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# An Epidemiologic Study of Cystic Fibrosis in the Gaza Strip

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**Keywords:** Epidemiologic; Cystic Fibrosis; Mutation; Gaza Strip.

**Abstract**

**Objective:** To determine the distribution, trend, manifestations, prognosis and genetic determinants of cystic fibrosis (CF) diseases in the past ten years (2009-2019) in The Gaza Strip (GS).

**Methods:** Hospital based cross-sectional study and retrospective review of health care facilities records was conducted. This study was performed in all CF cases (150 cases) of five governorates of GS. The study population was one hundred and fifty CF cases, where 71% of them were males. Questionnaire and checklist were the tools of data collection about the personal, socio-demographic, health status of CF patients. In addition, Hemoglobin examination was obtained in all cases. Also Allele-specific PCR technique was employed to study eight CFTR mutation types for subgroup of CF cases (100 CF cases). The records of health care facilities which provide services to CF patients for the past ten years were reviewed retrospectively to determine the number of children who were diagnosed and confirmed as CF.

**Results:** The average age of subjects was 70.6 ± 44 months. About 93.3% of cases were of white colored skin. About one third of the population were from North Gaza, while 34.7% of them were from Gaza City, 22% of them were from Mid-zone, and 11.3% of them from South Governorates. About 88.7% of cases' parents were first and second degree relatives. The results showed that the average of incidence of CF disease during the past ten years was 2.53 cases: 10,000 live births. Also the study showed increase in the prevalence of CF disease through the past ten years in GS, where the average of prevalence was 6.86 cases: 100,000 persons in 2009 and become 7.43 cases: 100,000 persons in 2019. About three quarter of CF cases were diagnosed during infantile period of their lives. Most of CF cases (91%) were diagnosed by both clinical manifestations and sweat tests. The most frequent respiratory manifestations among CF cases were recurrent chest infections, chronic cough with viscid sputum. While the most frequent gastrointestinal manifestations were recurrent gastroenteritis, abdominal colic and flatulence, and malabsorption. Also 86.7% of CF cases were anemic, where the average of hemoglobin

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among CF cases was 9.44 ± 0.52 g/dl. The results of the study showed that the average of mortality rate due to CF among population under 15 years through the last ten years (2009-2019) was 0.52 case: 100,000 persons in population under 15 years. Allele-specific PCR technique was employed to study eight CFTR mutation types for the CF cases among subgroup of CF cases (100 CF cases). The results of mutation testing revealed that 62.5% of known mutation-CF cases have at least single allele of F508. Moreover 12.5% of known mutation-CF cases were of homo 3120+1kb CFTR mutation. Also 14.07% of known mutation-CF cases were of homo N1303k CFTR mutation, homo G85E CFTR mutation, and homo 3120del 18.6kb CFTR mutation equally. According to CFTR mutations about half of CF cases were belonging to class II CF.

**Conclusion:** The incidence and prevalence rates of CF in the GS were around the rates of Caucasian Western Europe populations, where the average prevalence of CF disease through the last ten years in Gaza strip was 7.52 cases per 100,000 population. The average annual mortality rate among those less than 15 years was 0.52 case per 100,000. About two thirds of known mutation of CF cases have at least a single allele of DF508, which is considered of severe type of CFTR mutations. Also half of the cases belong to class II of CF disease (severe form of disease).

**Recommendations:** The main recommendation of the current study was the importance of establishing a reliable diagnosis of CF using a properly conducted sweat test. In addition, diagnostic radiology, and laboratory facilities for sputum culture and pulmonary function tests are important for both the initial diagnosis and the diagnosis of complications.

## Introduction

Cystic Fibrosis (CF) is condidered the most common fatal genetic disease among whites, affects approximately seventy thousands people worldwide [5]. The ainbasic defect in CF cells is the faulty chloride transport, which causes scanty, with hyper viscous secretions and leads to chronic airway obstruction, exocrine pancreatic insufficiency and intestinal malabsorption. Also multi-organs are affected in CF, Respiratory system disorder is the major cause of morbidity and mortality [36]. Chronic respiratory manifestations, bronchiectasis, or clubbing should alert a diagnostic evaluation for CF. The presence of nasal polyps some cases should suggest the possibility of CF [61].

The accurate knowledge of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutations is of obvious interest in clinical testing, where it improves CF prevention programs of neonatal screening, heterozygote screening in parents of CF patients or parents of carriers. Continuous updating the data specifically for each group of populations is also crucial for deeper understanding of CF genetics [14]. CFTR mutations vary in their frequency and distribution in different populations. CF was previously thought to be rare among Arabs, however there are some published data denoting its existence [6,7,21,57,55].

## Materials and method

Hospitals Cross-sectional descriptive study was conducted from December 2018 to December 2019, among all diagnosed cases of CF cases by sweat test in Gaza Strip (150 cases). All participants had to answer a questionnaire about the personal, socio-demographic, health status of CF patients. Response rate was 100% among the mothers of cases. Hemoglobin examination was obtained in all cases in Gaza Cystic Fibrosis Center (GCFC). Allele-specific PCR technique was employed to study eight CFTR mutation types for subgroup of CF cases (100 CF cases) in genetic laboratories of Islamic University Gaza.

The records of health care facilities for the past ten years were reviewed retrospectively to determine the number of children who were diagnosed and confirmed as CF and their outcomes to assess the magnitude, trend and outcome of CF disease in the past ten years (2009-2019).

An official letter of approval to conduct the study was obtained from the Palestinian MOH and Helsinki Committee in the GS. The researcher signed a contract with (CFFC) Laboratory for conducting the sweat tests and analysis of blood samples for CBC. Furthermore, the researcher signed a contract with the Islamic University of Gaza main laboratory for doing the molecular and genotype testing by PCR.

