

Assessment of Cystic Fibrosis Distribution Based on Air Pollution by Geographical Information System (GIS)

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Background: It is widely accepted that concerns have been recently raised regarding the impact of air pollution on the health of children with cystic fibrosis (CF). Air pollution probably affects the exacerbation of CF and its laboratory findings. On the other hand, the World Health Organization (WHO) has asked all countries to update their data and reports on the distribution and prevalence of CF in different areas. The purpose of the present study was to investigate the distribution and prevalence of CF based on the levels of atmospheric pollutants, such as PM₁₀, PM_{2.5}, SO₂, NO₂, CO, and O₃ in 22 zones of Tehran, and to report the abnormal laboratory findings that might indicate the exacerbation of CF.

Materials and Methods: The studied statistical population included children with CF referred to Masih Daneshvari Hospital from 2003 to 2020. Demographic data, location of living area, and laboratory findings were extracted from patient records. The geographic information system (GIS) was applied to indicate the distribution and dispersion of the disease. The information related to air pollutants was collected from all stations in Tehran during the studied period by the Department of Environment of Tehran Province, and the average levels were used for final reporting.

Results: The analysis results on 287 CF patients demonstrated that the risk of disease exacerbation significantly increased by the presence of air pollutants. In areas with multiple air pollutants, more laboratory findings were observed to be abnormal, and the lower survival rate for patients with CF was recorded. Investigating the CF distribution pattern based on climatic layers and above mean sea level (AMSL) indicated that distribution of the disease was higher in dry areas with lower AMSL and the higher volume of the atmospheric pollutants, which were primarily centralized in southern and central Tehran.

Conclusion: Environmental factors, such as air pollution, can be considered vital parameters, along with high-risk factors, such as pure and integrated race, migration, and mutation, influencing the prevalence and exacerbation of CF symptoms. Considering the higher prevalence of CF in deprived areas of Tehran, households' cultural and economic level appears to be a factor in the lack of diagnostic screening and prevention of CF in these areas. On the other hand, continuous monitoring of the air pollution caused by traffic and giving warnings to CF patients and their parents is particularly important.

Key words: Climatic processes; Cystic fibrosis; Disease mapping; Geographic information system; Medical informatics

INTRODUCTION

With the development of novel technologies and the increasing population growth rate in recent years, the world has faced the problem of air pollution. Atmospheric

pollutants are the factors that cause harm to human health at certain amounts and under specific conditions. Chemical pollutants of the tropospheric layer, along with the contaminants produced by human activities, alter the ratio

of the air compositions and affect the local, regional, and global climate. The US Environmental Protection Agency (USEPA) identified six major pollutants as indicators of air pollution and divided them into primary and secondary categories. The primary pollutants are substances that enter the ambient air directly from their sources and include carbon monoxide (CO), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), particulate matter (PM), and lead (Pb). Secondary pollutants, such as ozone (O₃), refer to substances created by interactions in the Earth's atmosphere (1). The WHO estimates that one out of every eight deaths (approximately 7 million in 2012) is globally attributable to air pollution, more than half of which are due to outdoor air pollution (both urban and rural) (2). Approximately 92% of the world's population live in areas that have failed to satisfy the WHO air quality objectives (3), and it is estimated that outdoor air pollution is responsible for the loss of 69.7 million years due to illness, disability, or premature deaths worldwide (4). Air pollution is associated with many diseases, including pneumonia (5), different types of cancers, asthma, diabetes, dementia, stroke, and heart diseases; however, different results have been reported for the intensity of this relationship (6). In recent years, Google's news coverage of air pollution has been increased by a factor of 919 from 2006 to 2016 (in comparison, "cystic fibrosis (CF)" has also been increased by a factor of 298) (7). CF is a genetic and autosomal recessive disorder that entangles various body systems. A mutation causes this disease in the CF transmembrane conductance regulator (CFTR) gene, located on the long arm of chromosome 7 (8). The natural allele of this gene is responsible for the production of a particular protein, which is, in fact, a protein channel for chloride ions and acts as a chlorine ion transmitter between specific cells and extracellular fluid (9). The balance of ions and water in the mucosa of the cells is disrupted in patients, and the mucus becomes more sticky than usual, followed by inflammation and infection, which consequently results in damage to the pancreatic mucosal cells, gastrointestinal tract, lungs, and other organs (10, 11). The disease is more commonly observed in white people in

Europa, especially northern Europeans (12). In Ireland, one out of 1353 live births is exposed to CF, which is higher in terms of disease incidence worldwide (13). This rate decreases from northern and western Europe to the east (14). The same trend is also observed in Asia, and the incidence of disease in Western Asia (one out of 6500-9200) is higher than that of Eastern Asia (one out of 40,000-100,000) (8, 15). In addition, Kamal and Nazer in Jordan (16), Nazer et al. in Saudi Arabia (17), and Al-Mohroos in Bahrain (18) proved that many children with CF remain undiagnosed due to the lack of clinical suspicion and inadequate diagnostic facilities, and it is noteworthy that there are no exact statistics in this regard (18). There are no accurate statistics on the prevalence and distribution of this disease in Iran and its different cities and regions. Goss et al. demonstrated that the annual average of air pollution is associated with reduced pulmonary function and the increased probability of CF exacerbation by integrating retrospective data from the CF National Foundation and documents of the US Environmental Protection Agency (19). Pulmonary exacerbation of CF significantly affects the disease severity, which will have a negative impact on the quality of life, disease cost, and pulmonary function (20, 21). Recently, concerns of the parents of CF patients regarding the impact of air pollution on their children's conditions have been increased, and it can be said that air pollution probably affects the exacerbation of CF and its laboratory findings (7). On the other hand, the WHO has previously listed CF as an important disease and has asked all countries to update their data and reports on CF distribution (22). Although Tehran (capital of Iran) is now one of the most polluted cities throughout the world, and it has been reported that the highest rate of mortality from air pollution-related diseases occurs in this city (23), no statistics regarding the distribution and laboratory findings of the CF has been reported based on environmental pollution in Tehran. Lack of accurate statistics on the distribution and prevalence of a disease results in reduced success, inefficient planning, and policymaking to prevent the development and progression of the disease. This is due to the uncertainty in the manner of disease

distribution in terms of location and climatic conditions, and consequently, the way of implementation of prevention and care programs in different regions (24).

