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Laleh Habibi (habibi@razi.tums.ac.ir)
Tehran University of Medical Sceinces

Masoud Tannazi
Tehran University of Medical Sciences

Seyed Mohammad Akrami
Tehran University of Medical Sciences

Research Article

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Possible synergistic effect of air pollution on increasing severity of SARS-CoV-2

Laleh Habibi. Ph.D[1*§], Masoud Tannazi. MSc[2§], Seyed Mohammad Akrami. MD, Ph.D[1,3*]

1. Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences

2. Technical Office, Vice-chancellor in administration and resources development affairs, Tehran University of Medical Sciences

3. Helal Iran Pharmaceuticals and Medical Complex, Tehran Iran

* Correspond to: habibi@razi.tums.ac.ir, akramism@tums.ac.ir

§ L.H. and M.T. worked equally in this study

Abstract

SARS-CoV-2 infection started in the last days of 2019 in China and affected a great number of people worldwide, causing many deaths in numerous countries. Major clinical symptoms of the infected patients are found to be fever, cough, and shortening of breath leading to acute respiratory distress syndrome (ARDS). Cytokine storm and inflammatory responses have been introduced as the main causes of respiratory distress in severe cases. Moreover, all these inflammatory factors have been systematically expressed in the human body through chronic exposure to ambient pollution due to an industrial lifestyle and lead to respiratory problems**.** In order to assess the possible synergistic effect of air pollution on the increased severity of COVID-19, the number of days and the value of air quality index (AQI) as well as the amount of four ambient pollutants ($PM_{2.5}$, PM_{10}, O_3, and NO_2) with unhealthy ranges were measured for three years in eight cities of Iran with different numbers of hospitalized patients affected with SARS-CoV-2. The correlation coefficient between the number of hospitalized patients and air pollution factors was calculated. The present data revealed a significant positive correlation between unhealthy ranges of O_3 and NO_2 and the number of hospitalized patients with COVID-19. No correlation was found between $PM_{2.5}$, PM_{10}, and AQIs and the increased number of severe cases. Conclusively, these primary results might show the synergistic effect of chronic exposure to air pollutants due to living in polluted areas and the increased severity of COVID-19 disease.

Key words: SARS-CoV-2, Air pollution, severity, O_3, NO_2

57 **Introduction**

58 The outbreak of a new coronavirus infection named SARS-CoV-2 (COVID-19),
59 which was firstly detected in China (Wuhan) at the end of 2019, had a deep impact on
60 human societies. Genetic studies have revealed that this virus could possibly be originated
61 from bats, since it has more than 96% genetic similarity with the BatCoV RaTG13 virus
62 (Zhou et al. 2020). Similar to its family members, SARS-CoV-2 uses the angiotensin-
63 converting enzyme 2 (ACE2) receptors to enter the epithelial cells of the respiratory system
64 (Zhou et al. 2020; Guo et al. 2020), which results in cellular damage (Xu et al. 2020),
65 inflammatory immune responses, and ultimately acute respiratory distress syndrome
66 (ARDS) (Ruan et al. 2020; Puja et al. 2020). Moreover, recent studies have shown that
67 inflammatory responses and cytokine storm might be involved in the main mechanisms of
68 ARDS and death in these patients (Puja et al. 2020; Li et al. 2020; Shi et al. 2020). It was
69 indicated that inflammatory cytokines (IL-2, IL-7, and IL-6) as well as inflammatory
70 proteins including tumor necrosis factor–α (TNF-α) and granulocyte colony-stimulating
71 factor (G-CSF) are elevated in severe cases of SARS-CoV-2 infection (Huang et al. 2020;
72 Zhou et al. 2020; Chen et al. 2020).

73 Air pollutants consisting of particulate matters ($PM_{2.5}$ and PM_{10}), ozone (O_3), nitrogen dioxide
74 (NO_2), carbon monoxide (CO), and sulfur dioxide (SO_2) are mainly produced by gasoline,
75 diesel, burning of fossil fuels, and dust storms. The concentrations of these pollutants are high,
76 especially in urban areas that are crowded with vehicle traffic, industrials factories, and dust
77 storms (Kurt Kar et al. 2016). Long- and short-term exposures to PMs, O_3, and NO_2 are
78 associated with respiratory epithelial and immune cell damage (Wu et al. 2018), which lead to
79 systematic inflammatory responses and oxidative stress (Carosino et al. 2015; Wiegman et al.
80 2014; MacNee and Donalson 2003). In addition, pro-inflammatory cytokines including IL-2,
81 IL-12, IL-10, TNF-α, and G-CSF have been shown to be highly expressed following PM

exposure in clinical, in vitro, and in vivo studies (Watanabe et al. 2015; Wu et al. 2018; Gruzieva et al. 2016).

