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Original Article

Differences in Clinical Outcomes between Smokers and Non-Smokers infected with COVID-19

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Abstract

Cigarette smoking is a risk factor associated with different diseases, claiming millions of lives annually. Smoking status has been studied for a long time and proved to be a major cause of smokers' decreased immunity. In the present pandemic COVID-19 disease, there was an unclear belief about the effect of smoking on patients with COVID-19. Therefore, the current cross-sectional study aimed to evaluate the effect of cigarette smoking on the sequelae of COVID-19. This cross-sectional study involved 200 COVID-19 patients (114 males and 86 females) aged 13-77 years. A number of 87 patients were smokers, and the rest of them were non-smokers. All patients underwent a comprehensive laboratory assessment and diagnosis by full medical history by the physicians. The results indicated a significant difference (P<0.001) between smokers and non-smokers in terms of hypertension, anticoagulant, steroid therapy, pulmonary lesion, oxygen saturation, and duration of disease. As an overall conclusion, it can be stated that COVID-19 is less severe in smokers and they require less intensive treatment.

Keywords: Cigarette smoking, COVID-19, Smokers, Non-smokers

1. Introduction

Since 2020, the World Health Organization (WHO) has designated coronavirus disease 2019 (COVID-19) as an international public health emergency (1). The COVID-19 has rapidly grown into a global pandemic of predominantly respiratory illness accompanied by significant mortality, particularly among the elderly, generating serious public health concerns (2). Many characteristics, including age, male gender, working in a health care setting, hypertension, diabetes, Chronic obstructive pulmonary disease (COPD), and asthma, have been linked to severity, mortality, and poor outcomes in infected hospitalized individuals (3). Cigarette smoking is an important factor correlated to the poor prognosis of multiple diseases since it affects every organ in the body (4).

There have been diverse reports on the influence of smoking status on the COVID-19 (5). A previous study indicated that severe cigarette smoking was not a significant predictor of COVID-19 severity. Moreover, it reported an unusually low prevalence of current smoking among hospitalized COVID-19 patients, compared to the smoking rates of the general population (6). Smokers are more likely to fall ill with Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as compared to no-smokers (7).

Although no statistically significant relationship was identified between smoking and death (8), other studies revealed that smoking is most likely associated with COVID-19 unfavorable progression and poor outcomes (5).

Recent case studies and publications have found that smoking has a deleterious effect on the course of COVID-19 infection (9). Furthermore, smoking has been identified as a serious factor in the development of COVID-19. In addition, smokers run a greater risk of COVID-19 progress, as compared to non-smokers (10). Since smoking includes the constant connection between hands, saliva, and devices, the viral transmission by smoking may first happen through direct contact (11). Furthermore, the virus is actively discovered on shared surfaces of smoking equipment for 4 hours to 2 to 3 days (11). After oral/nasal releasing, SARS-CoV-2 lives in surfaces (paper, plastic, and steel) and aerosols for numerous hours to days (12, 13).

Cigarette smoke produces high peroxynitrite, hydrogen peroxide, superoxide, and radical hydroxyl levels, exposing endothelium cells to high reactive oxygen species (ROS) and causing oxidative stress (OS) (14). Smoking can increase the expression of the angiotensin-converting enzyme 2 (ACE2) receptor (15), which serves as a binding site for the S protein of SARS-CoV-2. Several investigations revealed that the prevalence of COVID-19 was lower in current smokers, as compared to that in the overall population. Compared to never smokers and former smokers, current smokers had a lower likelihood of being tested positive.

Due to the low incidence of current smokers among COVID-19 patients, it was hypothesized that smoking nicotine intake could have a preventative impact (16). Nevertheless, in another study, it was expected that quitting smoking would lessen the risk of COVID-19 development and the likelihood of facing up to severe COVID-19 consequences. Consequently, clinicians should encourage these patients to quit smoking promptly (17) since smoking is the main risk factor for respiratory infections as a result of the suppressive effect of the immune response, which amplifies the effect of smoking on COVID-19 patients (18).