The purpose of this present study was to investigate the distribution and prevalence of CF based on climatic conditions and the levels of the atmospheric pollutants, including PM₁₀, PM_{2.5}, SO₂, NO₂, CO, and O₃ in 22 zones of Tehran, and to report the abnormal laboratory findings that might indicate the exacerbation of CF.

MATERIALS AND METHODS

The present study was a descriptive-analytical study to assess the distribution and prevalence of CF based on climatic conditions and atmospheric pollutants in 22 zones of Tehran and reported abnormal laboratory findings that might indicate the exacerbation of CF. The studied population consisted of children with CF referred to Masih Daneshvari Hospital from 2003 to 2020. Demographic and other required information, such as the place of residence, were extracted from patient records, and GIS was applied to demonstrate the disease distribution and dispersion. Considering the various geographical and social conditions in different regions of a city, the impact of these factors on different locations should be considered when investigating the effective factors on the prevalence and distribution of a disease. Spatial analysis methods are capable of indicating the geographical maps of spread, prevalence, and prediction of diseases. In such cases, it would be advantageous to use novel technologies, such as GIS (25), which is a tool for planning and entering objective information and also patterns and processes of qualitative/quantitative specialized planning models (26). This instrument enhances effective cognition and communication and assists in controlling the effects of managerial policies. The system is useful for collecting, sorting, retrieving, converting, and displaying real-world spatial information for specific purposes (27). GIS can be employed to monitor urban health, following changes and improvements of the day, to help citizens find the nearest centers to access health resources. GIS can also be applied to assess the distribution and diversity of diseases, spatial and temporal analysis of health information, epidemiological anticipation, epidemiological control and

management in disease tracking, and traffic management planning to reduce air pollution and waste management (28). Tehran is extended from 35° 35' N to 35° 47' N and 51° 17' E to 51° 33' E of the Alborz Mountains. Tehran covers 1500 km², and its metropolitan area is higher than 500 km². Its elevation around the area is approximately 4878 meters from Damavand Peak (5678 meters) to the lowlands of the Dasht-e-Kavir with about 800 meters AMSL. This elevation difference is also observable in Tehran, with the north and south of the city being approximately 1,700 and 900 meters AMSL, respectively (29). In the present study, data on the levels of the air pollutants, such as PM₁₀, PM_{2.5}, SO₂, NO₂, CO, and O₃, were collected from all stations in Tehran province from 2003 to 2020. These data were gathered hourly, and the present assessment applied the mean levels. ArcGIS 9.3 and Excel software were used to produce maps and graphs, and SPSS software was applied to estimate the descriptive statistics. The required permissions to use patient records were obtained from the Ethics Committee.

RESULTS

The age distribution, sweat test, and pancreatitis-associated protein (PAP), along with disease distribution and prevalence, were reported for 287 CF patients according to 22 zones of Tehran (Table 1). The diagrams A-1, B-1, C-1, D-1, E-1, F-1, G-1, and H-1 illustrate the distribution and prevalence of CF for 22 zones of Tehran according to the levels of air pollutants, including NO₂, O₃, PM₁₀, PM_{2.5}, SO₂, CO, AMSL, and climatic layers, respectively. Furthermore, figure A-2, B-2, C-2, D-2, E-2, F-2, G-2, and H-2 represent the distribution of CF in 22 zones of Tehran, based on the levels of the air pollutants, including NO₂, O₃, PM₁₀, PM_{2.5}, SO₂, CO, AMSL, and climatic layers, respectively (Table 2). Figure 1 compares the rankings of 22 zones of Tehran based on the levels of the air pollutants of NO₂, O₃, PM₁₀, PM_{2.5}, SO₂, and CO. Table 3 displays the age frequency and laboratory findings of CF patients in 22 zones of Tehran based on air pollutant levels, including NO₂, O₃, PM₁₀, PM_{2.5}, SO₂, and CO. In radar charts, the pollution rate is clockwise from the cleanest to the most polluted zone, so that the cleanest zone is on the assumed hour 12.

Table 1. Distribution, prevalence, and frequency of laboratory findings in CF patients in 22 zones of Tehran

Region	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Disease distribution	3	5	6-8	4	1	1	1	0	1	3	1	4	2	6-8	6-8	4	3	2	6-8	6-8	1	2
Prevalence	0.7	0.7	1.8	0.2	0.0	0.2	0.2	0.0	0.9	0.9	0.2	1.3	0.7	1.8	0.9	1.3	0.9	0.6	1.8	1.3	0.6	1.3
	0.8	0.8	2.9	0.5	0.1	0.5	0.5	1.1		1.2	0.5	1.7	0.8	2.9	1.2	1.7	1.2		2.9	1.7		1.7
Age %																						
<2years	100	100	70	50	100	100	100	-	-	70	100	50	50	85	75	70	70	50	50	100	10	10
2-5 years	-	-	15	25	-	-	-	-	-	-	-	25	-	15	12.5	30	-	50	-	-	0	0
6-10 years	-	-	-	-	-	-	-	-	-	-	-	25	-	-	12.5	-	-	-	30	-	-	-
11-15 years	-	-	15	25	-	-	-	-	-	-	-	-	50	-	-	-	-	-	20	-	-	-
>15 years	-	-	-	-	-	-	-	-	100	30	-	-	-	-	-	-	-	-	-	-	-	-
Sweat test %																						
<60	-	-	15	25	-	-	-	-	-	30	-	-	-	-	-	25	25	-	-	-	10	-
>60	100	100	85	75	100	100	100	-	100	70	60	100	100	100	100	75	75	100	100	100	0	10
Hb %																						
>12	70	80	75	50	-	-	100	-	100	70	-	100	50	73	38	50	50	50	85	80	10	10
<12	30	20	25	50	100	100	-	-	-	30	100	-	50	27	62	50	50	50	15	20	0	0
Vitamin D %																						
>100	-	-	-	-	-	-	-	-	-	33.3	100	-	-	-	-	-	-	-	-	-	-	-
30-100	100	100	75	75	100	100	100	-	-	33.3	75	50	50	38	70	50	50	100	40	100	10	10
11-29	-	-	12.5	25	-	-	-	-	-	33.3	12.5	25	50	62	15	-	-	-	30	-	0	0
1-10	-	-	12.5	-	-	-	-	-	100	-	12.5	25	-	-	15	50	50	-	30	-	-	-
*PAP%																						
Normal	70	100	85	100	100	100	-	-	100	70	100	75	100	75	85	100	70	100	85	80	10	10
Abnormal	30	-	15	-	-	-	100	-	-	30	-	25	-	25	15	-	30	-	15	20	0	0
ESR %																						
<20	70	100	75	75	-	100	-	-	-	30	100	50	50	30	40	25	-	50	28	70	10	50
>20	30	-	25	25	100	-	100	-	100	70	-	50	50	70	60	75	100	50	72	30	0	50
Sputum culture %																						
No growth	33.3	-	-	-	100	-	100	-	-	-	100	-	100	-	-	-	-	-	12	-	-	-
Normal flora	33.3	60	65	75	-	100	-	-	-	-	-	25	-	-	60	50	30	50	21	38	10	50
Pseudomonas	33.3	20	35	25	-	-	-	-	-	70	-	50	-	70	25	25	70	50	45	62	0	50
Staphylococcus	-	-	-	-	-	-	-	-	100	-	-	25	-	30	15	25	-	-	-	-	-	-
Candidiasis	-	20	-	-	-	-	-	-	-	30	-	-	-	-	-	-	-	-	-	-	-	-
Aspergillus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12	-	-	-