Since the severity of SARS-CoV-2 infection has a wide range and seems to depend on immune responses leading to respiratory inflammation, we assumed that chronic exposure to air pollutants might have a synergistic effect on inflammation in the affected patients and increasing the severity of the disease.

Material and Methods

COVID-19 patients

The number of hospitalized patients infected with SARS-CoV-2 in each province was obtained from the daily statistics declared by Iranian Ministry of Health. The graphs were generated from February 22 till March 22, 2020.

The relative population density was calculated for the selected cities based on the 2015 general population census (Table 1).

Air quality data

The air quality data including the number of days with unhealthy amounts of AQI, $PM_{2.5}$, PM_{10}, O_3, and NO_2 as well as the mean amount of these indices obtained from various stations were attained for 1095 days (three consecutive years, from 2017 to 2019) in eight cities (capitals of provinces) from the Air Pollution Monitoring System (Iran) (https://aqms.doe.ir, April 2020). These data were then classified based on the universal AQI category table (https://www.airnow.gov/index.cfm?action=aqibasics.aqi, updated June 18, 2019). Accordingly, these cities were chosen based on their geographical locations; in this regard, two cities from the west (Ilam and Tabriz), two from the center (Tehran and Yazd), two from the south (Ahwaz and Bushehr), and two from the east (Mashhad and Zahedan) of the country

were selected. The northern locations have been excluded from our study, because the increasing number of patients in these regions was due to the traveling of Tehran citizens to the north during the first days of the epidemic and before the mandatory quarantine.

Statistical analysis

The correlation coefficient amongst the number of hospitalized patients; mean amount of unhealthy ranges of AQI, $PM_{2.5}$, PM_{10}, O_3, and NO_2; number of days with unhealthy ranges of these indices; and population density were calculated using SPSS 16.0.

Results

Increasing number of SARS-CoV-2 patients in populated and industrial cities

In order to follow the growing condition of the epidemic, the number of confirmed COVID-19 cases who were hospitalized in 32 provinces of Iran (about 200 hospitals) has been monitored for 30 days, since the first day of the declaration of epidemic by Iranian Ministry of Health. The primary data showed that the growth of epidemic might be more prominent in the densely populated and industrial provinces such as Tehran, Isfahan, Shiraz, Razavi Khorasan, East Azerbaijan, and Khuzestan compared with other regions with lower population density and fewer industrial factories (Fig 1).

Unhealthy amount of O_3 and NO_2 is correlated with the increased number of hospitalized COVID-19 patients

To investigate the relationship between air pollution indices and the increased number of COVID-19 patients with severe symptoms, eight cities were randomly chosen from four geographical locations (Fig. 1) (two from each location; west, center, east, and south) in Iran, which were then analyzed for unhealthy ranges of AQI, $PM_{2.5}$, PM_{10}, O_3, and NO_2 for three

years. The data showed a significant positive correlation between unhealthy amounts of O_3 (r = 0.947, p-value < 0.000) and NO_2 (0.889, p-value < 0.003) and the number of hospitalized cases in eight cities (Fig. 2). The present data also revealed that people in cities with more severe patients had been exposed to unhealthy ranges of O_3 (r = 0.953, p-value < 0.000) and NO_2 (r = 0.946, p-value < 0.000) for more days. Moreover, a positive significant correlation was found between population density and the number of severe patients.

No correlation was found between the amounts of AQI, $PM_{2.5}$, and PM_{10}, the number of days with unhealthy ranges of these indices (Supp.Table 1) and the increased number of hospitalized COVID-19 patients (Fig 2).