Tobacco use is a well-known risk factor for asthma, COPD, and lung cancer which all lead to more severe diseases in patients with COVID-19 (19). Guan et al. studied 1,099 Chinese patients with COVID-19 and discovered that about 32% of participants with a smoking history (smokers and ex-smokers) upon admission were diagnosed with a serious type of COVID-19 pneumonia, in comparison to those who never smoked (1). In the present study, we attempted to demonstrate the link between cigarette smoking and COVID-19 sequelae in patients admitted to a major specialized quarantine hospital in Najaf, Iraq.

2. Materials and Methods

2.1. Participants

During one month (December 2020), the current cross-sectional study was conducted in Al-Sadder Teaching Hospital in Najaf Governorate, Iraq. The current study comprised 200 COVID-19 patients (78 smokers and 122 non-smokers). The study population included 114 males and 86 females within the age ranges of 49.18±15.14 and 46.57±13.89 for smokers and 46.57±13.89 for non-smokers. The physicians evaluated them based on their complete medical history. All of the patients had SARS-CoV-2 disease based on a positive COVID-19 test by reverse transcription real-time polymerase chain reaction (rRT-PCR), positive IgM, and other symptoms, such as temperature, cough, as well as loss of smell and taste.

The patients who had pre-diagnostic medical disorders, such as type one diabetes, as well as liver, renal, and cardiac diseases were excluded from the study. All patients underwent a thorough examination, which included a review of their medical history, including their name, age, gender, weight, height, employment, marital status, duration of disease, history of diseases, education, blood pressure, oxygen saturation (SpO2), body temperature, whether they took plasma or not, whether they used O2 aspiration or not,

mode of treatment, and smoking history. Before taking part in the current investigation, all individuals provided written informed permission.

2.2. Measurements

The serum concentrations of electrolytes (Na^+, K^+, and Cl^-) were determined using the HumaLyte Plus5 ion-selective electrolyte analyzer (HUMAN Gesellschaft für Biochemica und Diagnostica mbH, Wiesbaden, Germany). A five-part differential Mindray BC-5000 hematology analyzer was used to evaluate hematological indicators (Mindray Medical Electronics Co., Shenzhen, China). Spectrum Diagnostics Co. kits were used to spectrophotometrically detect serum copper, zinc, and lactate dehydrogenase (Cairo, Egypt). Glucose, albumin, urea, and creatinine were spectrophotometrically analyzed using Biolabo® (Maizy, France) ready-to-use kits. The RT-PCR assays were carried out with the Applied Biosystems® QuantStudioTM 5 Real-Time PCR System (Thermo Fisher Scientific) provided by Life Technologies Holdings Pte Ltd., Marsiling Industrial Estate, Singapore. Quidel Corporation, CA, USA, provided the Lyra® Direct SARS-CoV-2 Assay kits, and the methods were followed as indicated in the kit's manual. The real-time RT-PCR assay for determining the presence of human coronavirus SARS-CoV-2 in viral RNA was recovered from nasal, nasopharyngeal, or oropharyngeal swab tissues. The Assay is intended to detect the non-structural Polyprotein (pp1ab) of the SARS-CoV-2 virus. Patients underwent a chest X-ray and a chest computed tomography scan (CT-scan) to look for lung abnormalities. SOMATOM Definition AS, supplied by Seimens, Munchen, Germany, was used to create CT scans.

2.3. Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the distribution of the results, which revealed a normal statistical distribution for all of the measured values. All results were presented as mean, standard deviation, or median (25%-75%) interquartile. In the measured parameters, the pooled t-test was employed to compare the patients, control groups, and subdivided groups. The correlation between the parameters was estimated using Pearson's correlation coefficients (r). The effects of diagnosis were evaluated using a general linear model (GLM) while controlling for perplexing factors, such as body mass index (BMI) and age. A p-value less than 0.05 was considered statistically significant. The data were analyzed in SPSS software (version 25).

3. Results

3.1. Demographic and Clinical Information of Smokers and Non-Smokers Infected with COVID-19

The clinical and demographic characteristics of smokers and non-smokers with COVID-19 were presented in table 1. The results indicated a significant increase in the number of patients with hypertension ($P<0.001$) in smokers, as compared to that in non-smokers, where 28% of non-smokers had hypertension, in comparison with 30% of smokers ($P<0.001$). There was also a significant difference in the treatment taken by the two groups, where the non-smokers needed more anticoagulants and steroids, demonstrated pulmonary lesions in the chest CT-scan, and had lower SpO_2 and disease duration, as compared to non-smokers. About 63% of non-smokers and 50% of smokers needed anticoagulant and steroid therapy, respectively, in contrast to 17% and 19% of smokers. Moreover, a pulmonary lesion was found in 61% and 82% of smokers and non-smokers, respectively ($P<0.001$). In addition, SpO_2 was higher in smokers (95.10±2.79%), compared to that in non-smokers (88.49±6.01%). For disease duration, smokers spent (as a mean±SD) about 7.96±4.17 days, while non-smokers spent about 11.59±4.95 days ($P<0.001$). Other demographic characteristics showed no significant difference between the two groups.