*PAP: Pancreatitis-associated protein

According to Table 1, the highest distribution of CF was 6-8 people (averagely seven people) in zones 3, 14, 15, and 19, five people in zones 20 and 2, and four people in zones 4, 12, and 16. The lowest distribution of CF was in zones 5, 6, 7, 9, 11, and 21 (one person), and the distribution of CF in zone eight was equal to zero. As it is shown in Table 2 and figure A-1 and A-2, the investigation of atmospheric contamination with pollutants along with distribution and prevalence of CF indicated that the highest NO₂ pollution was related to zones 1, 2, 3, 4, and 19, and distribution and prevalence of CF were also higher in these areas. According to figure B-1 and B-2, O₃ pollution was higher in zones 4, 16, and 19, where CF's distribution and prevalence were considerable. As illustrated in figure C-1 and C-2, the highest PM₁₀ pollution was related to zones 14, 15, and 20; the distribution and prevalence of CF were also higher in these areas. According to figure D-1 and D-2, the highest PM_{2.5} pollution was observed in zones 3 and 20, where the distribution and prevalence of CF were considerable. As it can be seen from figure E-1 and E-2, the highest SO₂ pollution was related to zones 10, 16, 17, 19, and 20, and CF distribution and prevalence were higher in these areas. According to figure F-1 and F-2, the highest CO pollution was observed in zone 3, and the distribution and prevalence of CF were considerable in this region.

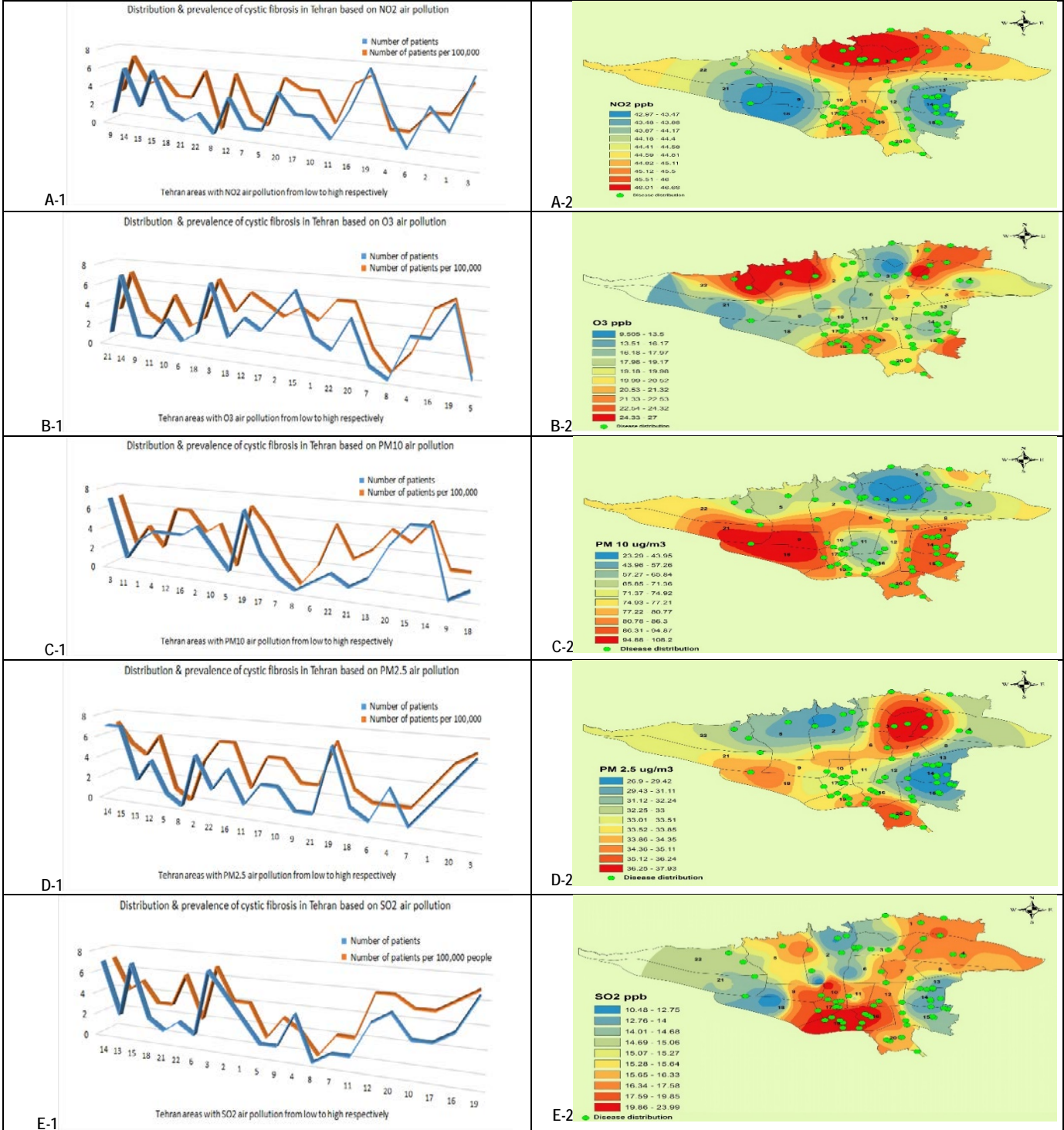
In Table 2, the highest distribution of CF was generally observed in the southern, eastern, and mid-northern zones of Tehran, respectively, and the distribution density was lower in the western regions. According to figure A-2, the highest NO₂ atmospheric pollution was observed in the north, south, and central regions, and northeast to east and northwest of Tehran, respectively. The lowest NO₂ pollution was in the southeast and southwest of Tehran. According to figure B-2, the highest O₃ pollution was observed in the northeast, northwest, and south regions, and the lowest O₃ pollution was detected in central, northern, and western Tehran. According to figure C-2, PM₁₀ pollutions were concentrated in the southwest and southeast and part of the south of the city. The lowest PM₁₀ pollution was in the northern and a part of the southern and central Tehran. As it is obvious from figure D-2, the concentration of PM_{2.5} pollution was related to the north, south, southwest, and west of Tehran. The lowest PM_{2.5}

