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Symptoms COVID 19 Positive Vapers Compared to COVID 19 Positive Non-vapers

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Abstract

Objectives: The purpose of the present study was to assess and describe the severity of symptoms reported by Covid-19 positive patients who vaped (smoked e-cigarettes) when compared to those who did not vape or smoke at the time of the diagnosis of Covid-19. **Methods:** Patients from this study are from a well-characterized patient cohort collected at Mayo Clinic between March 1, 2020 and February 28, 2021; with confirmed COVID-19 diagnosis defined as a positive result on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays from nasopharyngeal swab specimens. Among the 1734 eligible patients, 289 patients reported current vaping. The cohort of vapers (N = 289) was age and gender matched to 1445 covid-19 positive patients who did not vape. The data analyzed included: date of birth, gender, ethnicity, race, marital status, as well as lifestyle history such as vaping and smoking and reported covid-19 symptoms experienced. **Results:** A logistic regression analysis was performed separately for each symptom using generalized estimating equations (GEE) with robust variance estimates in order to account for the 1:5 age, sex, and race matched set study design. Patients who vaped and developed Covid-19 infection were more likely to have chest pain or tightness (16% vs 10%, vapers vs non vapers, $P = .005$), chills (25% vs 19%, vapers vs non vapers, $P = .0016$), myalgia (39% vs 32%, vapers vs non vapers, $P = .004$), headaches (49% vs 41% vapers vs non vapers, $P = .026$), anosmia/dysgeusia (37% vs 30%, vapers vs non vapers, $P = .009$), nausea/vomiting/abdominal pain (16% vs 10%, vapers vs non vapers, $P = .003$), diarrhea (16% vs 10%, vapers vs non vapers, $P = .004$), and non-severe light-headedness (16% vs 9%, vapers vs non vapers, $P < .001$). **Conclusion:** Vapers experience higher frequency of covid-19 related symptoms when compared with age and gender matched non-vapers. Further work should examine the impact vaping has on post-covid symptom experience.

Keywords

vaping, covid-19, e-cigarettes

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Introduction

Over the last 10 years, there has been a significant increase in use of e-cigarettes, particularly among high school students and young adults. Notably, there was a 78% increase in use of e-cigarettes from 2017 to 2018 among high school students.[1] In 2019, 10.5% of middle school students, 27.5% of high school students, 21% of millennials (age 23-28), and 18% of generation X (age 39-54) were vaping.[2] Approximately 32.6% of students reported frequent use of e-cigarettes and 8.2% of high school students currently used 2 or more tobacco products when surveyed in 2019.[3] There has also been a perception that use of e-cigarettes is safer than combustible cigarettes. In fact, e-cigarettes have been recommended for assistance in smoking cessation, notably in the U.K.[4] However, it is widely recognized in both the medical and public health communities that the short- and long-term health effects of e-cigarettes are unknown. These uncertainties are compounded by the heterogeneity of e-cigarette content and

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use. Individuals may purchase pre-packaged e-cigarettes but can also obtain them from informal sources or add ingredients to the vaping reservoir or e-liquid.

In 2019, there was an outbreak of e cigarette associated lung injury (EVALI) which ultimately resulted in 2807 cases and 68 deaths by February 2020, at which point the Centers for Disease Control and Prevention (CDC) stopped reporting on cases. This was due to the evolving COVID outbreak which overwhelmed the medical and public health communities. The main cause of the EVALI outbreak was felt to be inhalation of vitamin E acetate, which was added to vaping products as a diluent, particularly among those who were vaping *Tetrahydrocannabinol* (*THC*). Several reports have noted the difficulty in distinguishing between EVALI and COVID-19 as there is significant overlap in the presenting signs and symptoms, most notably cough, fever and shortness of breath.[5-7]

