that these areas are more populous. On the other hand, the lowest affected children were in Ningolai 3 and Kabal 4. Mothers between the ages 31-40 have many affected children.

Table 2. Mother's Age Wise Distribution of Children in Different Areas

Mother Age	Ningolai	Kabal	Bara Bandai	Kuza Bandai	Kanju	Hazara	Bar Abakhel
21-30	0	0	2	1	4	4	1
31-40	2	4	5	11	8	4	4
41-50	1	0	0	3	1	1	2
Mean	1	1.33	2.33	5	4.33	3	2.33
SD	1	2.31	2.52	5.30	3.51	1.73	1.53
SE	0.58	1.33	1.45	3.06	2.03	1	0.89

The distribution of cases was not uniform across the wards. The highest concentrations were identified in the most populous areas, namely Kalakalay with 16 cases and Kuz Abakhel with 14 cases (Table 3), while small number of affected children were in Deowlai 3 and Dardiyal 4, both Deowlai and Dardiyal had a smaller number of populations. There was an average distribution of children with DS in other regions represented in the

table below. Mothers between the ages 41-50 had a smaller number of children affected due to low birth rate in such age.

Table 3. Mother's Age Wise Distribution of Children in Different Areas

Mother Age	Kuz Abakhail	Kala Kalay	Deo wlai	Shah Dherai	Dardi yal	Qala gay	Totano Bandai
21-30	5	2	0	2	2	4	6
31-40	8	9	2	2	1	3	1
41-50	1	5	1	1	1	0	0
Mean	4.67	5.33	1	1.67	1.33	2.33	2.33
SD	3.51	3.51	1	0.58	0.58	2.08	3.21
SE	2.03	2.03	0.58	0.33	0.33	1.20	1.86

In the survey, Kalakalay was home to 16% of all the affected children with DS as shown in the Figure 3.3 below. A total of 15% of the affected children were from Kuza Bandai and 14% were from Kuz Abakhel. These areas had the highest ratio due to a slight increase in population. Deowlai, Dardiyal, and Kabal had 3% of the affected children which is the lowest.

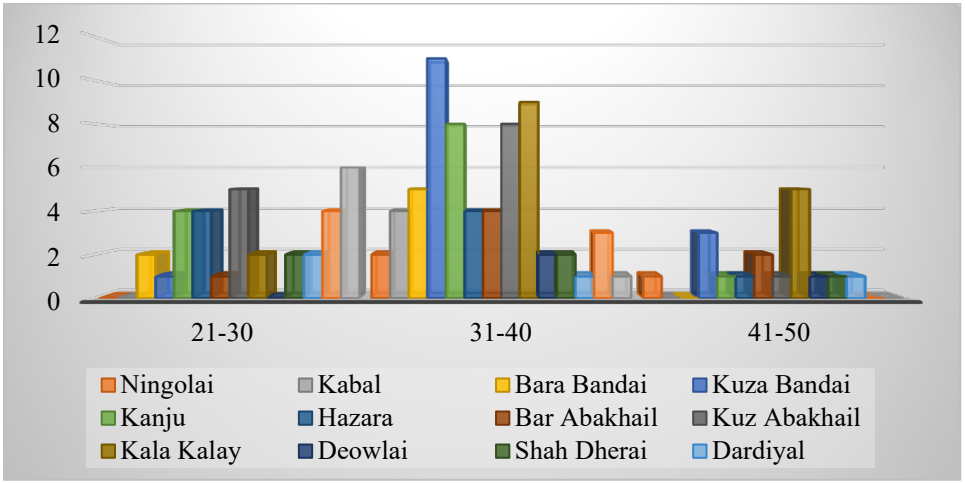

Figure 4. Area Wise Distribution of Affected Children on The Basis of Mother's Age

Three categories of mother's age, that is, 21-30, 31-40, and 41-50. There were 33 affected children having mother age from 21-30, 64 children having mother age in between 31-40, and 17 affected children having mother age in between 41-50. Mother age was divided into categories. Most children affected by DS were from the second category, which was 31–40, due to

the high birth rate at this age. Mother age in between 41-50 had low birth rate due to which data collected in the survey showed less children affected in this age, that is, 15% of all the affected children as shown in Figure 5. Mother age in between 21-30 had 29% children affected overall and 56% of affected children had their mother age in between 31-40.