## Results

The study included 150 CF. The percentage of males was 71.3%, while the female 28.7% (Table 1). The average age of cases was 70.60 ± 44 months (Table 1). About ninety three percent of cases were fair colored (Table 1). All the cases were Muslim. Thirty two percent of cases were from North of Gaza governorate, while 34.7% of them were from Gaza City governorate, also 22% of cases were from Mid-Zone governorate, 6% of cases were from Khanyounis governorate, and 5.3% of cases were from Rafah governorate (Table 1). Fifty percent of the cases lived in towns , while 28% of them lived in camps, and 22% lived in villages (Table 1). Thirty four percent of cases citizens, while sixty six percent were refugees. About thirty five percent of cases were living in extended families; while 65.7% of them were living in nuclear families (Table 1). The average crowding index in the homes of cases was 3.20 + 2.01 persons/room (Table 1). The average number of siblings of cases was 4.52 ± 2.89 for cases (Table 1).

Seventy four percent of the cases were born normally, while 25.3% of them were born by cesarean section (Table 1). The average birth weight of cases was 2432 ± 563.74 gm (Table 1). Regarding consanguinity, 11.3% of cases' parents were not consanguineous, while 80% of cases' parents were first degree relatives, and 8.7% of cases' parents were second degree relatives (Table 1). The average age of the fathers of the cases was 37.59 ± 8.09 years, while the average age of mothers of cases was 33.4 ± 7.86 years (Table 1). Regarding occupation of the fathers of the cases 40% of them were unskilled or not working. The majority of mothers of cases were housewives 87.3% (Table 1). It is important to mention that the average family income per month of cases was 1444.50 ± 1258.48 New Israeli Shekel (NIS)/month (Table 1).

**Table 1:** Summary characteristics of cystic fibrosis cases patients (Gaza, 2019).

| Characteristics | Cases | |
|---|---|---|
| | N0. | Value |
| Gender | | |
| Male | 107 | 71.3% |
| Female | 43 | 28.7% |
| Child Age (months) | 150 | 70.6 |
| Skin Color | | |
| Fair | 140 | 93.3% |
| Dark | 10 | 6.7% |
| Type of Delivery | | |
| NVD | 111 | 74% |
| CS | 38 | 25.3% |
| Other methods | 1 | 0.7% |
| Birth Weight (gm) | 150 | 2432 |
| Socio-Economic Variables | | |
| Governorate of residence | | |
| North Gaza | 48 | 32% |
| Gaza City | 52 | 34.7% |
| Mid-Zone | 33 | 22% |
| Khan-Younis | 9 | 6% |
| Rafah | 8 | 5.3% |
| Area of residence | | |
| Town | 75 | 50% |
| Camp | 42 | 28% |
| Village | 33 | 22% |
| Extended family | 53 | 35.3% |
| Crowding index (person/room) | 150 | 3.20 |
| Sibling number | 150 | 4.52 |
| Consanguinity | 133 | 88.7% |
| Paternal age (years) | 150 | 37.59 |
| Maternal age (years) | 150 | 33.41 |
| Paternal education (years) | 150 | 9.78 |
| Maternal education (years) | 150 | 9.76 |
| Paternal occupation (yes) | 90 | 60% |
| Maternal occupation (yes) | 19 | 12.7% |
| Family income (NIS/month) | 150 | 1444.5 |
| Paternal smoking (yes) | 71 | 47.3% |
| Maternal smoking (yes) | 30 | 20% |
| socioeconomic problems (yes) | 135 | 90% |

The average of incidence rate of CF disease through the last ten years (2009-2019) in the Gaza strip was 2.53 case: 10000 live births, where the highest incidence rate was in 2016 (3.18 case: 10000 live births), while the lowest incidence rate was in 2009 (1.49 case: 10000 live births) as shown in Figure 1. The average of new diagnosed cases through the last ten years (2009-2019) was approximately 14 cases/year, where the most frequency was in 2011 (24 new diagnosed cases), while the least frequency was in 2017 (5 new diagnosed cases). The average of prevalence of CF disease through the last ten years in Gaza strip was 7.52 cases: 100000 persons in population, where the highest prevalence was in 2018 (7.95 cases: 100000 persons), while the lowest prevalence was in 2009 (6.86 cases: 100000 persons) as shown in Figure 2. The highest frequency of accumulated CF disease cases was in 2018 (156 cases), while the lowest frequency was in 2009 (102 cases).