Evaluation of e-cigarette use and susceptibility to COVID-19 is made more complex by the heterogeneity of vaping products. E-cigarettes may or may not contain nicotine, the amount of nicotine varies and is not always accurately represented on the labeling. Other additives such as flavoring can change their effect on the respiratory epithelium and potential for harmful side effects. A recent review of available studies on the harms of e-cigarettes concluded that e-cigarette consumption is likely less toxic than tobacco smoking but not necessarily without harmful effects. There are many areas of study still needed, particularly regarding effects of long-term use.[8] With regard to susceptibility to COVID-19 and severity of disease, the data remain conflicting.[9-12] An article published by Gaiha et al[13] in July 2020, concluded that COVID-19 was "five times more likely among ever users of c-cigarettes and 7 times more likely amongst dual users." However, another study found that using e-cigarettes did not pose an increased risk for COVID-19.[14] There have been several letters and publications[15,16] which have been critical of the quality of data and analysis used by Gaiha et al.[13] Aside from the content and potential harms of e-cigarettes, sharing of vaping devices has been raised as a potential concern for the spread of COVID-19.

Although still unclear, there is a suggestion that both cigarettes and e-cigarettes can upregulate the ACE2 receptors in brain and lung tissue, thus creating an environment for increased COVID-19 viral binding and entry into host cells. Dual cigarette and e-cigarette use could pose a significant risk for worse outcomes in COVID.[17,18] A recently published study conducted in the United Kingdom, looked at 4 birth cohorts and compared self-reported symptoms, testing, diagnosis and social distancing behaviors across 4 product user groups: non-users, only cigarette and only e cigarette and dual users. Of the 3% of respondents that were dual users, statistically significant differences were found with regards to symptoms, COVID-19 infection and compliance with social distancing. Dual users had a 2.15 X higher odds of reporting COVID-19 infection and were less likely to comply with social distancing. Dual users also had the highest percentage of COVID-19 related symptoms (eg, dry cough, fever, loss of sense of smell or taste or shortness of breath) in the past 2 weeks.[19]

Given this overlap of pathologic findings, we considered that patients who use e-cigarettes were more likely to develop symptoms following infection by SARS-CoV-2 and were more likely to have severe symptoms than non-e-cigarette users.

Methods

This report is a retrospective analysis of a prospective study which was approved by the Institutional COVID-19 Research Committee. This initial prospective study, under which this analysis took place, was also reviewed by our Institutional Review Board (IRB) and determined to be exempt under section 45 CFR 46.101, item 2. During the study, all significant changes to study design and procedures were appropriately filed, reviewed, and approved by the IRB. The database resulting from this larger exempt study was maintained our COVID-19 Frontline Care Team (CFCT) utilizing Research Electronic Data Capture (REDCap) program.[20]

Setting

The COVID-19 pandemic placed an unprecedented strain on the global health care infrastructure, particularly on resources related to hospital bed space, ventilators, and healthcare personnel. Telemedicine allowed for teams to simultaneously extend reach of care, maintain continuity, and protect personnel from risk of infection. The majority of patients had asymptomatic or mild cases of infection, which could be effectively managed in the outpatient setting. Potential participants were recruited from a large health care facility in Midwestern United States. Within this practice there are 4 medical facilities within 2 states (Minnesota and Wisconsin). Multidisciplinary collaboration with effective communication protocols was critical to the successful implementation of telehealth monitoring. A collaborative working relationship with colleagues from general internal medicine, infectious disease, pediatrics, nephrology, oncology, emergency and hospital medicine, and Olmsted County Public Health facilitated coordinated care for complex patients. A partnership was formed with the Department of Connected Care. Connected Care provides technical support for the development of remote patient monitoring of vital signs through Bluetooth devices. Real time 24-h remote patient monitoring by nursing staff allowed for intensive monitoring of high risk and moderately ill patients and rapid triage of decompensating patients early identification of clusters of cases.