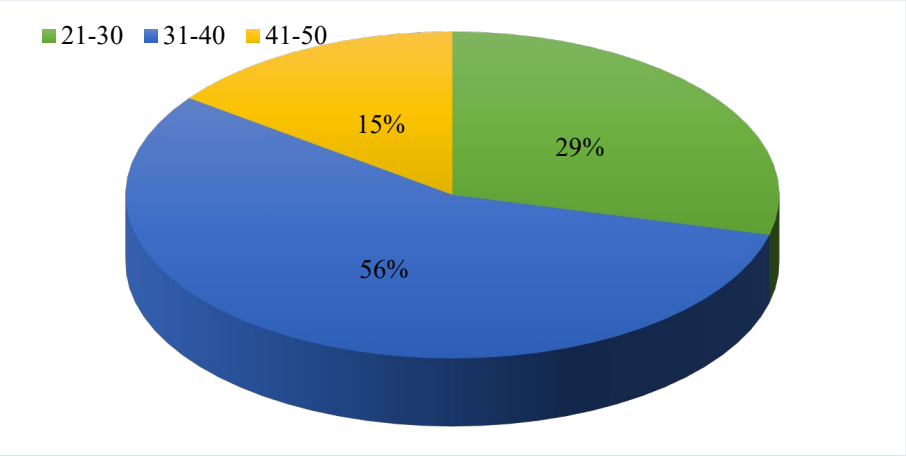

Figure 5. Details of Mother Age Categories and Percentage of Children Affected

During the survey, 4 age categories were found. Lowest age category was 4-10 and high age category was 41-50. Most of the children affected were between the ages 11-20, 54 affected children out of 114 were from this age category. This means that more than half of affected children in Tehsil Kabal were of that age. There were only 2 people out of 114 affected people from last age category, that is, 41-50 as given in Table 4 below.

Table 4. Details of Children and their Age Categories

Child Age	No. of Children
4-10	26
11-20	54
21-30	24
31-40	8
41-50	2
Mean	22.8
SD	20.23
SE	9.05

Affected children of age 11-20 were 47% as shown in Figure 6. During the study, it was found that 70% of all affected children belonged to the age group 4-20 and the remaining 30% had age in between 21 to 50. Out of 30%, 21% affected people's age was in between 21-30, the remaining 9% were in between 31-50.

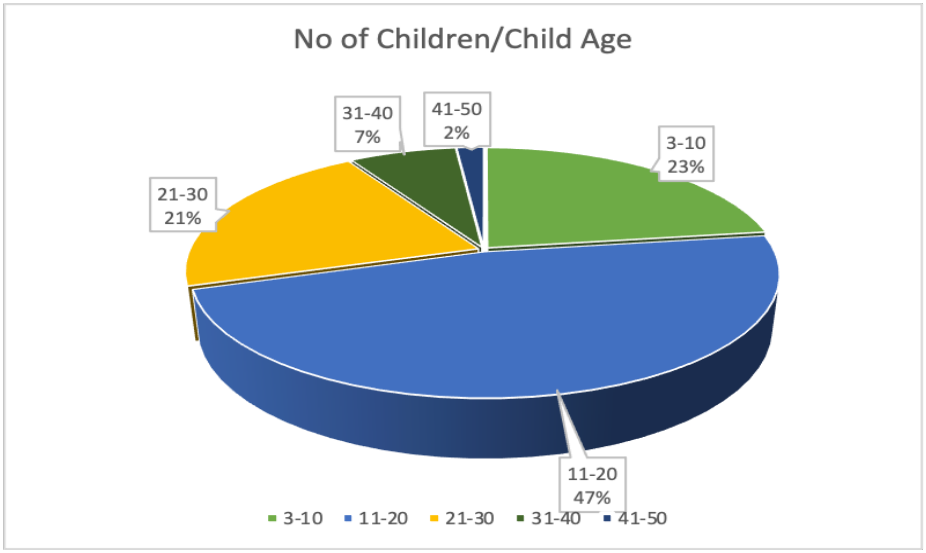

Figure 6. Children's Number Based on Different Age Categories

Approximately, 114 affected people were found in the survey. Out of these 114 people, only 2 were found with age above 40, 1 of them was from Kuz Abakhel and the other was from Bar Aba Khel as shown in Table 5. Studies show low ratio of survival in such age for affected people with DS. Out of all affected female children, 6 were from Kuz Abakhel which is the highest and out of all affected males, 15 were from Kuza Bandai which was the highest.