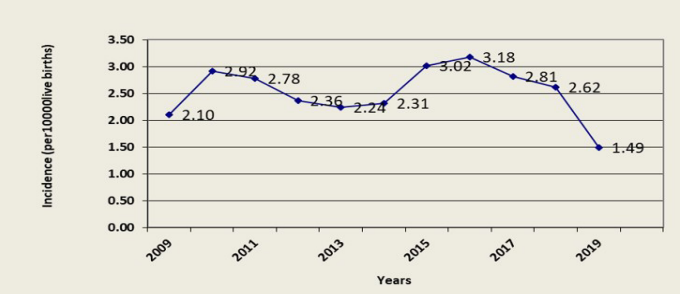


**Figure 1:** Incidence rates of Cystic Fibrosis disease (Gaza, 2009-2019).

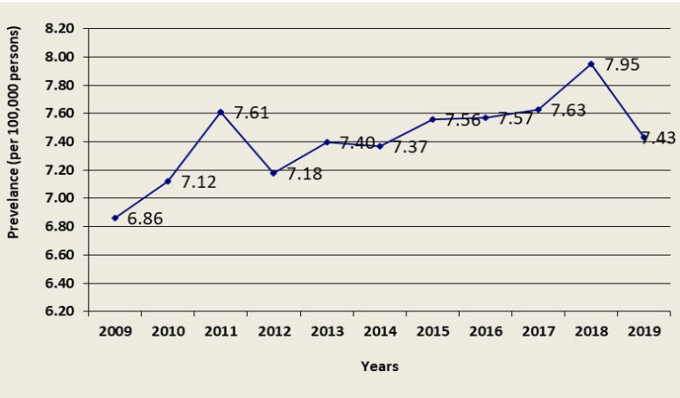


**Figure 2:** Prevalence rates of Cystic Fibrosis disease (Gaza,2009-2019).

The average age of cases at diagnosis of CF disease was 6.05 ± 4.57 months, where only 23% of cases were diagnosed at neonatal period and 74% cases were diagnosed during infantile age, while only 3% of them were diagnosed after the first year of age as illustrated in Figure 3. It is important to mention that 44% of cases were admitted the neonatal intensive care unit (NICU) as shown in Figure 4. The average day of admission in NICU for cases was approximately 5 ± 7.28 days. The results showed that 81% of cases are diagnosed as CF patients in Governmental pediatric hospitals in Gaza Strip, where 13% of them are diagnosed outside Palestinian health institutions and only 6% of them are diagnosed in Non-Governmental Palestinian health Organizations. Most of cases were diagnosed by both manifestations and sweat test (91%), while 6% of them were diagnosed by manifestations, sweat test and genetic study, and 3% of them were diagnosed by manifestations only as shown in Figure 5.

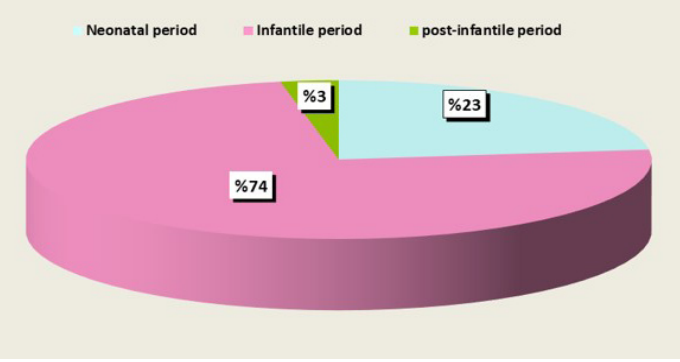


**Figure 3:** Distribution of CF cases by age period of cases at diagnosis of disease (Gaza, 2000-2019).

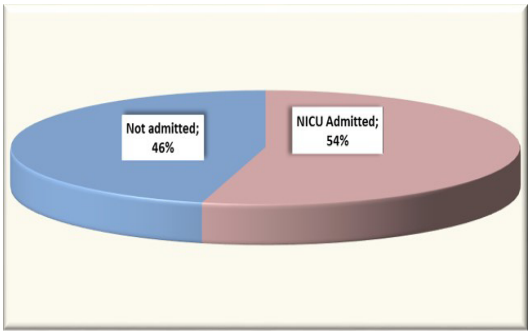


**Figure 4:** Distribution of CF cases by admission to NICU department (Gaza, 2009-2019).

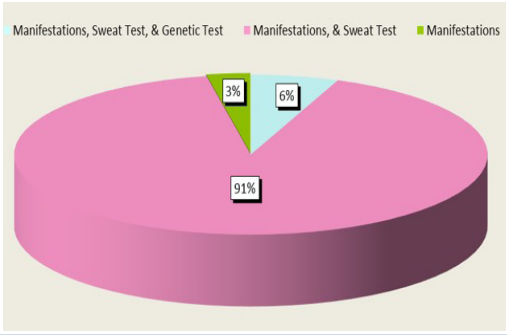


**Figure 5:** Distribution of CF cases by tools ofof diagnosis of disease(Gaza, 2009-2019).

Regarding the health problems and manifestations associated with CF disease, only 3% of CF cases complained of other chronic diseases rather than CF disease. It was clear that respiratory system was the most system affected by CF disease, where 49% of CF cases confirmed that the respiratory system was affected by CF disease, 55% of the cases reported that both gastrointestinal and respiratory systems were affected, while 8% of them showed that multisystem were affected. According to respiratory system manifestations; 96 CF cases were complaining of recurrent chest infection, also 90% of cases have history of permanent cough, 79% of them complained of chronic dyspnea, 88% had viscid sputum, 53% were complaining of cyanosis and 41% had history of recurrent sinusitis as shown in Figure 6. According to gastrointestinal manifestations; 56% of cases were complaining of recurrent gastroenteritis, 36% of them had history chronic diarrhea, 38% had history of steatorrhea, while 12% were complaining of chronic constipation and 49% were complaining of recurrent attacks of abdominal colic and flatulence and 45% were complaining of malabsorption as demonstrated in Figure 7. The percentage of anemia among them was 86.7%, where the average of hemoglobin among CF cases was 9.44 ± 0.52 g/dl as shown in table 2. Also the results revealed that all cases were admitted to hospital recurrently, where the average of admission times was 4.61 ± 1.23 times/year among cases as shown in table 2.