This report is based on all participants who were enrolled in this larger database between March 1, 2020 and February 28, 2021. The consort diagram presented in Figure 1 adheres to consort guidelines on reporting clinical trials.[21]

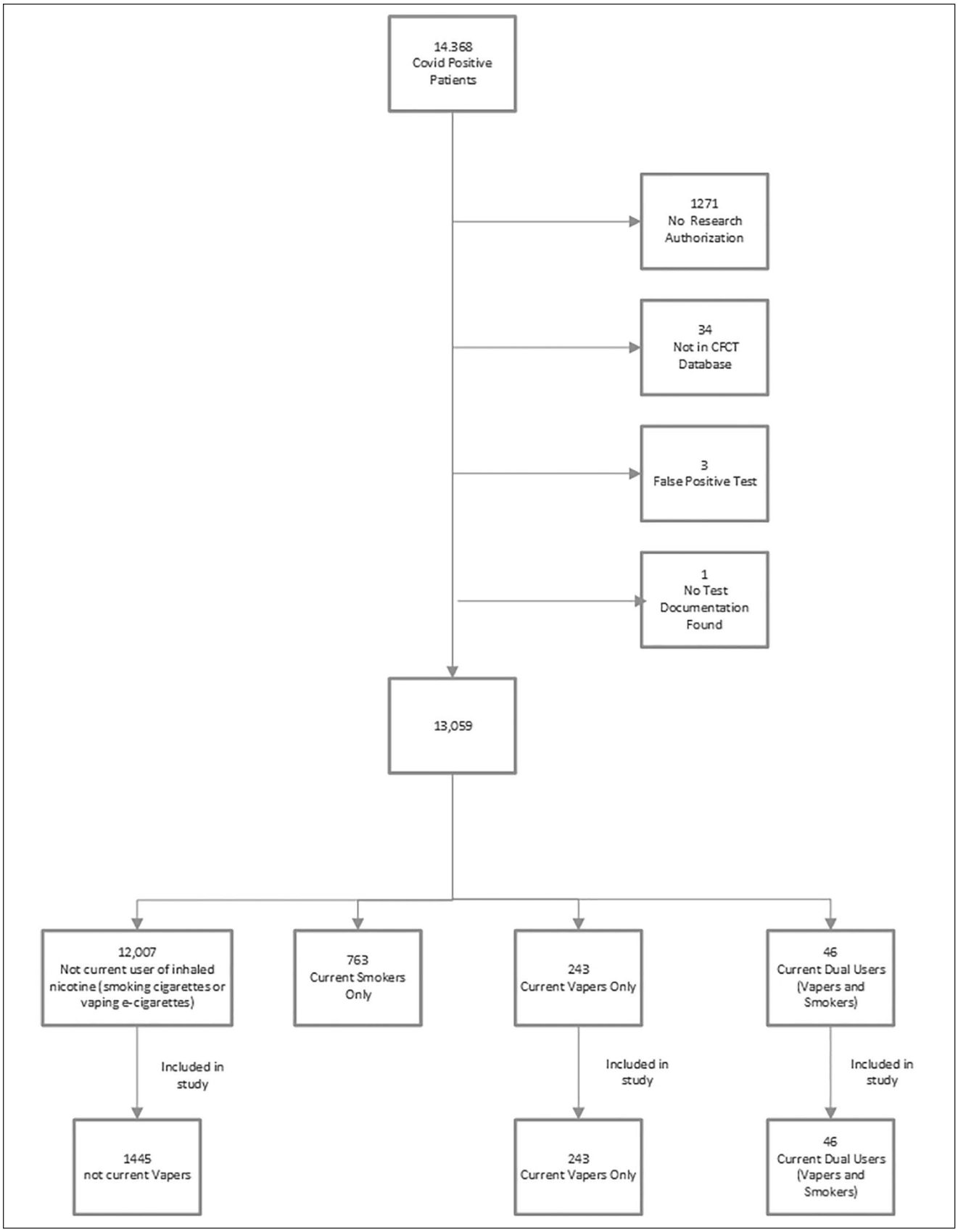

Figure 1. Study sample inclusion.

The database. Our Midwest Practice created the CFCT in March 2020 with the intent of having a centralized team to clinically manage patients in the outpatient setting that were diagnosed with COVID-19. CFCT was a multidisciplinary team composed of physicians, advanced practice providers, nursing, and allied health staff.

After detection of SARS-CoV-2 in nasopharyngeal samples at one of the outpatient testing centers, a provider with the CFCT received notice in the electronic health record of the positive test and contacted the patient for symptom and risk factor clinical assessment. The data from this assessment was captured in a clinical note and entered into the clinical database. The data entered into the database included items such as date of birth, gender, ethnicity, race, COVID-19 symptoms, emergency room visits/hospitalizations as well as lifestyle history such as vaping and smoking.