Discussion

Nowadays, ambient pollution is becoming a disaster worldwide. The increasing number of vehicles, continuous use of fossil fuels, and industrial lifestyle are known as the main sources of most pollutants. Moreover, the harmful effects of environmental pollutants on DNA and the human body (especially the respiratory system) by increasing the expression of inflammatory proteins have been described in various studies (Carosino et al. 2015; Wiegman et al. 2014; MacNee and Donalson 2003; Habibi et al. 2014; Habibi et al. 2013). In Iran, the air pollution problem has originated from different sources. The pollution in Bushehr and Yazd Provinces is mainly caused by dust storms (Geravandi et al. 2018); however, the air pollution occurring in Tehran and Razavi Khorasan (Mashhad) Provinces is due to heavy traffic and the industrial factor (Heger and Sarraf, 2018; Miri et al. 2016; Gholampour et al. 2014).

On the other hand, one of the major features of COVID-19 infection is a high range of clinical symptoms from asymptomatic carriers to severe cases hospitalized due to ARDS (Shi et al.,

2020). Although co-morbidities such as age, type II diabetes, cardiac and respiratory failure, immunodeficiency, and cancer background have been known to be associated with a severe form of COVID-19, less than 50% of the patients in ICU have mentioned a history of these risk factors (Lai et al. 2020; Wu et al. 2020). Therefore, introducing new risk factors could be helpful in explaining the cause of the severity of SARS-CoV-2 infection.

In this study, by comparing the amount of air pollution indices in different cities with various numbers of severe COVID-19 patients, we found that exposure to unhealthy amounts of O_3 and NO_2 for more days might be associated with the severity of SARS-CoV-2 infection, which leads to more severe symptoms in the inhabitants of these areas. The present results are also compatible with the data obtained in other countries (Ogen, 2020; Zhu et al. 2020). These ambient pollutants could cause inflammatory responses in the respiratory system (Zhang et al. 2019), which are also observed in severe forms of SARS-CoV-2 infection.

In conclusion, this study could only reveal the possible synergistic effect of chronic exposure to an unhealthy amount of air pollutants on increasing the severity of COVID-19; however, more long-term molecular, clinical, and environmental studies are needed to introduce air pollution as a risk factor that would result in ARDS among infected patients. Similar studies performed in other cities of Iran and also different countries could be advantageous to prove this effect not only on the severity of SARS-CoV-2 but also on future epidemic respiratory infections. The result of such studies could also be beneficial for considering anti-inflammatory drugs for the treatment of related severe cases.

Acknowledgement:
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Conflict of Interests:

The declared no conflict of interests

Author contribution:

L.H design study, data collection, writing MS. M.S data collection. S.M.A supervision