Table 5. Numbers of Children, Age Categories, Genders, and their Distribution in Different Areas

Area	No. of Children	4-10	11-20	21-30	31-40	41-50	Male	Female
Ningolai	3	0	1	2	0	0	3	0
Kabal	5	0	3	1	1	0	5	0
Bara Bandai	7	3	4	0	0	0	3	4
Kuza Bandai	16	4	8	3	1	0	15	1
Kanju	14	8	5	1	0	0	10	4
Hazara	11	2	8	1	0	0	9	2
Bar Abakhel	7	1	2	1	2	1	6	1

Area	No. of Children	4-10	11-20	21-30	31-40	41-50	Male	Female
Kuz Abakhel	14	3	6	2	2	1	8	6
Kala Kalay	13	0	10	4	0	0	11	2
Deowlai	5	0	2	2	0	0	4	1
Shah Dherai	3	0	2	1	0	0	2	1
Dardiyal	4	0	0	3	1	0	4	0
Qalagay	5	1	3	0	0	0	4	1
Totano Bandai	7	4	0	3	1	0	5	2
Mean	8.14	1.86	3.86	1.71	0.57	0.14	6.36	1.79
SD	4.52	2.35	3.13	1.20	0.76	0.36	3.73	1.76
SE	1.21	0.63	0.84	0.32	0.20	0.10	1.00	0.47

Affected children falling in the age group 4-20 were more than half as shown in the Figure **7**, 76 children out of 114 affected children fell in the age category of 4-20. However, there were no affected children in the age category of Dardiyal where only 4 children were affected with ages between 21-40.

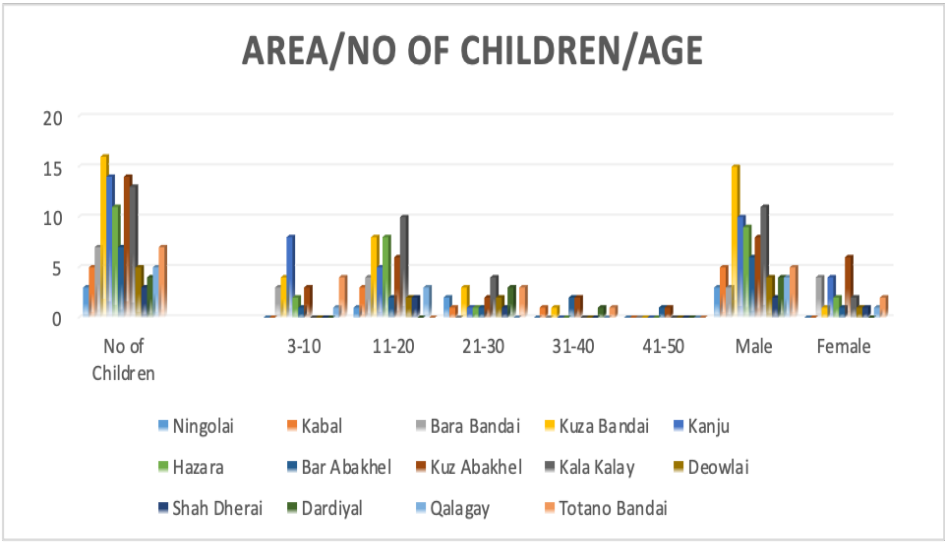

Figure 7. Number of Children, Age Categories of Children, and Area Wise Distribution of Children in Different Wards of Tehsil Kabal

Children in between 4-10 years of age affected were 26 in total out of which 17 were males and 9 were females. Children of age 11-20 were 54 in total out of which 42 were males and 12 were females. People of age falling between 21-30 were 24 in total out of which 21 were males and 3 were females. People of age 31-40 were 8 in total out of which 7 were males and

1 was female, and there were 2 males falling in the age group of 41-50as shown in Table 6.

Table 6. Age Categories, Age Wise Number of Children, Number of Affected Males and Females

Children's Age	No. of Children	Male	Female
4-10	26	17	9
11-20	54	42	12
21-30	24	21	3
31-40	8	7	1
41-50	2	2	0
Mean	22.8	17.8	5
SD	20.23	15.51	5.24
SE	9.05	6.94	2.35

Affected individuals were divided into 4 categories based on their ages as shown in Figure 8. A total of 42 affected male children and 12 affected female children out of 114 belonged to the age category 11-20 which is the highest among all. There was no female patient in age category 41-50 and only 2 males were found in that category.