For this database, the inclusion criteria consisted of patients with a positive SARS-CoV-2 test, age 18 years or older, and provided Minnesota Research Authorization. These patients were enrolled in CFCT from March 1, 2020 to February 28, 2021. The exclusion criteria for this study was age under 18 years old, declined Minnesota research authorization, care managed outside of inclusion date range, or were not able to be reached for assessment after a positive test.

Participants

We reviewed the database records of 13 059 patients who were 18 years of age or older and presented at the time of COVID-19 diagnosis, between March 1, 2020 and March 1, 2021. Patients were classified as vapers (N = 243) or smokers (N = 763) or both (N = 46) or no use of any nicotine product (N = 12 007). Preliminary review of patient characteristics showed that smokers were a much older group of patients when compared with patients who vaped (vaping only or vaping and smoking combined), therefore this report is limited to vapers (243 vapers only; 46 vapers and smokers combined) and matched controls (N = 1445) (Figure 1).

Data Collection

When initially contacting a COVID-positive patient, standard questionnaires were used to risk stratify patients. Emerging data at the time suggested that capturing vaping history might be important in risk stratifying patients. Questions assessing this information were quickly added to capture this data in the electronic record. Data collected included: demographics such as age, race, sex, lifestyle risk factors such as nicotine use (tobacco, as well as electronic cigarettes), Covid-19 related factors such as date of diagnosis, symptoms reported such as dyspnea, cough, chest pain, myalgia, anosmia, nausea, vomiting, abdominal pain, diarrhea, dizziness. Followup treatment, ER visits and hospitalizations were also documented.

Statistical Analysis

Data are summarized using mean ± SD for continuous variables and frequency counts and percentages for nominal variables. Patients were classified based on self-reported current use of inhaled nicotine as: *None*, *Smoking only, Vaping only, or Vaping and Smoking*. The frequency of inhaled nicotine use was summarized overall and according to age, sex, and race/ethnicity.

To assess whether the frequency of COVID-19 symptoms differed between patients who were current vapers compared to patients who did not use inhaled nicotine, a matched cohort design was employed with matching based on age, sex, and race/ethnicity. For each patient who reported current vaping (with or without concurrent smoking) a pool of potential matches was created which included all patients who were of the same age and sex and who did not use any inhaled nicotine (non-users). From this pool, a random sample of 5 patients were selected who also matched the race/ethnicity of the vaping patient. If the pool of potential matches included <5 patients who were in the same race/ethnicity category as the vaping patient, the additional matches were selected at random regardless of their race/ethnicity. Logistic regression analyses were performed separately for each of the 14 COVID-19 symptoms assessed. These analyses were performed using generalized estimating equations (GEE) with robust variance estimates to account for the 1:5 matched set study design. Odds ratios (OR) and 95% confidence intervals (CI) were calculated with odds ratios greater than 1.0 indicating an increased likelihood of the given symptoms for vapers compared to non-users. Secondary analyses were performed separately for the matched sets which included patients who were vaping only, and the matched sets which included patients who were both vaping and smoking. Similar logistic regression analyses were performed to compare the frequency of emergency department (ED) visits between vapers and non-users. Due to the limited number of events, the frequency of hospitalization was compared between groups using Fisher's exact test. In all cases, 2-tailed *P*-values were reported with no adjustments for multiple comparisons.

Results

There were 14 368 patients who were referred to the CFCT with an initial contact call completed between June 16, 2020 and March 12, 2021. Of these, 1309 were excluded from the present study because they declined to provide authorization for the use of their medical records for research purposes (n = 1271), were not followed by CFCT (N = 34), were found to have a false positive test (N = 3) or

Table 1. Frequency of Current Vaping and Smoking Among 13 059 COVID Patients*.