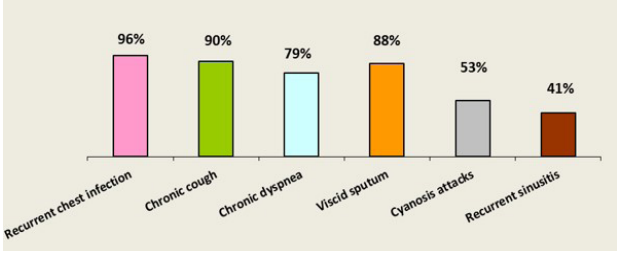


**Figure 6:** Distribution of CF cases by respiratory manifestations (Gaza, 2019).

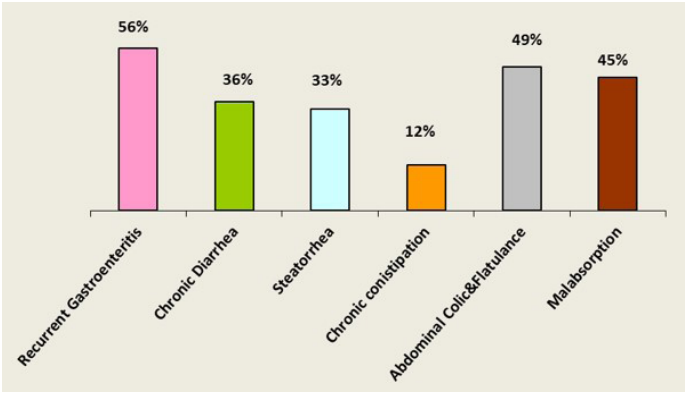


**Figure 7:** Distribution of CF cases by Gastrointestinal manifestations (Gaza, 2019).

**Table 2:** Averages of Hemoglobin level and Hospitalization and distribution of CF cases according anemia (Gaza, 2019).

| Variable | CF Cases | | |
|---|---|---|---|
| | No | Average or % | S.D |
| Hemoglobin level (g/dl) | 150 | 9.44 | 0.52 |
| Anemia | | | |
| Yes | 130 | 86.7% | - |
| No | 20 | 13.2% | - |
| Hospitalization (times/year) | 150 | 4.61 | 1.23 |

The results of the study revealed that the average of mortality rate due to CF among population under 15 years through the last ten years (2009-2019) was 0.52 case: 100,000 persons in population under 15 years, where the highest mortality rate due to CF among this age group was in 2012 (0.76 case: 100,000 persons in population under 15 years), while the lowest mortality rate among this age group was in 2017 (0.13 case: 100,000 persons in population under 15 years) as shown in Figure 8. Also Figure 9 revealed the linear trend of mortality rates of CF through the last ten years. There was no significant difference in the trend of mortality through the last ten years in the GS (X2= 0.142, P = 0.706). But there was a variation in the case fatality rate of CF through the last ten years (2009-2019). The highest case fatality rate was 15.63% in 2013, while the lowest rate was 2.06% in 2009 (Figure 10).

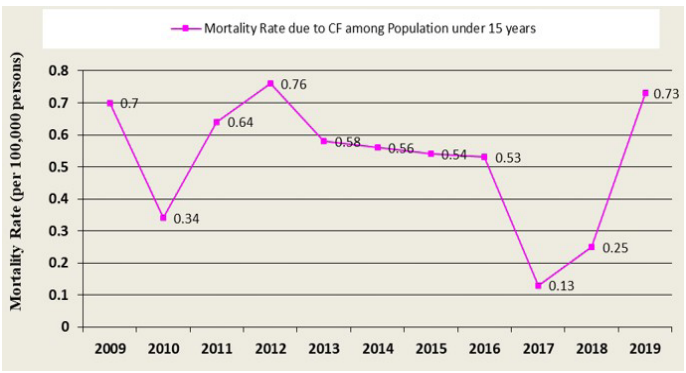


**Figure 8:** Mortality rates of Cystic Fibrosis disease (Gaza,2009-2019).

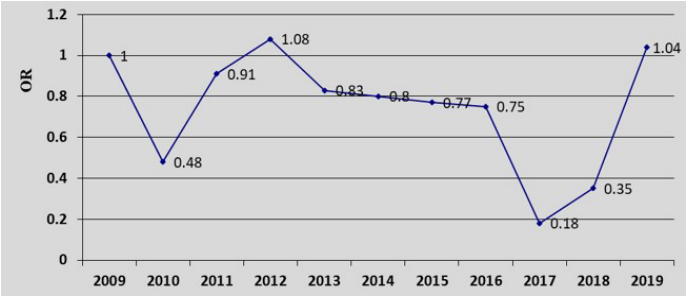


**Figure 9:** Linear trend of mortality rates of cystic fibrosis disease (Gaza, 2009- 2019).

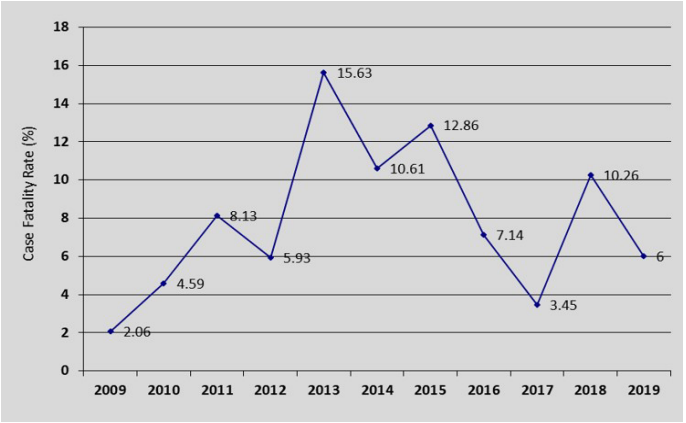


**Figure 10:** Case fatality rates of cystic fibrosis disease (Gaza, 2009- 2019).

Studying the survival of CF cases in the years 2009 – 2019, Figure 11 shows that the probability of survival decreased from 0.944 in 2009 to 0.166 in 2019 with a five years survival of 0.361.