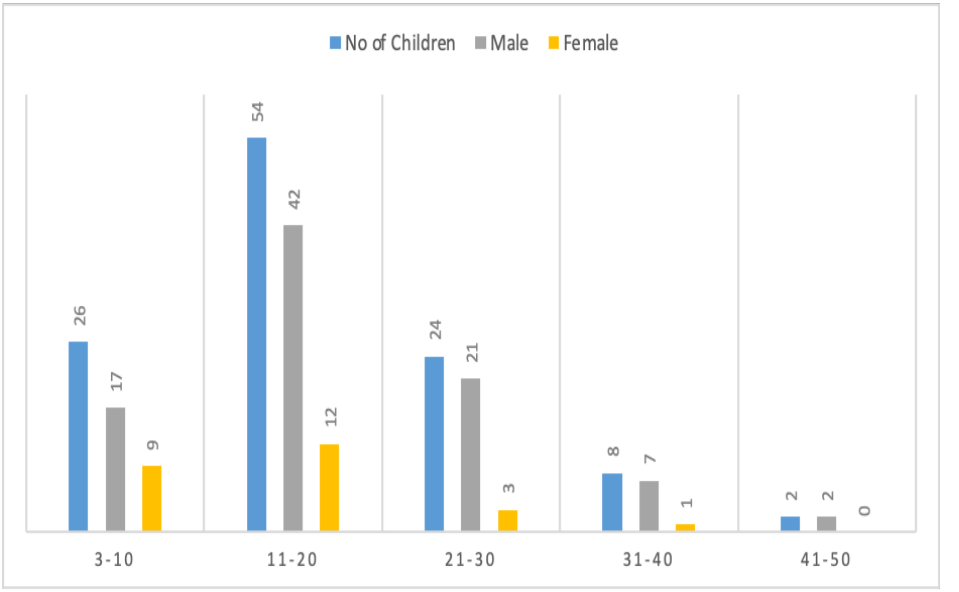

Figure 8. Number of Children (by Gender) in Different Age Categories

During data collection, physical features of the affected individuals were also examined. There were 114 children with DS in the study area. There are many features that can be seen in patients with DS, among many features a few were selected. Round face was the most common physical feature among them, and all of them had round faces. Other features included almond-shaped eyes, tiny spots on the iris of the eyes, small ears, small flat noses, short necks, small hands, small fingers, loose joints, and large sticky tongues. Out of 114 children, 109 had almond-shaped eyes which was the second most common symptom and can be seen in many children with DS. Loose sticky tongue and spots on the iris of eyes were in less children affected with DS. Out of 114, 42 affected children had spots on the iris of their eyes and 43 affected children had large sticky tongues. Other symptoms, such as small hands, small fingers, short necks, small ears, and small flat noses are shown in the Table 7 below.

Table 7. Frequency of Physical Characteristics and Neuropsychological Symptoms Observed in the Study Cohort (*N*=114)

Physical Characteristics	Number (n)	Percentage %	Neuropsychological Symptoms	Number (n)	Percentage %
Almond-shaped Eyes	109	95.6%	Anxiety	100	87.7%
Small Hands	105	92.1%	Abnormal Sleep	78	68.4%
Small Flat Nose	103	90.4%	Dementia	71	62.3%
Small Ears	95	83.3%	Loose Sticky Tongue	43	37.7%
Short Neck	91	79.8%	Social Withdrawal	16	14.0%
Small Fingers	99	86.8%	Other Abnormalities	6	5.3%
Loose Joints	70	61.4%	Depression	4	3.5%
Iris Spots	42	36.8%			

Mental complications were also examined among all 114 patients of DS. Mental problems that were examined in the study included depression, social withdrawal, dementia, and anxiety. Among 114 children, 100 patients had anxiety which was the most common mental problem in patients with DS. Seventy-one children had dementia and 16 children had social withdrawal problem. Four children had depression and 110 were free from this problem. Collected data showed that mental complications were connected to the society and environment around a DS patient. If people,

especially family members treat them well verbally and physically, the chance of having mental problems would be less.