Table 1. Demographic and clinical data in smokers and non-smokers infected with COVID-19

Variables		Non-Smokers (n=122)	Smokers (n=78)	F/χ^2	*P*
Gender	M/F	58/64	57/21	1.570	0.212
Age	years	46.57±13.89	49.18±15.14	1.570	0.212
Weight	kg	77.17±11.43	78.95±9.65	1.294	0.257
Height	cm	168.82±11.36	170.38±11.06	0.921	0.338
BMI	kg/m^2	27.22±4.25	27.32±3.43	0.027	0.870
Education	years	8.07±5.06	9.67±12.42	1.552	0.214
Employment	Y/N	33/89	24/54	1.294	0.257
Marital status	M/S	99/23	66/12	0.921	0.338
Autoimmune dis.	Y/N	3/119	1/77	0.027	0.870
Heart diseases	Y/N	4/118	7/71	1.552	0.214
Respiratory dis.	Y/N	6/116	8/70	0.320	0.572
T2DM	Y/N	29/93	10/68	0.166	0.685
Hypertension	Y/N	35/87	24/54	82.878	<0.001
Convalescent plasma	Y/N	48/74	8/70	0.033	0.856
O_2therapy	Y/N	88/34	12/66	0.532	0.467
Anticoagulant	Y/N	78/44	14/64	25.577	<0.001
Steroid therapy	Y/N	61/60	15/63	30.647	<0.001
Pulmonary lesion	Y/N	101/21	48/30	54.228	<0.001
SBP	mm/Hg	125.86±16.61	127.31±19.15	0.320	0.572
DBP	mm/Hg	82.72±13.85	81.99±9.85	0.166	0.685
SPO_2		88.49±6.01	95.10±2.79	82.878	<0.001
Duration of disease	days	11.59±4.95	7.96±4.17	28.791	<0.001
Body temperature	C°	38.94±0.57	38.18±0.60	1.864	0.562

3.2. Biochemical and Hematological Results of Smokers and Non-Smokers

All biochemical and hematological results of smokers and non-smokers with COVID-19 are illustrated in table 2. The results pointed to a significant increase ($P<0.05$) in the number of positive Anti-SARS-CoV-2 IgG and IgM, PCR, C-reactive protein (CRP), D-dimer, and Lactate dehydrogenase (LDH) in non-smokers, as compared to that in smokers. Smokers displayed higher hemoglobin and ferritin than non-smokers. Other factors demonstrated no significant difference between the studied groups.

3.3. Correlation between the Lab Results and Demographic and Clinical State of COVID-19 Patients

The results in table 3 revealed the correlation matrix of the measured biomarkers with the demographic and clinical biomarkers in all the study subjects. These results suggested that smoking is negatively correlated with CRP, D-dimer, LDH, and Ferritin, while it is positively correlated with hemoglobin. In addition, the results pointed to the different correlation of the measured biomarkers with the demographic and clinical biomarkers, as depicted in the referred table.

3.4. Correlation between the Lab Results and the Therapy of COVID-19

The correlation matrix of the measured biomarkers with the therapy of COVID-19 in all the study subjects is illustrated in table 4. It was indicated that Convalescent plasma and O2 therapy were positively correlated with IgG, IgM, CRP, urea, creatinine, D-dimer, ferritin, and LDH, while anticoagulant therapy was positively correlated with CRP, urea, creatinine, D-dimer, ferritin, LDH, and RBS and negatively correlated with PCR. Steroid therapy has a positive association with CRP, D-dimer, Ferritin, and LDH, as well as a negative correlation with random blood sugar (RBS).