pollution was observed in the northwestern and also eastern to southeastern regions of the city. According to figure E-2, the highest SO₂ pollution occurred in the northeast and northwest zones, and the lowest SO₂ pollution was in the north, southeast, west, and southwest of Tehran. As it can be seen in figure F-2, the highest concentration of CO pollution was related to the northern, southern, and central parts of Tehran, and the lowest CO pollution was detected in the east, west, northwest, and southwest regions. Accordingly, the concentration patterns of CO and NO₂ pollutants displayed the highest overlapping with the distribution of CF, so the comparison of the rankings of 22 zones of Tehran based on atmospheric pollution (Figure 1 and Table 3) demonstrated that in regions where the atmospheric pollution overlapped with multiple pollutants, the highest distribution of CF was observed. The highest overlapping of atmospheric pollution was related to zones 1, 3, and 4 with CO₂, PM_{2.5}, and NO₂, and most of the patients in these areas were <2 years old using sweat test >60 mEq/L. The overlapping of atmospheric pollution was detected with NO₂, O₃, SO₂, and CO in zone 16, and most of the patients in this area had ESR >20 mm/h with vitamin D3 levels of 1-10 ng/mL. The overlapping of atmospheric pollution was observed with O₃, PM₁₀, PM_{2.5}, and SO₂ in zone 20, and most of the patients in this area were <2 years using sweat test > 60 mEq/L. The overlapping of atmospheric pollution occurred with NO₂, O₃, PM_{2.5}, SO₂, and CO in zone 19, and most of the patients in this area had sweat test > 60 mEq/L, vitamin D3 levels in the range of 1-10 ng/mL, and ESR >20 mm/h. On the other hand, in zones 14 and 9, where the PM₁₀ pollution was significant, *Pseudomonas* was the most common microorganism discovered in the sputum culture of CF patients, and the diagrams of a sweat test and PM₁₀ confirmed that in more polluted areas, the sweat tests of most CF patients were at high levels (> 60 mEq/L). The radar charts of age and NO₂ indicated that most patients in more polluted areas were <2 years old. The diagram of Hb and NO₂ showed that most of the patients had Hb <12g/dL in more polluted areas. The diagrams of vitamin D3 and SO₂ indicated that most participants in the polluted areas suffered from severe vitamin D3 deficiency. Radar charts displayed that patients had abnormal PAP in areas with increased pollutants, including SO₂, PM_{2.5}, and CO.

Table 2. Images and diagrams related to the distribution and prevalence of CF based on air pollutants NO₂, O₃, PM₁₀, PM_{2.5}, SO₂, CO, AMSL and climatic layers in 22 zones of Tehran

Diagrams A-1, B-1, C-1, D-1, E-1, F-1, G-1, H-1: Distribution and prevalence of CF based on air pollutants NO₂, O₃, PM₁₀, PM_{2.5}, SO₂, and CO, AMSL and climatic layers, respectively.

Figures A-2, B-2, C-2, D-2, E-2, F-2, G-2, H-2: Distribution of CF based on air pollutants NO₂, O₃, PM₁₀, PM_{2.5}, SO₂, and CO, AMSL and climatic layers