Seventy-eight patients had sleeping problems which was also the most common among the patients of DS. Respondents stated that these children prefer to sleep in the afternoon most of the times. Six children out of 114 were deaf by birth and were also unable to speak.

In the survey, 4 out of 114 affected children had depression as shown in the Figure 9. Out of 114, 109 children had almond-shaped eyes which was the highest among all other symptoms and was the second most common feature of patients with DS found in the current study. The first one was round face found in all affected children, while spots on the iris of the eyes was the least common physical feature of patients with DS who were 42 in the current study.

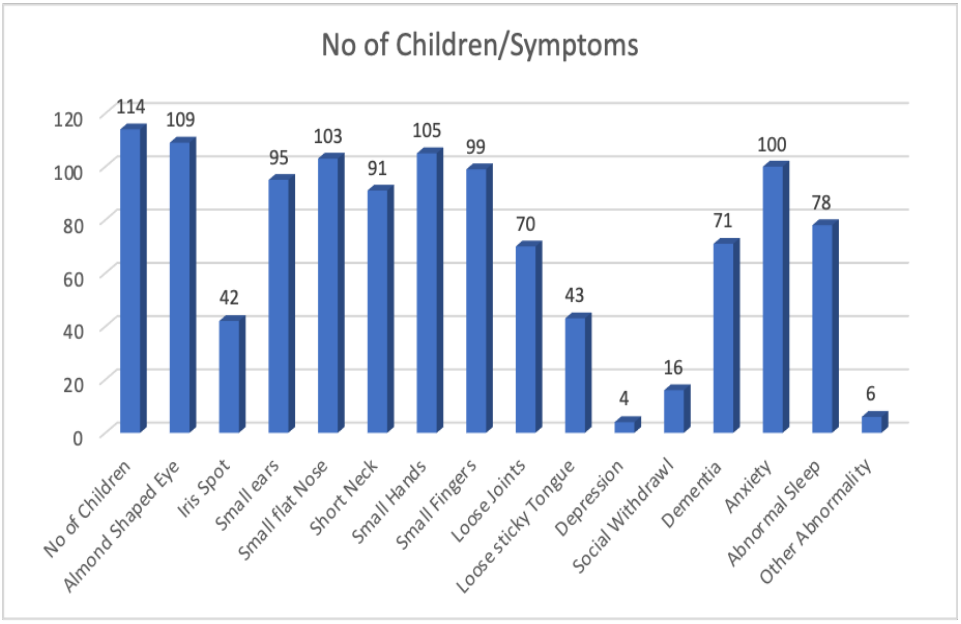

Figure 9. Number of Children and Symptoms

Physical features were present in all affected individuals irrespective of their age, which means that increasing age does not change physical features in patients. A slight difference can be seen in age wise data shown in Table 8. The most common physical feature among the affected individuals of all ages was almond-shaped eyes and less common was loose joints.

Table 8. Details of Age Categories and Symptoms (Physical Features)

Child Age	Almond-shaped Eyes	Iris Spots	Small Ears	Small Flat Noses	Short Necks	Small Hands	Small Fingers	Loose Joints
4-10	23	13	21	25	22	25	24	15
11-20	54	21	48	50	43	50	50	36
21-30	23	6	19	21	17	20	16	13
31-40	7	1	5	6	7	8	7	5
41-50	2	1	2	1	2	2	2	1
Mean	21.8	8.4	19	20.6	18.2	21	19.8	14
SD	20.32	8.59	18.23	19.24	15.96	18.63	18.87	13.56
SE	9.09	3.84	8.15	8.61	7.14	8.33	8.44	6.07

Mental complications, such as social withdrawal, dementia, and depression reduced with the passage of time in patients with DS as shown in Table 9. Social withdrawal and anxiety level slightly reduced with the increasing age which means that adult patients had less mental complications as compared to affected teens and children.