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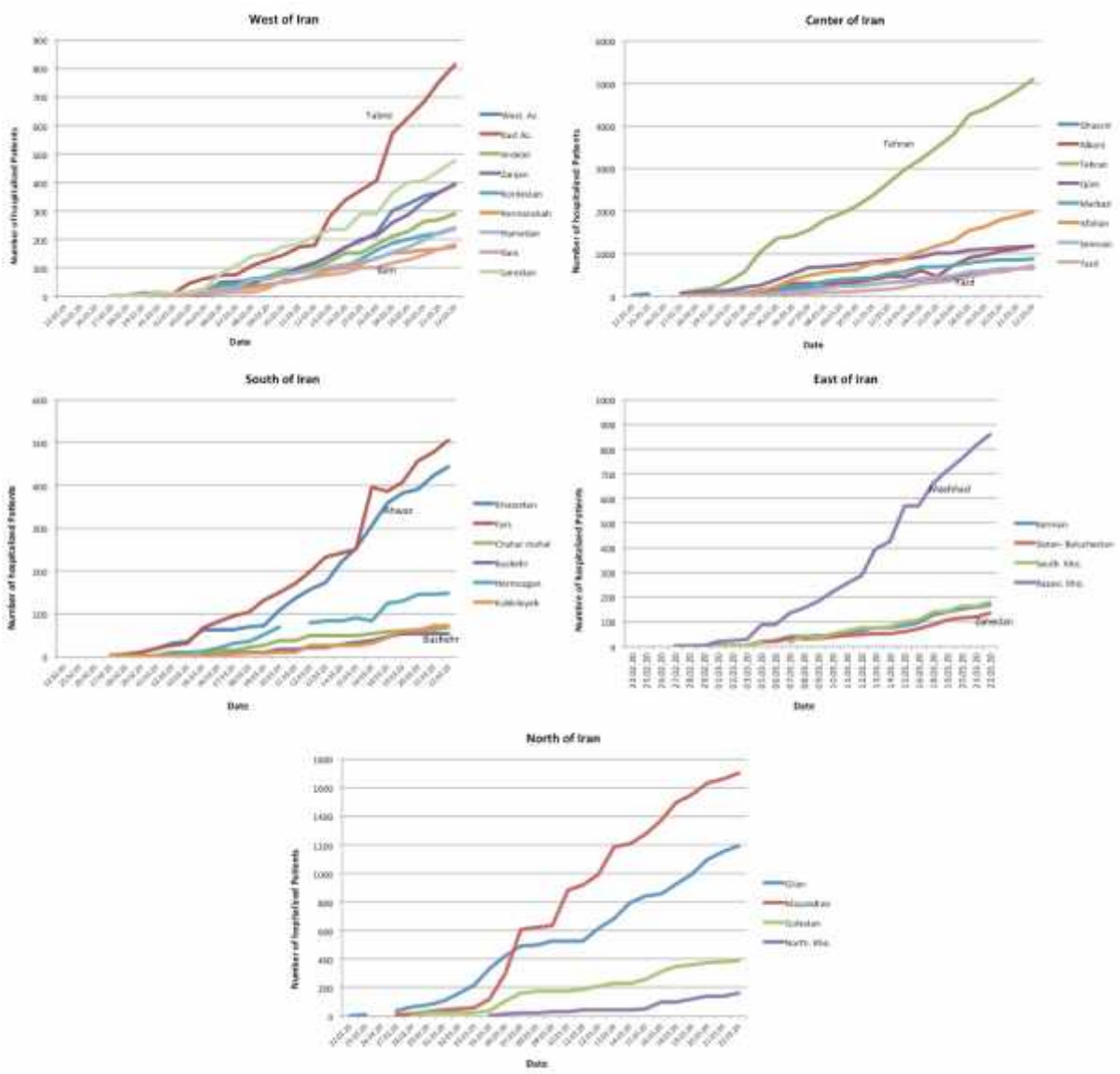

Fig 1. **Increasing number of hospitalized patients during first month of epidemic in Iran**. A) Provinces in five regions of Iran showed different rate of hospitalized patients. Industrial provinces such as Tehran, East Azarbayejan, Razavi Korasan, Khozestan showed higher rate of severe cases than other provinces. Deviation that could be seen for North of Iran was due to traveling of Tehran citizens to this region during the first days of epidemic and before forced quarantine.

Cities (Province) = Busheher (Busheher), Ilam (Ilam), Zahedan (Sistan-Balochestan), Tabriz (East Az.), Yazd (Yazd), Tehran (Tehran), Mashhad (Razavi. Kho), Ahwaz (Khozestan)