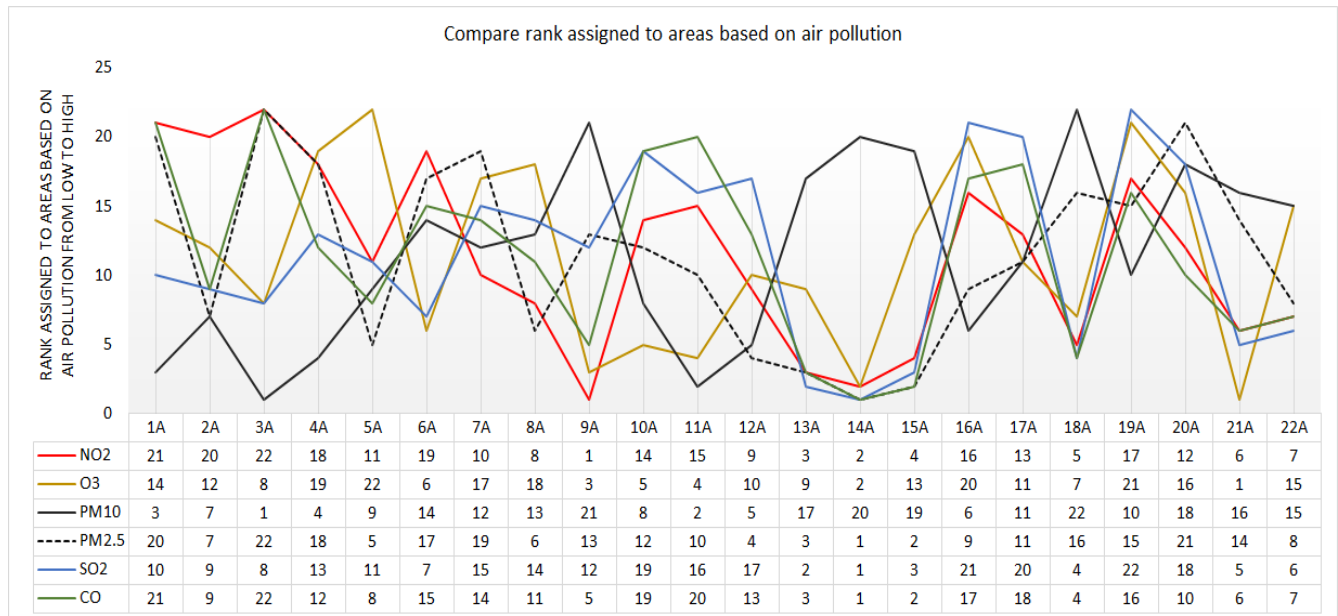
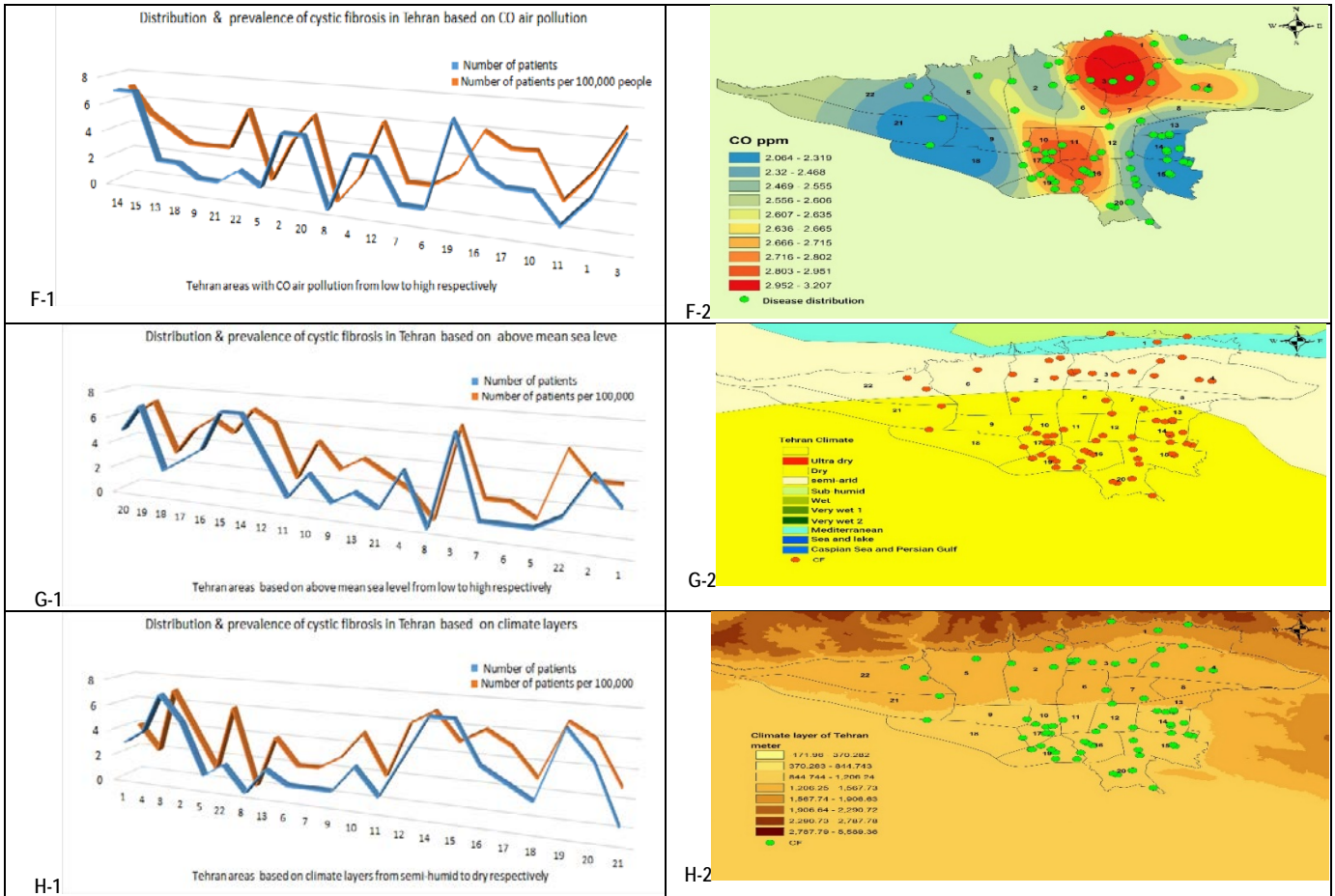