Table 9. Distribution of Physical and Neuropsychological Features among Individuals with Down Syndrome by Age Category

Child Age	Loose sticky Tongue	Depression	Social Withdrawal	Dementia	Anxiety	Abnormal Sleep	Other Abnormality
4-10	5	0	5	16	23	14	1
11-20	24	3	8	36	52	39	4
21-30	10	1	2	14	18	17	0
31-40	3	0	0	4	5	6	1
41-50	1	0	1	1	2	2	0
Mean	8.6	0.8	3.2	14.2	20	15.6	1.2
SD	9.24	1.30	3.27	13.75	19.91	14.40	1.64
SE	4.13	0.58	1.46	6.15	8.91	6.44	0.73

Physical features were present in patients by birth. Therefore, while moving up from low age to high age, no rapid change was observed in the graph as shown in Figure 10. Moreover, mental complications were due to environmental stress mostly. Hence, a rapid change can be seen in different age categories as shown in the figure below.

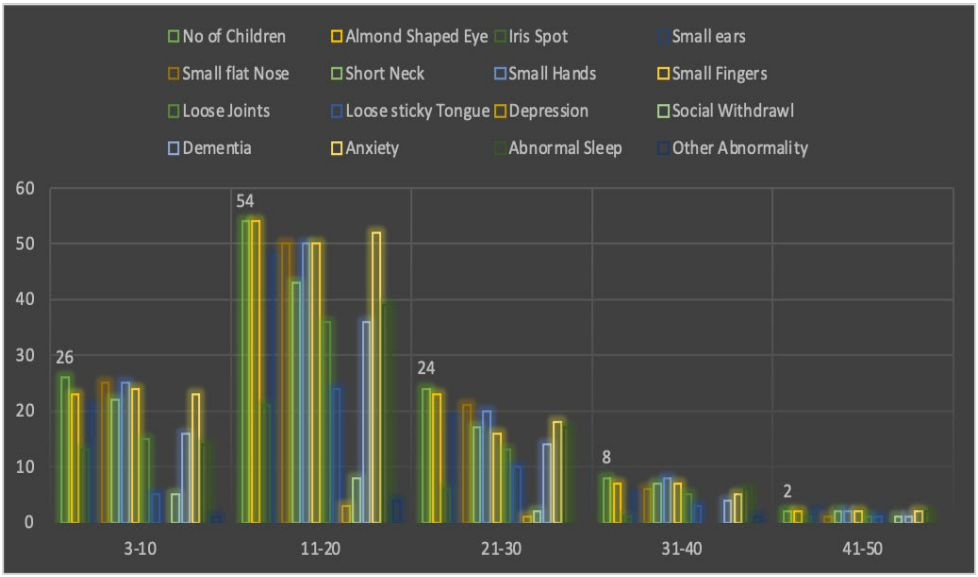

Figure 10. Physical Features (Symptoms), Mental Complications, and Number of Children on the Basis of Different Age Categories

4. DISCUSSION

This population-based study aimed to establish the first epidemiological baseline for DS in Tehsil Kabal, Pakistan, reporting a prevalence of 3 per 10,000 individuals. The findings confirmed the well-documented association between DS and advanced maternal age, with over half (56%) of the affected children born to mothers aged 31-40 [12]. The identified prevalence (3/10,000) was found to be substantially lower than rates reported in high-income countries, such as the United States (8.27/10,000) and the United Kingdom (6.6/10,000).

This discrepancy is unlikely to reflect a true lower biological incidence rather points to critical systemic and societal factors. Potential explanations include:

(1) Under Ascertainment: Limited access to healthcare and diagnostic services in rural areas likely leads to underdiagnosis, especially in females or milder cases.

(2) High Early Mortality: Significantly higher infant and child mortality rates among individuals with DS, due to lack of access to life-saving interventions (e.g., cardiac surgery), would reduce the observed prevalence in a population-based survey.

(3) Cultural and Socioeconomic Factors: Stigma or a lack of awareness may prevent families from seeking a formal diagnosis.

In Pakistan, there is limited data available regarding the prevalence of DS but it has been estimated to be 2 out of 1000 women to have DS in Karachi city [15]. In the current survey, a total of 114 individuals (children, teenagers, and adults) were found to be affected with DS in total estimated population of Tehsil Kabal, which is 0.03% of the total population. From that it is estimated that 1 out of 3400 individuals have DS in Tehsil Kabal which is approximately 3 in per 10,000. This is significantly lower than the average incidence occurring worldwide. In 2015, a total of 111,304 people out of 192,084,414 (0.05%) were affected with DS in Western Europe, 69,760 people out of 103,518,966 (0.06%) were affected in Northern Europe, 96,075 out of 153,064,910 (0.06%) people were affected in Southern Europe, and 139,997 people out of 294,390,745 (0.04%) were affected with DS in Eastern Europe. This shows a little difference, justifying the current study [16].