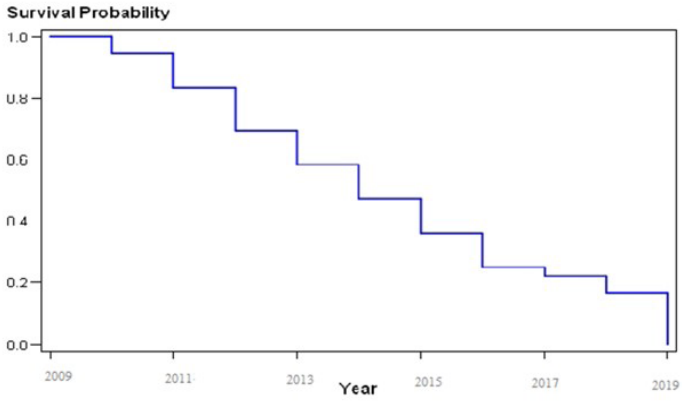


**Figure 11:** Survival probability of cystic fibrosis cases (Gaza, 2009- 2019).

The study showed that only 24% of CF cases' parents had conducted genetic counseling to determine the CFTR mutation type. In this study, subgroup of 100 CF cases were underwent for genetic testing of eight types of CFTR mutations (F508, 3120+1kb, N1303k, G85E, 1717+1GA, G542X, W1282X, and 1209G-A). The results of genetic mutation testing identified the type of CFTR mutation for 64 CF cases from the 100 cases (64.00%).

About 37.5% of known mutation-CF cases were of homo F508 CFTR mutation. It is important to mention that 62.5% of known mutation-CF cases have at least single allele of F508. This means that about one quarter of known mutation-CF cases were of hetero F508 CFTR mutation, nearly 68.75% of them were of unknown mutation on the other allele, while 31.25 of them were of G542X mutation or W1282X mutation on the other allele. Moreover 12.5% of known mutation-CF cases were of homo 3120+1kb CFTR mutation. Also 14.07% of known mutation-CF cases were of homo N1303k CFTR mutation, homo G85E CFTR mutation, and homo 3120del 18.6kb CFTR mutation equally. In addition 3.12% of known mutation-CF cases were of homo 1717+1GA CFTR mutation and homo 1209G-A CFTR mutation equally. On other hand 7.81% of known mutation-CF cases were of G542X CFTR mutation, this means that 7.81% of them have single allele of G542X at least, where 60% of hetero G542X CFTR mutation cases have F508 on the other allele, while 40% of them were of unknown mutation on the other allele. Also 7.81% of known mutation-CF cases were of hetero W1282X CFTR mutation, where 40% of them have F508 CFTR mutation on the other allele, while 60% of them were of unknown CFTR mutation on the other allele as shown in Table 3.

According to CFTR mutation types among known mutation-CF cases, 46.88% of them belong to class II, 17.19% belong to class V, 1.56% belong to class I, also 1.56% belong to class IV, and 32.81% were still of unknown class because they are of compound CFTR mutations as illustrated in Table 4.

**Table 3:** Distribution of CF cases by CFTR mutations (Gaza, 2009-2019).

| CFTR Mutations | CF Cases | |
|---|---|---|
| | No | % |
| HomoF508 | 24 | 37.50 |
| Homo3120+1kb | 8 | 12.50 |
| Homo N1303K | 3 | 4.69 |
| Homo G85E | 3 | 4.69 |
| Homo3120del18.6kb | 3 | 4.69 |
| Homo1717+1GA | 1 | 1.56 |
| Homo 1209G-A | 1 | 1.56 |
| Hetero F508/G542X | 3 | 4.69 |
| HeteroF508/W1282X | 2 | 3.13 |
| HeteroF508/Unknown | 11 | 17.17 |
| Hetero G542X/Unknown | 2 | 3.13 |
| HeteroW1282X/Unknown | 3 | 4.69 |
| Total | 64 | 100 |

**Table 4:** Distribution of CF cases by CF disease Classes (Gaza, 20009-019).

| CF disease Classes | CF Cases | |
|---|---|---|
| | No | % |
| **Class I** | 1 | 1.56 |
| **Class II** | 30 | 46.88 |
| **Class III** | 0 | 0.00 |
| **Class IV** | 1 | 1.56 |
| **Class V** | 11 | 17.19 |
| **Compound** | 21 | 32.81 |
| **Total** | 64 | 100 |

## Discussion

The researcher continue to explore the distribution, trend, manifestations, prognosis and genetic determinants of cystic fibrosis (CF) diseases in the past ten years (2009-2019) in The Gaza strip (GS). The study revealed the magnitude and the trend of CF in the GS by showing the incidence, prevalence, and mortality through the last ten years (2009 to 2019).

According to the results of present study, CF disease was associated significantly with male gender, white skin color, outside Gaza governorate and consanguinity. It was observed that that more than two third of CF children were male, the majority (93.3%) of CF children were of fair skin color, about 89% of them had consanguineous parents, and about one third of them were from North Gaza governorate.

The prominence of male gender is consistent with some of literature review about CF [6,7,32,31], Some other studies showed that CF occurs equally in male and female and that female CF have significantly poorer prognosis than male CF and earlier mortality [11,13,62,49] that explains the prominence of male cases with increasing age.