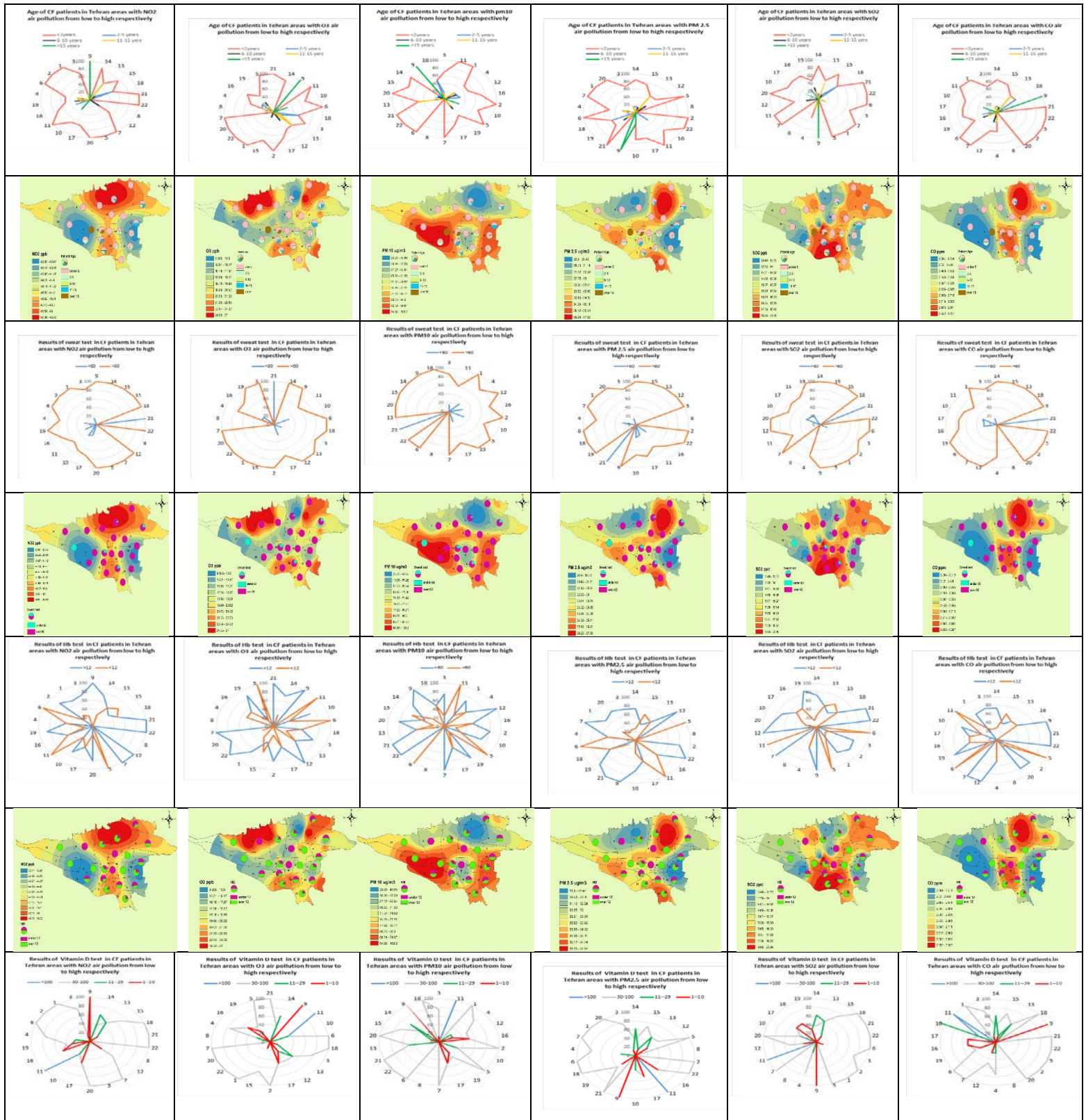
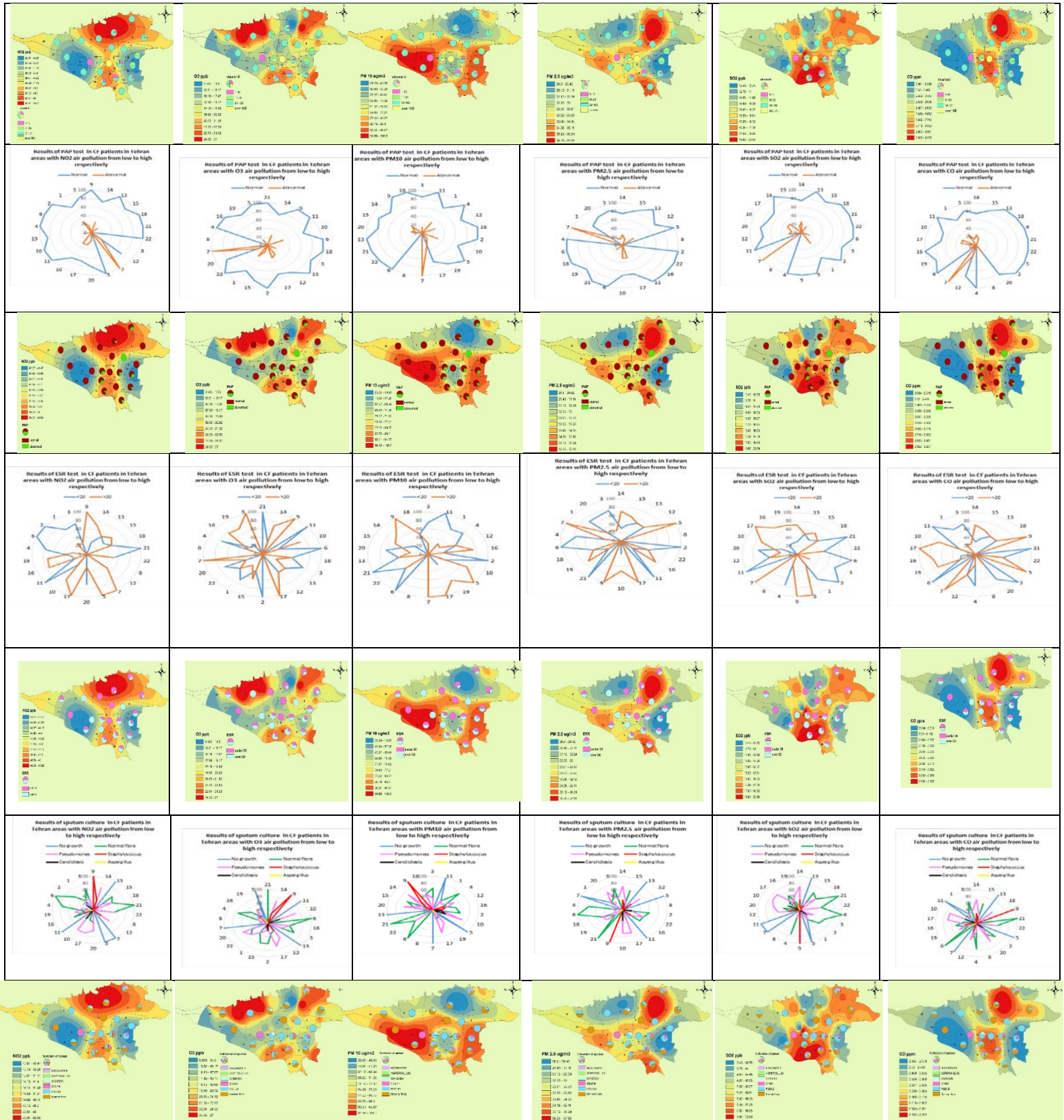