On January 7th, 2014, the CPRD database's overall prevalence of DS was 6.3 per 10,000 (95% confidence interval [CI]: 6.1; 6.6), or 5.9 per 10,000 [17]. In 2011, there were 6.6 cases of DS for every 10,000 people in England and Wales [18]. In 2008, there were 8.27 cases of DS for every 10,000 people in the United States [19] and the Netherlands had 7.7 per 10,000 in 2010 [20]. This difference is due to some factors, firstly early marriages. The most appropriate age for marriage is 18-25 for females and the risk to have an effected baby is much less. Also, DS rate varied in different regions, as said by Shin [21], these estimates differed by area, race/ethnicity, and gender, suggesting that prevalence may vary.

These results indicated that out of 114 affected people, 89 were males and 25 were females, affected males were 78% and affected females were 22%. In contrast, different results were found in southern Thailand, for instance 226 DS cases were diagnosed, out of 226,121 (53.5%) were males and 105 (47.5%) were females. A particularly striking and unexpected finding was the pronounced male predominance, with a ratio of 3.5:1 (78% male). This contrasts sharply with the near 1:1 ratio or slight male predominance (~1.3:1) typically reported in the global literature [22]. This significant disparity suggests a powerful sociocultural influence. The study posits that a strong cultural preference for sons may lead towards a gender bias in healthcare-seeking behavior, where families are more likely to

pursue evaluation and diagnosis for male children, resulting in the systematic under-identification of females with DS. This represents a critical issue of health equity that warrants urgent further investigation. The observed male-to-female ratio differs from the findings of the present study, which may be attributed to the higher proportion of females in the population of Thailand compared with Pakistan. In Thailand, female population is 51.4% and in Pakistan female population is 48.5%. The difference may also be attributed due to area differences. Geographical location, maternal education, marital status, and Hispanic ethnicity are among the demographic characteristics that influence the probability that a child may be born with Down Syndrome [23].

The distribution of cases aligns with the established biological model of meiotic nondisjunction; the highest proportion of affected children (56%) was born to mothers aged 31-40, the demographic with the highest fertility rates in this region. Notably, the smaller proportion from mothers aged 41-50 (15%) is not indicative of a lower risk but is almost certainly a function of the dramatically lower birth rate in this older maternal age group within the study population. This pattern is consistent with global studies that identify advanced maternal age as the primary risk factor. Mothers' age of affected children was divided in 3 categories, from 21-30, 31-40, and 41-50, and numbers of children were 33, 64, and 17. By percentage, 21-30 were 29%, 31-40 were 56%, and 41-50 were 15%. The mean maternal age category with more children affected with DS was 31-40 (56%). This is because birth rate is high at this age due to which most of the cases are of that age category. Mothers above 35 years of age are at a high risk to have a baby affected with DS which is true for the results. Similarly, results from [24] show that two third of the cases were of mothers of age above 30, and 85 affected children out of 153 had mother age above 30 which is 58% of all, this result is almost same to the results of the current study. Results from [25] show variations in different regions of mother aged 35 and above. This is because it was concluded from the results that Mexican Americans had the highest rate of DS attributable to maternal age of 35 or older, followed by African Americans and non-Hispanic Whites. for a study [26] concluded that Except for Kuwait, the UAE population in Dubai has a greater incidence of DS than the majority of other Arab nations. The average mother age of UAE citizens is 33.48 years old, which is slightly older than Lebanon's median maternal age of 32.19 years but lower than that of Egypt (38.2 years) and Qatar (35.4 years) [27].

The number of mothers in the advanced maternal age group of 35 years in Lebanon is 41.5% and in Qatar is 48.5% [28]. All these results show similarity to the results of the current study despite a slight difference that maybe due to geographical and genetic factors. In the current study, 33 of 114 children (29%) born to mothers aged 21–30 years were affected. Similarly, results from [29] showed that 149 out of 565 affected children had their mothers' age between 21-30 which is 26.4%. Mothers of age 41-50 had 17 affected children out of 114 of total affected children, the percentage of this is 15%. Similar results were obtained in a study conducted by [30] in New York, 70 affected children out of 438 affected children had their mothers' age in between 41-50. The percentage of their results was 15%. Both the results seem to be less than that of the estimated value. However, the reason is that birth rate (in mothers) is low in such age (41-50) in the area where this study was conducted. The results show that out of 114 patients 23% children had ages in between 3-10, while the results of [18] show that the percentage of the affected people of that same age category was 20 in England and Wales. In the current survey, 47% of all the patients had ages in between 11-20 which is the highest, whereas Wu et al. reported 26% in the same age group.