Demographic category	N	Vaping/smoking category			
		None	Smoking only	Vaping only	Vaping and smoking
Overall	13 059	12 007 (91.9)	763 (5.8)	243 (1.9)	46 (0.4)
Age					
18-19	545	486 (89.2)	15 (2.8)	39 (7.2)	5 (0.9)
20-29	2417	2114 (87.5)	129 (5.3)	142 (5.9)	32 (1.3)
30-39	1690	1498 (88.6)	156 (9.2)	30 (1.8)	6 (0.4)
40-49	1783	1611 (90.4)	156 (8.8)	15 (0.8)	1 (0.1)
50-59	2119	1961 (92.5)	144 (6.8)	12 (0.6)	2 (0.1)
60-69	2273	2164 (95.2)	106 (4.7)	3 (0.1)	0 (0.0)
70-79	1567	1521 (97.1)	44 (2.8)	2 (0.1)	0 (0.0)
80 or more	665	652 (98.1)	13 (2.0)	0 (0.0)	0 (0.0)
Sex					
Female	6949	6395 (92.0)	398 (5.7)	137 (2.0)	19 (0.3)
Male	6110	5612 (91.9)	365 (6.0)	106 (1.7)	27 (0.4)
Race/ethnicity					
White	10 055	9272 (92.2)	569 (5.7)	178 (1.8)	36 (0.4)
Hispanic or Latino	1090	1007 (92.4)	70 (6.4)	13 (1.2)	0 (0.0)
Black	477	425 (89.1)	43 (9.0)	8 (1.7)	1 (0.2)
Asian	220	203 (92.3)	15 (6.8)	1 (0.5)	1 (0.5)
Other	193	168 (87.1)	16 (8.3)	6 (3.1)	3 (1.6)
Missing	1024	932 (91.0)	50 (4.9)	37 (3.6)	5 (0.5)

*The frequency of each vaping/smoking category is summarized overall and according to age, sex, and race/ethnicity. Data are presented as n (%) with percentages calculated using the total number of patients in the given demographic category (N) as the denominator.

no positive test result could be found (N = 1) (Figure 1). The final study cohort includes a total of 13 059 COVID-19 patients of which 6949 (53.2%) are female and 6110 (46.8%) are male. The overall mean ± standard deviation (SD) in years of age was 49.0 ± 19.6 years (range: 18-100 years). Among the 13 059 COVID-19 patients there were 12 007 (91.2%) who indicated that they were not a current user of inhaled nicotine (ie, no current smoking or vaping), 763 (5.8%) who reported current smoking only, 243 (1.9%) who reported current vaping only, and 46 (0.4%) who reported both current smoking and current vaping. The frequency of current smoking/vaping is summarized in Table 1. The percentage of patients who reported vaping with or without concurrent smoking decreased significantly with age and was 7.4%, 2.1%, 0.9%, 0.7%, and 0.1% for those 18 to 29, 30 to 39, 40 to 49, 50 to 59, and ≥60 years of age respectively.

To assess whether presenting symptoms differed between patients who reported current vaping compared to patients who did not use inhaled nicotine, a 1:5 matched cohort design was used. The 289 patients who reported current vaping (243 vaping only, 46 vaping + smoking) were matched based on age, sex, and race/ethnicity to 1445 non-users of inhaled nicotine. The demographics and comorbidities/COVID-19 risk factors of the matched cohorts are summarized in Table 2.

The frequency of presenting symptoms for the overall sample of vapers and matched non-users of inhaled nicotine is summarized in Table 3. Compared to non-users, vapers had an increased likelihood of reporting headache (OR = 1.35, $P = .027$), myalgia (OR = 1.40, $P = .004$), anosmia/dysgeusia (OR = 1.39, $P = .009$), chills (OR = 1.45, $P = .016$), lightheadedness (OR = 1.76, $P < .001$), chest pain (OR = 1.68, $P = .005$), nausea/vomiting (OR = 1.74, $P = .003$), and diarrhea (OR = 1.74, $P = .005$). Results from secondary analyses performed separately for vapers who reported vaping only and those reporting both vaping and smoking are summarized in Table 4. For most of the presenting symptoms the magnitude and direction of the odds ratio estimate for vapers compared to non-users is similar for those who were vaping only and those who were both vaping and smoking. The notable exception is for dyspnea where there was no evidence of an increased likelihood of dyspnea for those who were vaping only compared to non-users (OR = 1.19, $P = .328$) whereas there was a significantly increased likelihood of dyspnea for those who were both vaping and smoking compared to non-users (OR = 2.87, $P = .004$).