3.5. The Smoking Size Effect on the Lab Results of COVID-19 Patients

Table 5 demonstrates the multivariate GLM analysis results of examining the effect of smoking on the measured parameters in COVID-19 patients. The analysis was made to find out the effect of cofounders

on the levels of the measured biomarkers. The following cofounders had a significant effect on the biomarkers: gender (F=3.947, *P*<0.001, Partial η^2 =0.189), smoking (F=1.912, *P*=0.047, Partial η^2=0.102), age (F=1.894, *P*=0.049, Partial η^2 =0.101), and SPO_2 (F=4.472, *P*<0.001, Partial η^2=0.209). To explore the biomarker that was mostly affected by smoking, we performed the between-subject effect analysis. Smoking had a significant effect on CRP (F=10.959, *P*<0.001, Partial η^2=0.058) and LDH (F=5.116, *P*=0.025, Partial η^2=0.028). The overall findings indicated a small effect size of smoking on the clinical parameters of COVID-19 patients. Another important finding of the between-subject analysis was the significant effect of SPO2 (F=24.018, *P*<0.001) on CRP results in patients with an effect size (partial eta=0.119). Furthermore, gender had a significant effect (F=30404, *P*<0.001) on the results of hemoglobin in COVID-19 patients with an effect size (partial eta=0.149).

Table 2. Biochemical and hematological results of smokers and non-smokers infected with COVID-19

Variables		Non-Smokers (n=122)	Smoker (n=78)	F/χ^2	*P*
Anti-SARS-CoV-2 IgG	+/-	44 (36%)/78 (70%)	27 (34%)/51(65%)	28.791	<0.001
Anti-SARS-CoV-2 IgM	+/-	83 (68%)/39 (31%)	55 (70%)/23 (29%)	83.864	<0.001
PCR result	+/-	96 (78%)/26 (21%)	69 (88%)/9 (12%)	67.491	<0.001
CRP	mg/l	48 (25-79.25)	8.9 (5.95-23.2)	67.491	<0.001
Urea	mg/dl	28 (23-35.25)	28.5(23.75-34)	0.033	0.856
Creatinine	mg/dl	0.8 (0.6-0.905)	0.8 (0.7-0.905)	0.532	0.467
D-Dimer	µg/ml	0.9 (0.6-1.425)	0.6 (0.3925-0.8)	25.577	<0.001
S.Ferritin	ng/ml	200.47±65.71	293.73±139.08	30.647	<0.001
LDH	U/L	260.11±78.98	182.64±61.13	54.228	<0.001
Glucose	mg/dl	117.5 (103-132.25)	120 (106.5-130)	3.859	0.051
WBC	$*10^9$/L	7.1 (5.35-9.5)	7.15 (5.05-10)	0.489	0.485
Lymphocytes	%	32.4 (24.9-38.63)	31.9 (25.18-39.03)	0.036	0.849
Monocytes	%	8.25 (6.55-10.25)	7.9 (6.475-9.925)	1.794	0.182
Granulocytes	%	58.55 (52.05-65.825)	57.5 (52.4-66.88)	0.326	0.569
Hemoglubin	g/dl	12.58 (11.8-14.13)	13.9 (12.2-15)	4.903	0.028
RBC	$*10^{12}$/L	4.69 (4.36-5.03)	4.85 (4.47-5.21)	1.082	0.299
Hematocrit	%	38 (34.85-40.65)	39.2 (35.48-42.9)	2.241	0.136
MCV	fL	81.6 (76.8-84.9)	81.7 (77.88-85.13)	0.471	0.493
MCH	pg	27.6 (25.6-29.43)	28.6 (26.28-30.5)	2.015	0.157
MCHC	g/dl	33.85 (32.7-35.63)	34.4 (33.3-36.73)	4.147	0.058
RDW-CV	%	14 (13.15-14.8)	13.75 (13-15.03)	0.210	0.647
RDW-SD	fL	42.5 (38.5-45.7)	42.5 (38.28-45)	0.132	0.717
Platelets count	$*10^9$/L	253 (217.5-293.5)	253.5 (215.75-313.5)	0.000	0.987

CRP: C-reactive protein, LDH: Lactate dehydrogenase, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, MCV: *mean corpuscular volume*, RBC: Red blood cells count, RDW-SD: red cell *distribution width-standard deviation*, RDW-CV%: red cell *distribution width-coefficient of variance*, and WBC: White blood cells count