Regarding the skin color, although CF occurs in all races, it is most common in white people of northern European ancestry [43]. This fact is compatible with the results of current study, where most of CF children were fair. Also one third of cases were from North Gaza governorate and the other third from Gaza governorate and most of CF children in North Gaza governorate were from Jabalia. It is worth mentioning that the Roman historian Zmanus mentioned that the Romans in the late fourth century AD set up on the part of Jabalia territory Azalea village, where the Roman set up 31 cities and 442 villages in historical Palestine, but when the Roman era had been finished and the Palestinians entered early in Islam, its residents expressed Arabic language with connection with the Arab tribes from Arabian peninsula and Egyptian people [48]. This historical fact is mentioned to confirm that there is European ancestry in Palestinian population especially Italian. Cystic Fibrosis is an inherited disease, where the ancestry had effect on genetic expression among generations. It is also important to mention that most of Jabalia populations in North Governorate in Gaza Strip are blond and fair like European populations. On the other hand it is observed that incidence of CF among Italian population (1: 4700 live births) [22] was approximately around the incidence of CF in the GS (1:3953). Moreover the CFTR mutations types of CF children in the GS were similar for the most common CFTR mutations among Italian newborns, where fifteen different mutations were detected in analysis of 31 CFTR mutations by polymerase chain reaction/oligonucleotide ligation assay in a pilot screening of 4476 Italian newborns for CF, the most common being DF508, which accounted for more than half of the total. Other mutations found with greater than normal frequency were G542X, which are particularly common in southern Italy, N1303K, and R117H, which was detected only in the northern centre [24]. Also it is important to note that the Gaza City governorate are a variety of different races including the philistines, Greeks, Romans, Canaanites, Phoenicians, Jews, and the Pharaohs, the Persians and the Bedouin [17].

Consanguinity, particularly between close relatives, is known to increase the risk of recessively inherited diseases and multifactorial disorders; but the effects of inbreeding on the prevalence and type of autosomal recessive diseases in a community are complex and difficult to quantify [35]. Many different factors are involved: the degree of consanguinity of the parents; the number of generations over which inbreeding has been practiced; whether the genetic abnormality alters biological fitness and the mutation rate of the genetic abnormality [25]. The current study (88.7%). This rate was compatible with the rates of consanguineous marriages among parents of blind cases in the GS (89.5%) (281). Also this finding is compatible with multiple studies about CF in Arab countries where consanguinity and family history of CF was recorded in high percentage 70-80% [1,2,6,7,32].

Maternal smoking and suffering from problems especially psycho-social problems during pregnancy were significantly associated with occurrence of CF disease occurrence in the present study. Maternal exposure to tobacco smoke is known to have deleterious effects on the developing fetus, but it has only recently been shown that there may be life-long consequences due to genotoxic damage. Analysis of newborn cord bloods with the somatic mutation assay demonstrates a significant effect of maternal active smoking and suggests that similar mutational induction occurs in mothers who experience only secondary exposure to environmental tobacco smoke (ETS) [58]. Despite the risks, many women still smoke during pregnancy; 17% in England and Wales [45] and 14% in the USA [60]. Also it was found that percentage of smoker mothers of CF children was 20% in the present study. This high percentage of smoking among mothers of CF children could be attributed to the psychosocial problems which the mothers suffering from during and after pregnancy, where 90 % of mothers of CF children in the GS were suffering from psychosocial problems. Those problems and stress include the daily general irritants of life, and particularly those specific to parenting, those associated with major life events, and disease specific stresses which are due to living with the child's chronic illness and are experienced in proportion to the degree of the child's illness [47].

According the present study, the health professionals should take in their consideration the previous socio-demographic factors for recurrent chest infection, chronic gastrointestinal disorders, malabsorption, and failure to thrive, to predict the CF cases. Those factors can be summarized as: male gender, white skin color of consanguineous parents and maternal smoking and suffering from psycho-social problems during pregnancy.

It has been found that the birth incidence of CF disease in the GS was not low in comparison with neighboring and Arab countries, where the average annual incidence of CF through the last ten years (2009-2019) in the GS was 2.53 cases per 10,000 live births (i.e. 1 case: 3952) with the average of new diagnosed cases was approximately 14 cases annually. In Addition the average prevalence of CF in the GS in the same period was 7.52 cases per 100000 population with the accumulated cases in 2019 (150 cases).

It is observed by reviewing the studies conducted in Arab countries to identify the incidence and prevalence of CF in their countries there is a consensus between the results of the current study and other Arab studies such as; Al Arrayed and Abdulla study in 1996 [1] and Al-Mahroos study in 1998 in Bahrain [2], Kakish study in Jordan in 2001 [32]. Nazer study in Saudi Arabia in 1989 [44] Rajab study in Oman in 2005 [50] and Maggie study in Egypt in 2007 [38] ,where the conclusion was that CF disease in general is not rare in Arab countries. This conclusion was documented by [66] which found that CF mutations are not rare among Arabs living in Israel [66]. So that there is need further studies to explore its actual magnitude, and the pattern. In addition Estivill et al. (1997) indicated that the point mutations that were found in Israeli Arabs (Palestinian population) and in Middle East countries, were found in European populations and share common haplotypes, an indication of a common ancestral origin [20].

Regarding the prevalence rate of CF, there was similarity between Canada and GS in the prevalence rate, where the prev-

alence rate according to Report of the Canadian Patient Data Registry 2002 [10]. This rate could be considered high in comparison with some Arab countries such as Bahrain where the prevalence rate according to Al-Mahroos (1998) study was 3 cases per 100,000 population [2] the increased prevalence rate in the GS through the last ten years could be justified by multiple reasons such as continuous progression in medical care and increasing awareness about CF among health care professionals. This leads to increase in the rate of diagnosis of new cases and decrease in the mortality rates.

The results of the present study revealed that about 98% of cases were diagnosed during infancy, where 26% of them were diagnosed during neonatal period. Thus the average age of cases at diagnosis of CF was about 6 months. This is consistent with many Arab studies which showed that all CF patients were diagnosed within the first year of life, where Al arrayed and Abdulla study showed that 60% of Bahraini CF patients were diagnosed by three months of age [1], also Al-Mahroos study documented that the mean age at diagnosis was two months [2]. But Banjar and Mogarri study reported the mean age at diagnosis of 84 during 12 year period was 33 months [4,6,7]. Also Nazer et al study showed that duration of symptoms prior to diagnosis varied from 1 month to 5 years with mean 23 months among Saudi CF patients [44] Eskandarani (2002) concluded that severe form of the disease was presented in 19 Bahraini children with CF at an early age [19].