The frequency of ED visits and hospitalizations for vapers and matched non-users are summarized in Table 5. The frequency of hospitalization was low for vapers and matched non-users (0.4% vs 1.0%, $P = .496$). The frequency

Table 2. Demographics of Vapers and Matched Non-Users of Inhaled Tobacco.

	All matched sets		Vaping only matched sets		Vaping and smoking matched sets	
Variable	Non-users (N = 1445)	Any vaping (N = 289)	Non-users (N = 1215)	Vaping only (N = 243)	Non-users (N = 230)	Vaping + smoking (N = 46)
Age, n (%)						
18-19	220 (15.2)	44 (15.2)	195 (16.0)	39 (16.0)	25 (10.9)	5 (10.9)
20-29	870 (60.2)	174 (60.2)	710 (58.4)	142 (58.4)	160 (69.6)	32 (69.6)
30-39	180 (12.5)	36 (12.5)	150 (12.3)	30 (12.3)	30 (13.0)	6 (13.0)
40-49	80 (5.5)	16 (5.5)	75 (6.2)	15 (6.2)	5 (2.2)	1 (2.2)
50-59	70 (4.8)	14 (4.8)	60 (4.9)	12 (4.9)	10 (4.3)	2 (4.3)
60-69	15 (1.0)	3 (1.0)	15 (1.2)	3 (1.2)	0 (0.0)	0 (0.0)
70-79	10 (0.7)	2 (0.7)	10 (0.8)	2 (0.8)	0 (0.0)	0 (0.0)
Sex, n (%)						
Female	780 (54.0)	156 (54.0)	685 (56.4)	137 (56.4)	95 (41.3)	19 (41.3)
Male	665 (46.0)	133 (46.0)	530 (43.6)	106 (43.6)	135 (58.7)	27 (58.7)
Race/ethnicity, n (%)						
White	1084 (75.0)	214 (74.1)	899 (74.0)	178 (73.3)	185 (80.4)	36 (78.3)
Hispanic or Latino	68 (4.7)	13 (4.5)	64 (5.3)	13 (5.4)	4 (1.7)	0 (0.0)
Black	48 (3.3)	9 (3.1)	43 (3.5)	8 (3.3)	5 (2.2)	1 (2.2)
Asian	8 (0.6)	2 (0.7)	5 (0.4)	1 (0.4)	3 (1.3)	1 (2.2)
Other	20 (1.4)	9 (3.1)	13 (1.1)	6 (2.5)	7 (3.0)	3 (6.5)
Missing	217 (15.0)	42 (14.5)	191 (15.7)	37 (15.2)	26 (11.3)	5 (10.9)
Comorbidity/risk factors, n (%)						
Obesity	187 (12.9)	43 (14.9)	154 (12.7)	35 (14.4)	33 (14.4)	8 (17.4)
Asthma	186 (12.9)	35 (12.1)	155 (12.8)	23 (9.5)	31 (13.5)	12 (26.1)
Diabetes	76 (5.3)	9 (3.1)	64 (5.3)	7 (2.9)	12 (5.2)	2 (4.4)
Immunocompromised†	37 (2.6)	8 (2.8)	27 (2.2)	6 (2.5)	10 (4.4)	2 (4.4)
Other‡	23 (1.6)	3 (1.0)	21 (1.7)	2 (0.8)	2 (0.9)	1 (2.2)

†Active chemotherapy, bone marrow transplant, solid organ transplant, or other immunocompromised condition.
‡COPD/emphysema, chronic lung disease, congestive heart failure, coronary artery disease, end stage renal disease, or end stage liver disease.

Table 3. Overall Analysis of COVID Symptoms for all Matched Vapers and Non-Users.