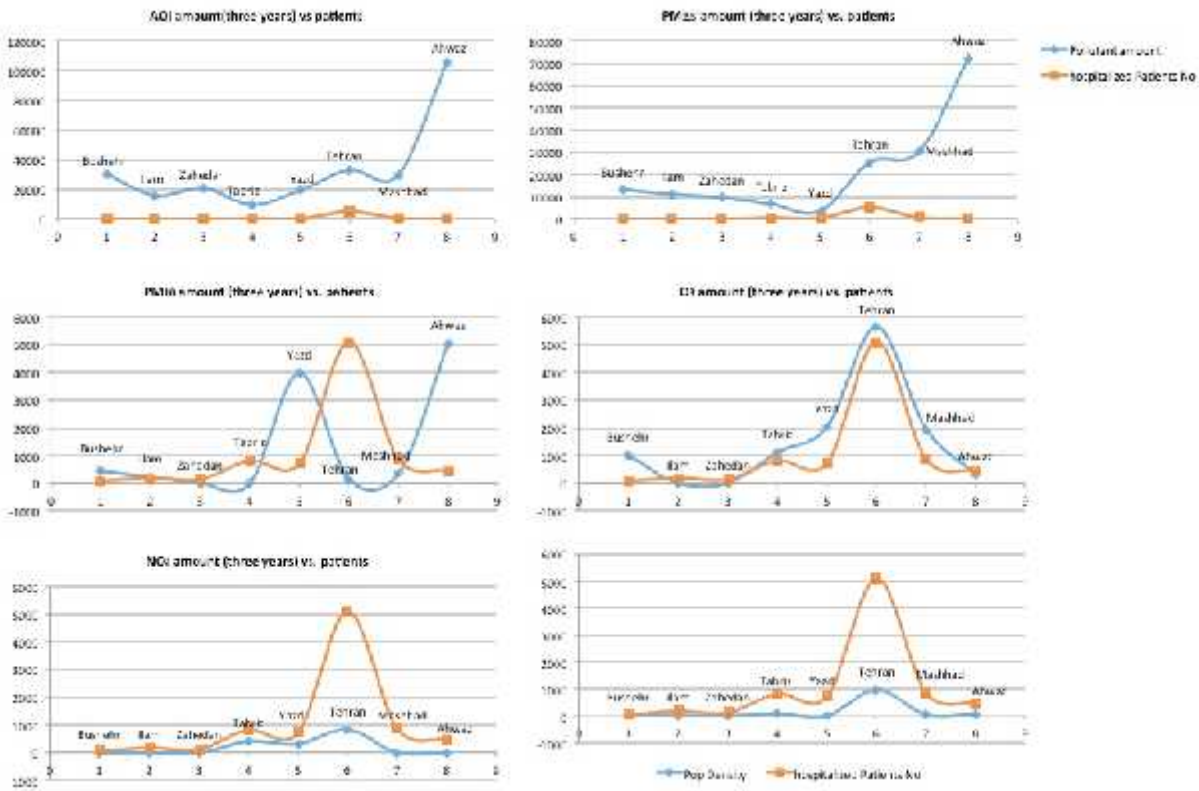

Fig 2. Correlation coefficient between amount of Air pollution indices and number of hospitalized patients in eight cities. Positive significant correlation ($p < 0.05$) could be found for O3 and NO2 concentration for three years (2017-2019) and number of COVID-19 sever cases. Any correlation could be found for AQI, $PM_{2.5}$ and PM_{10}.

Table 1. The result of general population census in eight provinces.

Results of the General Population Census 2015							
Province	Population	PR*	RPD**	Province	Population	PR*	RPD**
Tehran	13,267,637	13,689	969	Yazd	1,138,533	73,872	15
East Az.	3,909,652	45,650	86	Bushehr	1,163,400	22,742	51
Razavi Kho.	6,434,501	118,851	54	Sistan -Baluchestan	2,775,014	181,785	15
Khuzestan	4,710,509	64,054	74	Ilam	1,163,400	20,132	29
Iran	79,926,270	1,628,762	49				

* PR: Province area (Km^2)
**RPD: Relative population density (People per square kilometer)
Az.: Azarbayejan, Kho.: Khorasan

Supp. Table 1: Correlation between air pollution indices (for one year:2019) and number of COVID-19 severe patients in 8 cities of Iran

Variables	Correlation with Number of hospitalized patient in different cities	
	R (p-value > 0.005)	**R (p-value < 0.05)**
Total amount of AQI↑ (2019)	0.276 (0.507)	
Total amount of PM2.5↑ (2019)	0.205 (0.626)	
Total amount of PM10↑ (2019)	-0.184 (0.662)	
Total amount of O3↑ (2019)		**0.769 (0.026)**
Total amount of NO2↑ (2019)		**0.854 (0.007)**
Number of days with AQI↑ (2019)	0.290 (0.485)	
Number of days with PM2.5↑ (2019)	0.229 (0.585)	
Number of days with PM10↑ (2019)	-0.186 (0.659)	
Number of days with O3↑ (2019)		**0.803 (0.016)**
Number of days with NO2↑ (2019)		**0.858 (0.006)**

↑: All air pollution indices reflected to unhealthy for sensitive group or higher