In the United States, 70% of all CF patients were diagnosed before their first birthday [23] and 90% before their eighth birthday. The proportion diagnosed before one year was similar, although slightly lower in series from New Zealand (61%) [63] , and Ireland (55%) [42], although the latter patients were adolescents and adults. In the UK, the median age at diagnosis since 2001 has been 4-5 months; and of all newly diagnosed children in 2003, 64% were diagnosed under the age of one year [41,40]. However, late diagnosis continues to be made, with occasional cases being diagnosed as late as the seventh decade of life. In the UK, 12% of newly diagnosed patients in 2003 were over 16 years of age [41,40]. patients late diagnosed represent the mild end of clinical spectrum presented by CF. This has very important implications when considering studies looking at the long-term benefits of neonatal screening for CF.

It is clear that the CF cases in the GS were of severe form and the diagnosis was early in comparison with other CF cases in different regions in the world. Also this fact should not cancel the hypothesis that there could be mild form of CF but not diagnosed early during childhood. On the other hand there could be severe form of CF cases who died early without correct diagnosis in the GS. So it is important to implicate the neonatal screening for CF in the GS to guarantee the early diagnosis of CF cases to ensure mild outcomes of CF disease among CF cases. This is consistent with the results of study which described the clinical features of CF disease. The results of current study revealed that all cases were admitted to hospital recurrently (average of admission was 4.6 times/year). In addition about half of CF cases were admitted to NICU with average 5 days of admission in NICU after birth. The previous results and facts reflect a low index of suspicion for the CF disease among Palestinians even in Western and other countries.

Regarding the clinical manifestations of CF diseases in the GS, the results of study documented that most of CF cases were suffering from manifestations related to respiratory system and more than half of patients were suffering from manifestations related to gastrointestinal system. The clinical feature of CF disease was the essential tool for diagnosis of CF cases in the GS, where 91% of CF cases were diagnosed by clinical manifestations and sweat test, 6% of them were diagnosed by manifestations, sweat, and genetic tests. An International consensus statement also suggests similar guidelines for making a diagnosis of CF [51,52].

Furthermore the clinical features in CF cases in the GS were similar to that classically described [51,52,54]. The commonest clinical presentation of CF remains acute or persistent respiratory symptoms, appearing in 51% of all cases diagnosed in the United States [23]. Other common clinical features in USA were failure to thrive or malnutrition (43%), steatorrhea or abnormal stools (35%) and meconium ileus or intestinal obstruction (19.5%). The proportions of respiratory or gastrointestinal features of CF among Palestinian Cases and American cases were approximately equal.

It was clear from the findings of the study that there was no difference in trend of mortality through the last ten years in the GS. This means that the mortality rates through the last ten years (2009-2019) in the GS were approximately convergent. In spite of this finding, it was observed that there was slowly declining in the mortality rate from the year 2013 till the year 2017. This leads to increase prevalence rates of CF in the GS correspondingly. Also there was obvious declining in the case fatality of CF in the GS since 2013 till 2017. This could be attributed to increase the awareness of health staff about the diagnosis and management of the disease. It is important to mention that during this period there was an improvement in the health services in MOH in spite of the Israel Siege to Gaza strip economically. National Authority continued an improvement in the quality of health services of Paramedical departments such as laboratory services, physiotherapy services, nursing staff. All these factors could play a role in increasing the awareness among the health staff about CF disease diagnosis and give them correct knowledge about the accurate protocols for managing the CF cases.

The case fatality of the CF disease was high in the GS compared to the rates in the western countries. [3,12,15,18] but it was around the rates reported in some studies conducted in Arab countries [32]. There was an obvious decline in the case fatality rate due to CF during the last ten years (2013-2017) in the GS, where it was 15.63% in 2013 and decreased to 3.45% in 2017. The dramatic decline in fatality and mortality of CF disease was attributed to the continuous progression in medical care and increasing awareness about CF among medical professionals either in Arab or Western countries. These reasons are the same in the GS as mentioned previously.

According to the current study results about 62.5% of known mutation of CF cases have at least a single allele of DF50 and 37.5% of known mutation of CF cases were of homo DF508 and 25% of them were of hetero DF508 CFTR mutation, More than two third (68.75%) of hetero DF508 were of unknown mutation on the other allele, while less than one third of them were of G542X mutation or W1282X mutation on the other allele. Moreover 12.5% of known CF mutation cases were of homo 3120+1kb CFTR mutation. Also homo N1303K, homo G85E and homo 3120del 8.6kb CFTR mutations were found among 14.07% of Known mutation of CF. The previous findings are consistent with the studies which reported that some mutations in the Middle East are shared with many other regions in the world [20,66], i.e. DF508, N1303, W1282X and 3120+1G-A. The

most frequent mutation, present on about 67% of CF chromosomes worldwide, results in the deletion of a phenylalanine residue at codon 508 (DF508) [33,34,64]. The clinical manifestations in homozygous patients have been extensively studied. [8,9,30,33,34,53]. They generally have pancreatic insufficiency of early onset with markedly elevated sweat chloride concentrations, but the pulmonary manifestations are widely variable.