Table 3. Correlation matrix of the measured biomarkers with the demographic and clinical biomarkers in all the study subjects

	IgG	IgM	PCR	CRP	Urea	Creatinine	D-Dimer	Ferritin	LDH	RBS	WBC	HGB	RBC	PLT
Sex	-0.123	-0.139	0.136	-0.186*	-0.147	-0.058	-0.116	-0.061	-0.13	-0.069	0.103	.509*	.334*	-0.08
White lesion	0.098	0.178	-0.179	0.411*	0.197*	0.147	0.319*	0.308*	0.395*	0.104	0.07	0.037	0.165	-0.01
Age	0.138	0.117	-0.096	0.213*	0.286*	0.354*	0.216*	0.115	0.129	0.076	-0.06	0.025	0.102	-0.023
BMI	0.093	0.107	-0.032	0.105	0.008	0.071	0.043	-0.025	0.122	0.121	-0.074	-0.166	-0.170	0.044
SBP	0.102	0.209*	-0.181	0.021	0.205*	0.326*	0.097	0.003	0.032	0.272*	-0.039	-0.045	0.047	0.021
DBP	0.097	0.180	-0.064	0.118	0.215*	0.323*	0.179	0.04	0.148	0.240*	-0.048	-0.009	0.028	0.038
SPO_2	-0.152	-0.164	0.137	-0.697*	-0.174	-0.195*	-0.491*	-0.549*	-0.588*	-0.125	-0.038	0.055	-0.014	-0.041
Duration of disease	0.179	0.114	-0.096	0.429*	0.042	0.074	0.364*	.374*	0.397*	0.150	0.083	0.013	0.113	0.058
Body Temp.	0.143	0.153	-0.068	0.580*	0.019	0.006	0.388*	0.359*	0.471*	0.09	0.019	-0.097	-0.07	-0.08
Smoking	-0.015	0.026	0.125	-0.504*	-0.013	-0.052	-0.338*	-0.366*	-0.464*	-0.138	0.05	0.155	0.074	-0.001

* Correlation is significant at the 0.01 level (2-tailed). CRP: C-reactive protein, LDH: Lactate dehydrogenase, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, MCV: *mean corpuscular volume*, RBC: Red blood cells count, RDW-SD: red cell *distribution width-standard deviation*, RDW-CV%: red cell *distribution width-coefficient of variance*,and WBC: White blood cells count

Table 4. Correlation matrix of the measured biomarkers with the therapy of COVID-19 in all the study subjects

	IgG	IgM	PCR	CRP	Urea	Creatinine	D-Dimer	Ferritin	LDH	RBS
Convalescent plasma	0.142*	0.153*	-0.035	0.393**	0.175*	0.142*	0.396**	0.347**	0.379**	0.003
O2 therapy	0.199**	0.238**	-0.118	0.584**	0.142*	0.170*	0.460**	0.472**	0.540**	0.062
Anticoagulanttherapy	0.112	0.12	-0.156*	0.521**	0.175*	0.196**	0.426**	0.497**	0.554**	0.170*
Steroid therapy	0.075	-0.009	-0.012	0.366**	0.048	0.017	0.320**	0.242**	0.415**	-0.169*

Table 5. Results of multivariate generalized linear model analysis examining the effect of smoking on the measured parameters in COVID-19 patients

Tests	Dependent variables	Explanatory variables	F	*P*	Partial η^2
Multivariate	All 10 Biomarkers	Sex	3.947	<0.001	0.189
		Autoimmune disease	0.640	0.778	0.036
		Heart diseases	0.536	0.863	0.031
		Respiratory disease	0.577	0.832	0.033
		T2DM	1.164	0.319	0.064
		Hypertension	1.320	0.223	0.072
		Convalescent plasma	0.618	0.797	0.035
		O_2aspiration	0.282	0.984	0.016
		VD-Zn-Panadol-Azthr	1.172	0.313	0.065
		Anticoagulant	1.467	0.156	0.080
		Steroid therapy	1.403	0.183	0.077
		Smoking	1.912	0.047	0.102
		White lesion inCTscan orXR	1.649	0.097	0.089
		Age	1.894	0.049	0.101
		BMI	0.953	0.486	0.053
		SBP	0.551	0.852	0.032
		DBP	0.359	0.962	0.021
		SPO_2	4.472	<0.001	0.209
		Duration of disease	1.094	0.370	0.061
		Body Temperature	1.088	0.374	0.060
Between-subject effects	CRP	Smoking	10.959	0.001	0.058
	B.Urea		0.093	0.761	0.001
	S.Cr		0.739	0.391	0.004
	D-Dimer		0.596	0.441	0.003
	S.Ferritin		0.075	0.785	<0.001
	LDH		5.116	0.025	0.028
	WBC		0.524	0.470	0.003
	HGB		1.768	0.185	0.010
	RBC		0.765	0.383	0.004
	PLT		0.517	0.473	0.003