Figures

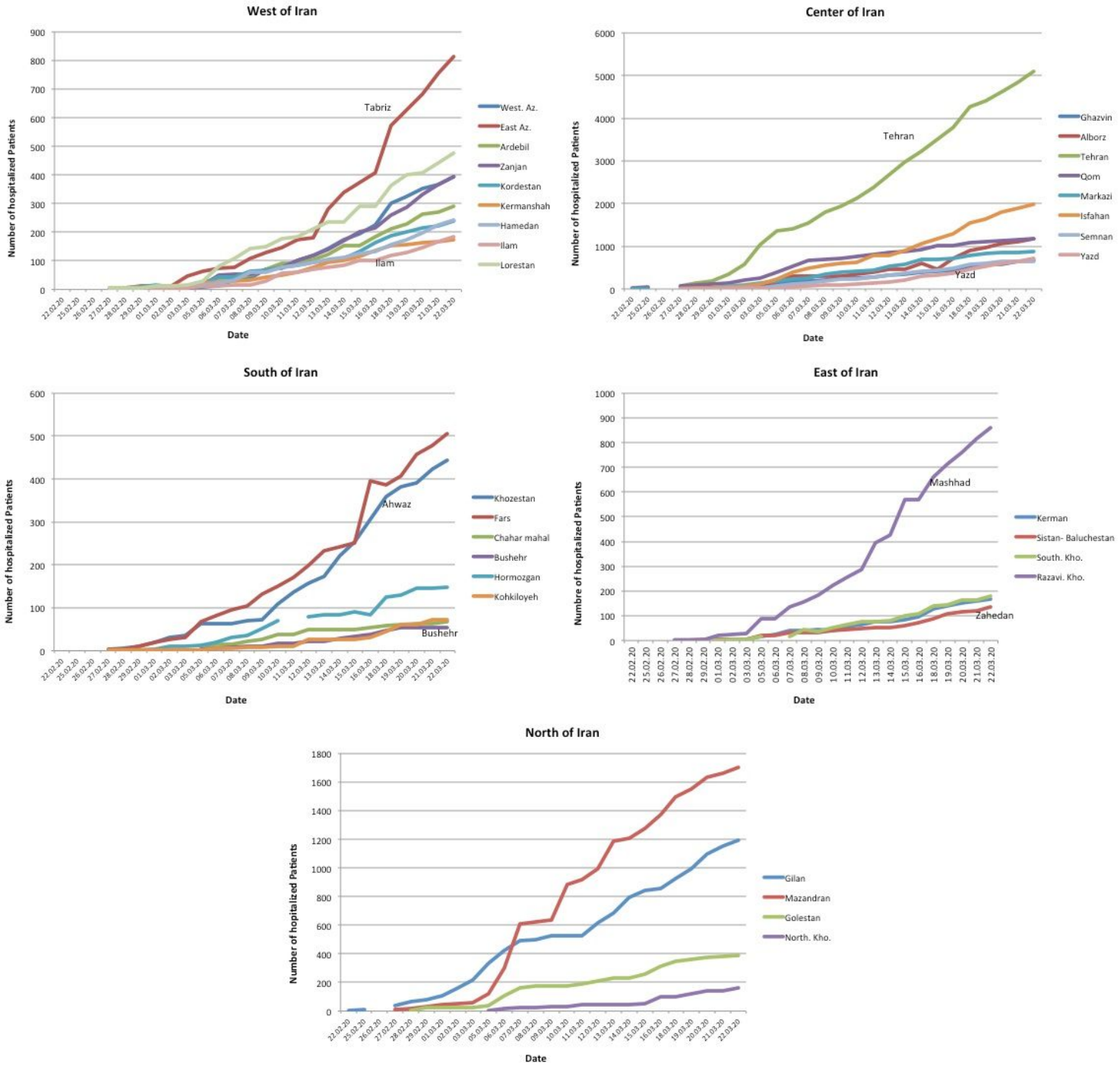

Figure 1

Increasing number of hospitalized patients during first month of epidemic in Iran. A) Provinces in five regions of Iran showed different rate of hospitalized patients. Industrial provinces such as Tehran, East Azarbayejan, Razavi Korasan, Khozestan showed higher rate of severe cases than other provinces. Deviation that could be seen for North of Iran was due to traveling of Tehran citizens to this region during the first days of epidemic and before forced quarantine. Cities (Province) = Busheher (Busheher), Ilam

(Ilam), Zahedan (Sistan-Balochestan), Tabriz (East Az.), Yazd (Yazd), Tehran (Tehran), Mashhad (Razavi. Kho), Ahwaz (Khozestan)