			Logistic regression results*		
Symptom	Non-users (N = 1445)	Any vaping (N = 289)	OR	(95% CI)	*P*
Congestion	624 (43.2)	140 (48.4)	1.24	(0.97, 1.57)	.082
Cough	606 (41.9)	133 (46.0)	1.18	(0.89, 1.57)	.252
Headache	599 (41.5)	141 (48.8)	1.35	(1.03, 1.75)	.027
Myalgia	459 (31.8)	114 (39.4)	1.40	(1.11, 1.76)	.004
Anosmia/dysgeusia	434 (30.0)	108 (37.4)	1.39	(1.08, 1.78)	.009
Sore throat	404 (28.0)	80 (27.7)	0.99	(0.77, 1.26)	.913
Fever	298 (20.6)	58 (20.1)	0.97	(0.74, 1.26)	.800
Chills	269 (18.6)	72 (24.9)	1.45	(1.07, 1.97)	.016
Dyspnea	231 (16.0)	61 (21.1)	1.41	(0.99, 1.99)	.056
Lightheaded	170 (11.8)	55 (19.0)	1.76	(1.28, 2.42)	<.001
Chest pain	150 (10.4)	47 (16.3)	1.68	(1.17, 2.40)	.005
Nausea/vomiting	145 (10.0)	47 (16.3)	1.74	(1.21, 2.50)	.003
Diarrhea	145 (10.0)	47 (16.3)	1.74	(1.18, 2.56)	.005
Fatigue	98 (6.8)	24 (8.3)	1.24	(0.73, 2.13)	.423

*A logistic regression analysis was performed separately for each symptom using generalized estimating equations (GEE) with robust variance estimates to account for the 1:5 matched set study design. Results are summarized by presenting the odds ratio (OR), 95% confidence interval (CI), and *P*-value. Odds ratios greater than 1.0 indicate that the likelihood of having the given symptom is higher for vapers compared to non-users.

Table 4. Analysis of COVID Symptoms With Vapers Stratified According to Concurrent Smoking Status.

	Vaping only matched sets					Vaping and smoking matched sets				
			Logistic regression results*					Logistic regression results*		
Symptom	Non-users (N = 1215)	Vaping only (N = 243)	OR	95% CI	*P*	Non-users (N = 230)	Vaping and smoking (N = 46)	OR	95% CI	*P*
Congestion	524 (43.1)	116 (47.7)	1.20	(0.90, 1.61)	.207	100 (43.5)	24 (52.2)	1.42	(0.58, 3.47)	.444
Cough	512 (42.1)	111 (45.7)	1.15	(0.83, 1.61)	.400	94 (40.9)	22 (47.8)	1.33	(0.74, 2.37)	.340
Headache	502 (41.3)	116 (47.7)	1.30	(0.97, 1.74)	.082	97 (42.2)	25 (54.3)	1.63	(0.91, 2.94)	.103
Myalgia	384 (31.6)	98 (40.3)	1.46	(1.14, 1.87)	.003	75 (32.6)	16 (34.8)	1.10	(0.61, 2.00)	.750
Anosmia/Dysgeusia	363 (29.9)	92 (37.9)	1.43	(1.09, 1.88)	.011	71 (30.9)	16 (34.8)	1.19	(0.63, 2.27)	.588
Sore throat	338 (27.8)	68 (28.0)	1.01	(0.79, 1.29)	.949	66 (28.7)	12 (26.1)	0.88	(0.42, 1.85)	.730
Fever	250 (20.6)	48 (19.8)	0.95	(0.70, 1.28)	.739	48 (20.9)	10 (21.7)	1.05	(0.54, 2.05)	.879
Chills	231 (19.0)	63 (25.9)	1.49	(1.09, 2.04)	.013	38 (16.5)	9 (19.6)	1.23	(0.55, 2.75)	.615
Dyspnea	195 (16.0)	45 (18.5)	1.19	(0.84, 1.68)	.328	36 (15.7)	16 (34.8)	2.87	(1.40, 5.90)	.004
Lightheaded	141 (11.6)	47 (19.3)	1.83	(1.28, 2.60)	<.001	29 (12.6)	8 (17.4)	1.46	(0.72, 2.94)	.290
Chest pain	120 (9.9)	38 (15.6)	1.69	(1.19, 2.40)	.003	30 (13.0)	9 (19.6)	1.62	(0.69, 3.83)	.270
Nausea/Vomiting	124 (10.2)	39 (16.0)	1.68	(1.11, 2.55)	.015	21 (9.1)	8 (17.4)	2.10	(0.96, 4.59)	.064
Diarrhea	119 (9.8)	40 (16.5)	1.81	(1.20, 2.75)	.005	26 (11.3)	7 (15.2)	1.41	(0.58, 3.43)	.451
Fatigue	87 (7.2)	21 (8.6)	1.23	(0.69, 2.18)	.487	11 (4.8)	3 (6.5)	1.39	(0.36, 5.32)	.632