All results of the multivariate generalized linear model analysis with the biomarkers as dependent variables and diagnosis as an explanatory variable while adjusting for extraneous variables .MI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

SPO_2 has a significant effect (F=24.018, *P*<0.001) on the results of CRP in COVID-19 patients with an effect size (partial eta=0.119).
Gender has a significant effect (F=30404, *P*<0.001) on the results of HGB in COVID-19 patients with an effect size (partial eta=0.149).

4. Discussion

Since the Covid-19 pandemic is still in its early stages, there is a paucity of data on the clinical features of patients just as their predictive factors, particularly smoking (20). Until now, smoking has been believed to be conceivably related to poor illness prediction (1, 21) due to significant evidence highlighting the deleterious effect of cigarette smoke on lung health and the causative relationship with an assortment of respiratory problems (22). The immune system and its ability to respond to infections are also affected by smoking, making smokers defenseless against infectious illnesses (23). Preceding research has found that smokers are twice pretty much as reasonable as non-smokers to get flu, have more serious symptoms, and their death rate was higher during the COVID-19 outbreak (10). According to Prats-Uribe, Xie (24), the effect of smoking on COVID-19 infection with eventual death is influenced by age. Mortality was also shown to be higher among infected smokers, when compared to never smokers (25).

Although smoking increases the risk of infection with bacterial and viral diseases, such as the common cold, influenza, and tuberculosis (26), multiple observational

studies have recently discovered an inverse link between smoking and SARS-CoV-2 infection (COVID-19). In a cohort study which involved 78 COVID-19 participants, the investigators reported that the health of an elevated percentage of smokers quickly deteriorated after admission, in comparison to that of non-smokers (27% versus 3%, P=0018), implying that smoking might harm COVID-19 prognosis (9). In the same context, Williamson, Walker (27) discovered a small protecting influence against COVID-19 mortality in existing smokers.

Inhaled smoke causes matrix degradation, a lack of flow of blood, and epithelial cells death; moreover, it causes inflammatory cells to infiltrate the mucosa and glandular tissue (28). Furthermore, smoking is linked to various changes in the cellular and humoral immune systems (29). Nicotine affects renin-angiotensin system (RAS) homeostasis (30) and contributes to the up-regulation of the angiotensin-converting enzyme (ACE)/angiotensin (ANG)-II/ANG II type one receptor axis, which leads to heart and respiratory disorders (30).

Smoking may increase COVID-19 risk via upregulating the ACE2 (15) and encouraging the blood-brain barrier (BBB) integrity loss and viability (31). According to a recent study, cigarette smoking can enhance cellular uptake of the SARS CoV-2 virus via the 7nAChR signaling mechanism. Since 7nAChR is found in neuronal and nonneuronal cells, smoking may play a pathogenesis role for SARS-CoV-2 and influence various body organs, containing the brain (32). In another study, smokers were less inclined to be determined to have COVID-19; nonetheless, the extent of patients screened for COVID-19 with smoking was fundamentally not the same as the local area smoking predominance (33). Other investigations discovered a link between smoking and poor outcomes in hospitalized COVID-19 patients (5, 10). No significant variations were found in laboratory results, including D-dimer and CRP values, except for different covariances for lymphocyte and neutrophil density (34).