The age distribution within our cohort is highly revealing. The vast majority (70%) of identified individuals were under 20 years, with only two individuals (1.8%) over the age of 40. This stands in stark contrast to the data from developed nations, where improved medical care has extended the average life expectancy for individuals with DS to over 60 years [30]. This stark demographic profile is a potent indicator of a severely reduced life expectancy in this population, directly attributable to a lack of access to essential specialized healthcare, rehabilitative therapies, and inclusive social support systems. Twenty-one percent out of total affected children had their age between 21-30 and 10% affected children's age was in between 31-45. The results from the survey of Wu et al in 2011 in England found that 25% of the affected children had age in between 21-30 and 41% of the affected children had age in between 31-45 which is very high from the results of Tehsil Kabal. The huge difference is due to the health facilities and awareness in England. There are proper treatments, therapies, care, proper diet, and job opportunities for such patients in developed countries as stated by [31]. The average life-span of a DS-affected person is 55 years in developed countries. Unfortunately, in Pakistan and other undeveloped

countries there is no such facilities due to which most of the people affected with DS die early as shown in the current study.

Depression has been frequently reported in individuals affected by DS [32]. Data collected during the survey shows that 4 out of all affected children had depression which is 3.5%. The estimated prevalence of depression in individuals with DS is 1–11% in Denmark, whereas a study from New England reported depression in 10 of 164 patients [33]. Children affected with DS are generally friendly, social, and lively. However, behaviors of the surrounding people affect them easily. Furthermore, due to the abnormal behavior of people around them, they show a significant increase in their internalizing symptoms, especially social withdrawal, anxiety, being more secretive and quiet, and preferring to be alone [34]. Due to this reason, 16 out of 114 children showed social withdrawal and they did not want to be around people, 100 of the children had anxiety.

In the survey, physical features of the children affected with DS were also noted in which almond-shaped eye was the most common with 98% and 86% had small flat noses. On the other hand, spots on the iris of eyes were least common in the affected children, that is, 39% and the prevalence of loose sticky tongue was 40%. There is no data available which shows the percentage of symptoms except for the one by [35] which says that children with DS are born with unique facial features, which can be attributed in part to their abnormal skull structure.

4.1. Limitations

The interpretations of this study must be kept in view considering its limitations. Firstly, diagnosis was based on clinical evaluation rather than genetic karyotyping, the gold standard, which may lead to misclassification. Secondly, the exclusion of children under three years of age likely resulted in an underestimation of the true birth prevalence. Finally, the cross-sectional nature of this study can identify associations but cannot establish causation.

4.2. Conclusion

In conclusion, this study provided crucial initial data on DS in a previously unstudied region of Pakistan. While the biological link with maternal age is reaffirmed, the results illuminate more profound public health challenges: likely underdiagnoses, an alarming gender gap, and a tragically low life expectancy. These findings underscore an urgent need for

actionable strategies aimed at improving access to genetic diagnostic services, specialized medical care, and community-based support systems. Future research must employ cytogenetic confirmation and use qualitative methods to explore the sociocultural barriers to diagnosis and care, particularly for females. Public health initiatives should focus on raising awareness about prenatal care and empowering families of all children with DS.

Author Contribution

Fayaz Khan: conceptualization, methodology, investigation, data curation, supervision, writing - review and editing. **Muhammad Rahiyab:** conceptualization, methodology, investigation, data curation, supervision, writing -review and editing. **Israr Hussain:** investigation, data curation, validation, writing – review & editing. **Awais Ahmad:** investigation, data curation, validation, writing - review and editing. **Shah Faisal Khan:** investigation, data curation, validation. **Rooh Ullah:** investigation, data curation, validation. **Syed Shujait Ali:** methodology, supervision, writing - review and editing. **Arshad Iqbal:** conceptualization, supervision, project administration, writing - review and editing.

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability Statement

Data supporting the findings of this study will be made available by the corresponding author upon request.

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