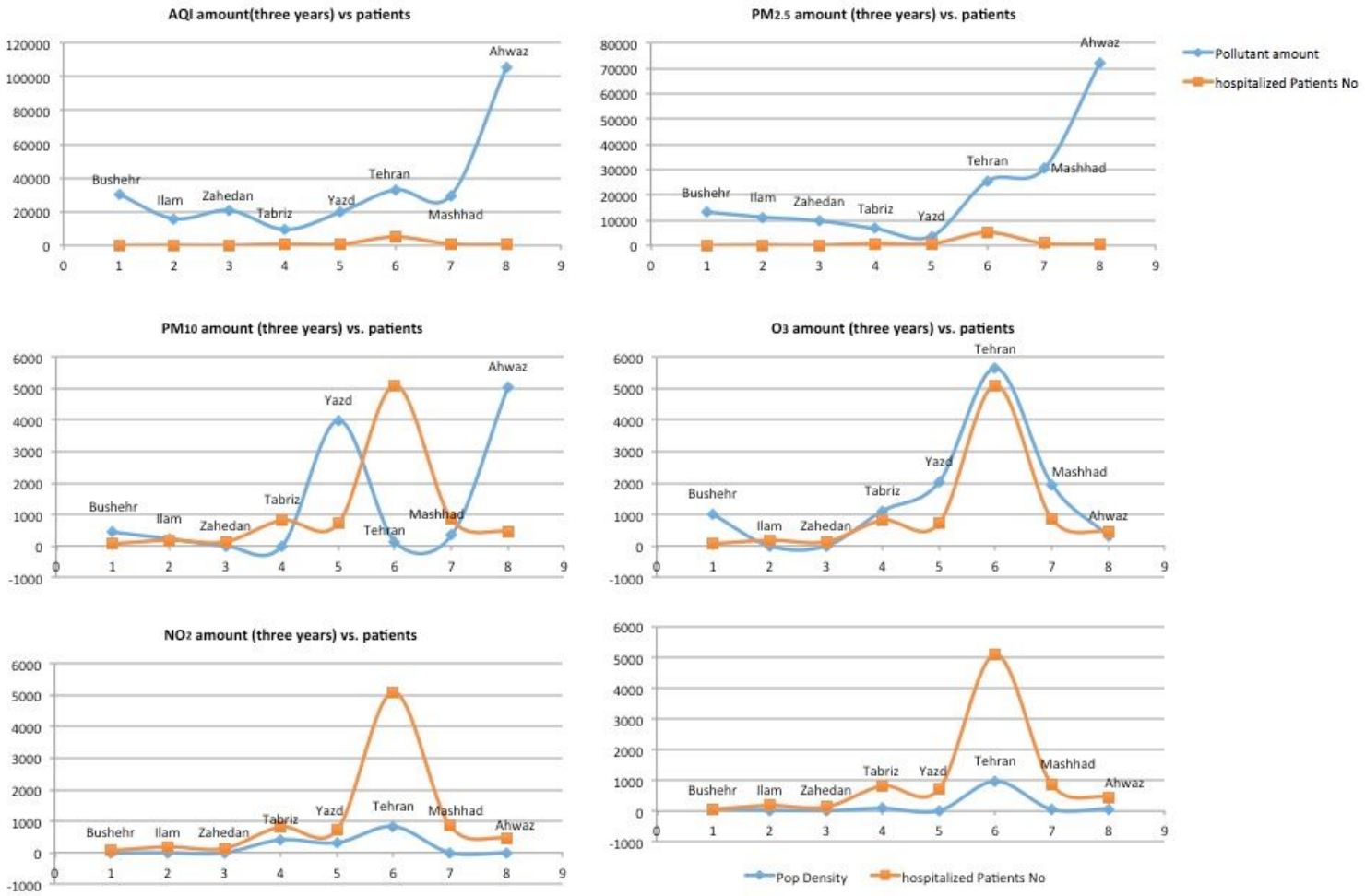

Figure 2

Correlation coefficient between amount of Air pollution indices and number of hospitalized patients in eight cities. Positive significant correlation ($p < 0.05$) could be found for O3 and NO2 concentration for three years (2017-2019) and number of COVID-19 sever cases. Any correlation could be found for AQI, PM2.5 and PM10.

Supplementary Files

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- Supp.Table1.docx