This could indicate that the CF Children of homo DF508 could be presented with severe form of CF, where they had failure to thrive. Also this proportion is almost coinciding with of CF cases who were complaining of malabsorption (45%) which is a sign of pancreatic insufficiency. Also the frequency of Respiratory manifestations among CF children in the GS was very high (41-96%). This is compatible with the hypothesis which assumes that pancreatic phenotype can sometimes be predicted by genotype, and pancreatic insufficiency is almost invariably associated with two severe mutations. The correlation between genotype and phenotype for pulmonary phenotype is not reliably predictive and the course of lung disease in CF is especially vulnerable to environmental and modifier gene [39].

Case reports of patients with various mutations have been reviewed [27], and several studies of groups of patients with defined genotypes have been published in the previous decade [16,24,26,28,37,46,56].

Homozygotes for W1282X, the most common cystic fibrosis mutation in the Ashkenazi Jewish population, were compared with W1282X/DF508 compound heterozygotes. The groups were similar to each other and to DF508 homozygotes described elsewhere [56]. The DF508 mutation is usually associated with a more severe clinical presentation and higher sweat chloride levels, while a few other mutations are associated with a mild phenotype. Patients carrying at least 1 mild mutation may present with late onset of symptoms, better nutritional status, pancreatic sufficiency, and lower sweat chloride levels [59]. In an attempt to ascertain a relationship between genotype and phenotype, Borgo G et al, studied the pulmonary and nutritional status of 123 CF patients with known genotype at an age of 8.5-10 years. Patients represent a cohort as they are almost all those born and diagnosed in a given area and period. They were followed at a single centre using uniform diagnostic and treatment protocols. Pulmonary and nutritional status of homozygous DF 508 patients did not differ from that of compound heterozygotes or patients with other unspecified genotypes. Pulmonary manifestations varied widely in all genotype groups. With the given number of patients, a slightly higher mortality of delta F508 homozygotes could have been coincidental. It was concluded that up to the age of 8.5-10 years the severity of pulmonary lesions and nutritional deficiencies is not related to the delta F508 mutation [59].

A report of patients carrying the N1303K mutation revealed that this mutation is associated with pancreatic insufficiency of early onset and widely variable pulmonary disease [28]. Compound heterozygotes for G551D and DF508 were indistinguishable from matched DF508 homozygotes except for a decreased risk of meconium ileus [16]. Studies of patients carrying the R553X mutation found inconsistent results with regard to sweat chloride concentrations and growth [16,37] Highsmith et al, studied 23 patients with pulmonary disease characteristic of CF but with normal sweat testing, and identified a point mutation in intron 19 of the CFTR gene, termed 3849+10kb C-T. Published data show mild phenotypic characteristics among CF patients who are homozygous for this mutation [29]. The onset of pulmonary disease was delayed in most of them, but then became severe in some [29].

The concept of “mild” and “severe” mutations was proposed by Kerem et al. [33,34] as an explanation of the clinical heterogeneity of CF. However, because of the high clinical variability and the large number of identified mutations, it is very difficult to characterize genotype-phenotype correlations in CF, except for the most common mutations. But a classification system according to the functional properties of the gene product was proposed by Welsh and Smith [65]. Mutations in CFTR gene have been classified into five different groups according to the mechanism by which they disrupt CFTR function. In the current study, about half of CF children belonged to class II. Also the manifestations of disease among CF children are compatible with the expected phenotype related to this classification.

## Conclusion

The incidence and prevalence rates of CF in the GS were around the rates of Caucasian Western Europe populations. The average annual incidence rate of CF disease through the last ten years (2009-2019) in the Gaza strip was one case per 3952 live births. The average prevalence of CF disease through the last ten years in Gaza strip was 7.52 cases per 100,000 population with no significant difference in incidence through the last ten years.

The majority of the cases was diagnosed during infantile age and was diagnosed in Governmental Pediatric Hospitals by both manifestations and sweat test. Respiratory system was the most system affected by CF disease.

The average annual mortality rate among those less than 15 years was 0.52 case per 100,000. The average annual case fatality rate of CF through the last ten years was 7.87%. The five years survival of CF cases was 0.361 (more than one third of the cases).

About two thirds of known mutation of CF cases have at least a single allele of DF508, which is considered of severe type of CFTR mutations. Also 12.50% of known mutations of CF cases were of homo 3120+1kb CFTR mutation. On other hand about half of the cases belong to class II of CF disease (severe form of disease).

## Recommendations

Based on the results obtained from this study, the researcher proposes There is a need for establishment and implementation of CF services including:

- Neonatal screening programs for CF disease should be set up to determine its incidence and identify affected infants early to avoid the complications of CF disease and to guarantee high quality life of CF cases in the future with long survival and may be of particular value in estimating the burden of CF in a population where it is underdiagnosed.
- The importance of establishing a reliable diagnosis of CF using a properly conducted sweat test. In addition, diagnostic radiology, and laboratory facilities for sputum culture and pulmonary function tests are important for both the initial diagnosis and the diagnosis of complications.
- National and regional genetic laboratories should be encouraged to identify the specific CF mutations most com-

monly found in their populations, in order to help clinicians recognize the variations they may encounter.

- Integration of genetic counseling and services for CF cases' families into primary health care to avoid getting child with CF disease in future pregnancy.
- It is essential for the dedicated physicians with an interest in CF to be highly motivated and willing to provide the starting point for a diagnostic and clinical service for the CF condition and to provide leadership.
- It is essential for health authorities to know the magnitude of the problem if they are to make appropriate provisions for CF care.
- It is important to establish and maintain a national CF registry in order to identify and predict the need for services and to monitor survival trends. Essential data include name, date of birth, sex, age at diagnosis, and date of death. Other useful information includes the mode of presentation, the cause of death, and, when available, the genotype.
- Further studies are required to clarify the relationship between different mutation genotypes of CF disease and the variety phenotypes among the cases in the GS.

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