Figure 1. Comparison of the ranking of 22 zones of Tehran based on air pollutants NO2, O3, PM10, PM2.5, SO2, and CO

Table 3. Age-frequency and laboratory findings of CF patients based on the pollution rank of NO₂, O₃, PM₁₀, PM_{2.5}, SO₂, and CO in 22 zones of Tehran
The pollution rate is clockwise from the cleanest to the most polluted zone (the assumed hour 12 is the cleanest zone).





According to Table 2 and Figures G-1 and G-2 and H-1 and H-2, based on climatic layers and AMSL, the distribution of CF was higher in dry areas with lower AMSL; the southern and central parts of Tehran have similar characteristics.

DISCUSSION

The analysis results on 287 CF patients demonstrated that the distribution and prevalence of the disease were higher in polluted areas, and the risk of exacerbation of disease conditions was significantly increased by the presence of air pollutants. In regions with overlapping atmospheric pollution with multiple pollutants, CF's highest distribution and prevalence were observed. The study by Goss et al. on the association of CF and atmospheric pollution indicated a significant relationship between the mean annual exposure to PM₁₀, O₃ and the rate of CF exacerbation, where the hospitalization and receiving intravenous antibiotics at home and in the hospital were indicators of CF exacerbation (19). Goeminne et al. conducted a study to reduce the impact of cross-over interfering factors on CF conditions and demonstrated that disease exacerbations were increased by exposure to air pollution. In this study, antibiotic intake was the criterion for the exacerbation of CF (30). In the present study, the zones with the highest NO₂ pollution exhibited more abnormal laboratory findings as well as higher distribution of CF. The patients in these areas had sweat test > 60 mEq/L and ESR > 20 mm/h, vitamin D3 level in the range of 1-10 ng/mL, HB < 12g/dL, and most of them were < 2 years old, indicating that patients living in more NO₂-polluted areas may have a shorter life expectancy due to worsening of the disease.

NO₂ is mainly emitted by combustion processes, such as motor and heating vehicles, as well as power generation. It is a powerful proxy for the global mixture of traffic-related air pollution. The particulate matter fraction that best relates to the traffic-related NO₂ is black carbon, which is much more correlated with NO₂ than PM₁₀ or PM_{2.5} (31). In the present study, the highest pollution levels were

related to the north and center of Tehran, and the highest traffic was also observed in these regions. In the study by Goeminne et al., the highest odds ratio (OR) was to initiate antibiotic treatment for NO₂, and they explicitly suggested that the air pollution associated with traffic is responsible for the observed relationship between NO₂ and exacerbation of CF symptoms (30). The correlation between the higher NO₂ exposure and the risk of abnormal variations in the laboratory findings of CF patients was also confirmed in the present study. The WHO has announced that traffic-related air pollution is associated with the increased risk of respiratory symptoms and side effects of CF (32). The traffic-related air pollution reduces ventilation function and increases respiratory symptoms in children (33); even a low-level or short-term exposure to NO₂ pollutants increases the probability of hospitalization of patients with respiratory diseases (34).

The highest overlapping of atmospheric pollution was in zones 1, 3, and 4 with CO₂, PM_{2.5}, and NO₂; most of the patients in these areas were < 2 years old with sweat test > 60 mEq/L. The overlapping of atmospheric pollution was observed with NO₂, O₃, SO₂, and CO in zone 16, and most of the patients in this area had ESR > 20 mm/h, and their vitamin D3 level was 1-10 ng/mL. The overlapping of atmospheric pollution with O₃, PM₁₀, PM_{2.5}, and SO₂ was observed in zone 20, and most of the patients in this area were < 2 years old with sweat test > 60 mEq/L. The overlapping of atmospheric pollution occurred with NO₂, O₃, PM_{2.5}, SO₂, and CO in zone 19, and most of the patients in this area had sweat test > 60 mEq/L, vitamin D3 level in the range of 1-10 ng/mL, and ESR > 20 mm/h. Patients displayed abnormal PAP in areas with increased SO₂, PM_{2.5}, and CO pollutants concentrations.

Furthermore, Tramuto et al. reported a similar effect of air pollution on exacerbation and deterioration of the conditions of CF patients, so there was a positive relationship between referral to the clinic for respiratory symptoms and exposure to the contaminated environments caused by motor vehicle pollutants, such as PM₁₀, NO₂, SO, and CO (35). Farhat et al. indicated that an

interquartile range (IQR) (45.62 $\mu\text{g}/\text{m}^3$) increase in O_3 concentration can lead to a 52% increase (from 34% at lag0 to 86% at lag2) in the risk of exacerbation of respiration in children and adolescents with CF within 48 hours after exposure, even after controlling other risk factors. It means that exposure to air pollutants, such as O_3 , is detrimental to the respiratory health of these high-risk groups (36).

In a 5-year retrospective study, Jassal et al. assessed the impact of residential proximity of passages to pollutants O_3 and $\text{PM}_{2.5}$ on pulmonary exacerbation rates in 145 patients at the CF Care Center of the Children's Hospital, Los Angeles. They demonstrated that CF patients who lived in the vicinity of the main road might experience two times or more exacerbations of symptoms, along with the need to be hospitalized and receive intravenous antibiotics (37). Despite the methodological differences between the studies by Jassal et al. (37) and Farhat et al. (36) (design, exacerbation criteria, and statistical analysis), both introduced the relation of the air pollution with vehicles (primary or secondary) as a factor in the respiratory exacerbation of CF patients.