Patients hospitalized with COVID-19 had a lower rate of active smoking than the general population. There was no link between smoking status and disease severity, prognosis, or mortality in this investigation (35). Smokers are thought to be at a higher risk of death and severe pneumonia in the current COVID-19 epidemic. On the other hand, contrary to previous results, smoking was not related to increased in-patient mortality in COVID-19 pneumonia. The demographic and clinical findings of the current cross-sectional investigation, as displayed in tables 1 and 2, revealed a substantial difference in many of the examined factors for smokers and non-smokers. The findings pointed out that non-smokers had higher levels of these characteristics than smokers. Consequently, the results of the current research are consistent with those reported in a previous study that found an inverse connection between smoking status and SARS-CoV-2 infection.

A meta-analysis and systematic review focusing on smoking with COVID-19 progression pointed to serious progress of the disease in 17.8% of smokers compared to 9.3% of non-smokers, as well as the significant correlation of smoking with disease severity (10). Numerous studies revealed that the reported prevalence of smoking in hospitalized patients was significantly less than that in the respective demographics. Smoking may worsen the sternness of SARS-CoV-2 by reducing the BBB integrity and increasing the ACE2 expression (it is the main mediator of SARS-CoV-2 cell invasion and proliferation) in glia endothelial cells and neurons (36).

Cigarette smoking appears to promote a dose-dependent increase in angiotensin-converting-enzyme-2 (the virus cellular entry receptor) that could clarify why smokers have a higher risk of severe COVID-19 (37). Nicotine may protect against COVID-19 due to its anti-inflammatory characteristics, as well as a possible direct interaction between SARS-CoV-2 and nicotinic acetylcholine receptors (38). The plausible mechanisms of action of smoking provide some protection against seriously symptomatic COVID-19. Smoking appears to

affect and increase the expression of the ACE2 receptor which is a recognized receptor for SARS-CoV and the human respiratory coronavirus. The ACE2 has the potential to serve as a novel adhesion molecule for SARS-CoV-2, which leads to COVID-19, as well as a possible therapeutic target for the avoidance of fatal microbiological infections, and therefore, it should be prioritized for research and development (15, 39). Downregulation is easily recognized as potentially beneficial against infection, while upregulation may be preventive against the development of serious lung disease (40).

Intensive fatiguing activities, such as sport and smoking, that require high respirational volumes, changing breathing from nose to mouth, deep inhalation, progressive cooling and drying of respiratory tract mucous, decreased movement of ciliated cells, and increased mucosal viscosity impair the filtering of microorganisms from the upper respiratory tract system. These methods are thought to let the virus move to lower airways and alveoli by bypassing the natural immune response in the oral cavity and upper respiratory airways and allowing virus penetration to lower airways at a stage when an adaptive immune response has not yet been begun (40). Another mechanism of concern is nitric oxide (NO) which is related to nicotine and abundant in cigarettes. Smokers are exposed to elevated NO in inhaled smoke and endogenously produce NO after being uptaken by nicotine in the brain (41). Nitric oxide has an effect against viruses and has been revealed in vitro to diminish H1N1 infectivity (42). Increased nitric oxide levels are linked to faster virus clearance (43).

The smokers infected with COVID-19 have lower rates of pulmonary lesions in the chest CT-scan and shorter disease duration than non-smokers. Non-smokers need anticoagulant and steroid therapy more than smokers and have lower SPO_2, as compared to smokers. The number of positive Anti-SARS-CoV-2 IgG and IgM, PCR, CRP, as well as the levels of D-dimer and LDH, was higher in non-smokers, as compared to that in smokers. Smoking was negatively correlated with CRP, D-dimer, LDH, and ferritin, while it was positively associated with hemoglobin. To explore the biomarker that was mostly affected by smoking, we performed the between-subjects effect analysis. The effect size of smoking was significant on CRP and LDH. The results of the present study pointed out that COVID-19 is less severe in non-smokers and they require less intensive treatment.

Authors' Contribution

Study concept and design: N. H. A. A.
Acquisition of data: S. Z. A.
Analysis and interpretation of data: D. M. M. A.
Drafting of the manuscript: H. K. A.
Critical revision of the manuscript for important intellectual content: N. H. A. A.
Statistical analysis: S. Z. A.
Administrative, technical, and material support: D. M. M. A.

Ethics

All processes were accomplished as per the perceived moral norms. The Iraqi institutional audit board (IRB) at the University of Kufa (611/2021), Kufa, Iraq, authorized the protocol.

Conflict of Interest

The authors declare that they have no conflict of interest.

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