O_3 is a potent oxidizing compound that causes damage to the lungs and strengthens the inflammation of the airways. The interaction between O_3 and the epithelial lining fluid of the lung in CF patients probably produces the oxidized species that may be responsible for stimulating lung inflammation and contributing to acute bronchoconstriction and airway hyperreactivity, which is similar to the changes observed in asthma (38, 39). Additionally, O_3 can lead to the induction of apoptosis, DNA damage, and toxicity of the human alveolar type-1 epithelial cells and ciliated airway epithelial cells, in addition to a deficiency of the CFTR protein, which controls the flow of chloride ions across the epithelial cells and can exacerbate the airway inflammation in CF patients (40, 41). Considering the high oxidative capacity of O_3 , these processes can be the result of the presence of O_3 or the overall effect of all existing pollutants in the photochemical mixture of air pollution, which is not regularly measured by environmental agencies (36).

In the present study, in zones 9 and 14 with high concentrations of PM_{10} pollution, which were located in a dry area and below the AMSL in comparison with other zones, *Pseudomonas* was the most common microorganism discovered in the sputum culture of CF patients, and most of the CF patients exposed to PM_{10} had sweet test >60 mEq/L. PM_{10} and particles smaller than 2.5 μm in diameter ($\text{PM}_{2.5}$) also contain contaminated particles that are not locally developed by combustion processes, but they result from the formation of secondary aerosols and transmission of particles of distant origins (31). High concentrations of PM_{10} are observed in southwestern, southeastern, and a part of southern Tehran. Goeminne et al. reported that the particle effect was not prominent in contrary to the present study; however, the analysis of *Pseudomonas* infection in CF patients confirmed that its chronic colonization is the representation of a subset of patients with exacerbation of CF, in which the impact of atmospheric pollution on the risk of receiving antibiotic therapy appears to be stronger than that of the patients without chronic colonization. This difference may be due to the high inflammatory or infectious condition of patients with chronic colonization of *Pseudomonas*. This condition may lower the threshold of receiving antibiotic treatment in the case of exposure to a stimulus, such as increased air pollution (30).

A recent study, in which the macrophages isolated from mice were exposed to environmental particles collected during winter, spring, and summer (in Amsterdam, Netherlands; Lodz, Poland; Oslo, Norway; Rome, Italy) showed that PM_{10} samples gathered in summer were more potent in stimulating inflammatory cytokines, including IL-6 and tumor necrosis factor- α (TNF- α) (42), and it has been previously shown that TNF- α polymorphisms are associated with CF (43). Other studies have demonstrated correlations between PM_{10} and indoor and outdoor air in the range of 0.4-0.79, and in general, it was revealed that the correlation during the colder periods of the year was lower (43, 44). Increased ambient temperature is associated with the prevalence of *Pseudomonas aeruginosa* and lower pulmonary function in

CF patients (45); this might be a biological mechanism for explaining the observed effects in warmer periods of the year. In the present study, in zone 9, which had a dry climate and lowered AMSL compared to other zones, the pollution composition was mainly PM₁₀, and the patients displayed 100% *Pseudomonas* sputum culture. On the other hand, 100% of the patients were >15 years old in this area. Khanbabaei et al. showed that the most common mass extracted from the sputum culture of CF patients were *Pseudomonas*, the incidence rate of which increased by age, and the rate of drug resistance was also increasing at the same rate (46). On the contrary, Collaco et al. revealed that the prevalence of *Pseudomonas* was higher in CF patients who lived in areas with warmer annual temperatures and the cases developed *Pseudomonas* infection at younger ages. They also estimated that the pulmonary function of patients living in the warmest regions of the USA was 10% lower than that of people living in the coldest area of the USA, where their living temperature was lower, on average, 30 degrees Fahrenheit (45).

Continuous increase of the awareness of the impact of traffic-related air pollution on health is required to reduce its hazards. Cesaroni et al. revealed that the local policies to reduce the number of motor vehicles lead to a reduction in NO₂ and PM₁₀, and as a result, 921 years of life per 100,000 people increases by a reduction in NO₂ (47). According to the results, it can be claimed that if the concentration of air pollution increases by 10 mg/m³, it is needed to warn the patients. Prospective studies are also required to investigate the other pollutants and particles and determine threshold values and evaluate preventive measures with their potential impact on the exacerbation of CF (30).

CONCLUSION

The climatic parameters, including weather, AMSL, and the amount of solar radiation, play roles in increasing the rates of atmospheric pollutants. On the other hand, humans have harmed themselves and the environment and exposed their life and health to danger by altering the composition and disrupting the balance of the most effective gases on the lives of the creatures on the Earth.

Results of the analysis on 287 CF patients revealed that the distribution and prevalence of CF were higher in the polluted areas, and the risk of the exacerbation of CF was significantly increased with the presence of air pollutants. The highest distribution and prevalence of CF were observed in the zones with the overlapping of atmospheric pollution with multiple pollutants. In the present study, the pattern of CF distribution based on climatic layers and AMSL showed that its distribution was higher in dry areas with lower AMSL; the atmospheric pollutants were also more abundant in these areas. Various risk factors, such as full blood, migration, integrated race, mutation, and environmental parameters, can be considered influential factors associated with the prevalence of CF or exacerbation of the symptoms; hence, probably a reason for rapid alterations in laboratory findings. Regarding the higher prevalence of CF in deprived regions of Tehran, the cultural and economic level of households seems to be a factor in the lack of diagnostic screening and prevention of CF in these areas; hence, it is required to plan for diagnostic screening and prevention of the disease from the birth of a newborn with CF in deprived areas of Tehran. However, the distribution of the risk factors can be different in various groups of population; thus, the researchers of the present study recommend designing the epidemiologic studies with the purposes of investigating the infection, temperature, or pulmonary function test and also performing clinical trials in extended geographic areas in the care and treatment centers for CF patients.

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