*A logistic regression analysis was performed separately for each symptom using generalized estimating equations (GEE) with robust variance estimates to account for the 1:5 matched set study design. Results are summarized by presenting the odds ratio (OR), 95% confidence interval (CI), and *P*-value. Odds ratios greater than 1.0 indicate that the likelihood of having the given symptom is higher for vapers compared to non-users.

Table 5. Emergency Department (ED) Visits and Hospitalizations*.

			Logistic regression results		
Outcome	Non-users	Vapers	OR	(95% CI)	*P*
Overall—all matched sets	(N = 1445)	(N = 289)			
Any ED visit	54 (3.7)	13 (4.5)	1.21	(0.68, 2.15)	.508
COVID ED visit	48 (3.3)	11 (3.8)	1.15	(0.60, 2.22)	.674
Hospitalization	15 (1.0)	1 (0.4)			.496**
Vaping only matched sets	(N = 1215)	(N = 243)			
Any ED visit	45 (3.7)	7 (2.9)	0.77	(0.34, 1.73)	.527
COVID ED visit	39 (3.2)	6 (2.5)	0.76	(0.33, 1.77)	.529
Hospitalization	13 (1.1)	1 (0.4)			.488**
Vaping and smoking matched sets	(N = 230)	(N = 46)			
Any ED visit	9 (3.9)	6 (13.0)	3.68	(1.92, 7.07)	<.001
COVID ED visit	9 (3.9)	5 (10.9)	3.00	(1.21, 7.39)	.017
Hospitalization	2 (0.9)	0 (0.0)			1.00**

*Analyses were performed overall and with vapers stratified according to concurrent smoking status. All hospitalizations were COVID related. For ED outcomes, logistic regression analyses were performed using generalized estimating equations (GEE) with robust variance estimates to account for the 1:5 matched set study design.

**Due to the small numbers, the frequency of hospitalizations were compared between groups using Fisher's exact test.

of any ED visit was 4.5% among vapers which was similar to the frequency of 3.7% observed in matched non-users ($P = .508$). From analyses performed separately for those who were vaping only and those who were both vaping and smoking, the frequency of any ED visit was found to be similar for those who were vaping only compared to matched non-users (2.9% vs 3.7%, OR = 0.77 $P = .527$), but the frequency of any ED visit for those who were both vaping and smoking was significantly higher than that observed for matched non-users (13.0% vs 3.9%, OR = 3.68, $P < .001$). Findings were similar when the analysis was restricted to COVID-19 related ED visits.

Discussion

Whereas previous studies have shown no association with greater risk for being infected with COVID-19 for those individuals who vape (use e-cigarettes).[14] This analysis of clinical data collected from COVID-19 positive patients revealed a higher frequency of COVID-19 symptoms among those individuals who vape when compared to those who do not vape. Using logistic regression, we identified a significantly higher frequency of Covid-19 symptoms such as headaches, myalgia, anosmia/dysgeusia, chills, light-headedness, chest pain, nausea/vomiting, and diarrhea among those individuals who used only e-cigarettes; whereas those who vaped and smoked had a significantly higher occurrence of dyspnea and ED visits (related and not related to COVID-19).

Significant overlap exists between clinical and imaging features of EVALI and COVID-19 infection raising the question as to whether there may be shared mechanisms of injury involved in the development of these disparate conditions.[22] The SARS-CoV-2 virus infects the host when inhaled through aerosols and subsequently binds to nasal and airway epithelial ACE-2 cellular surface protein.[23] It is now apparent that both cigarette smoke and nicotine upregulate ACE-2 receptor expression in lung cells, thereby potentially facilitating binding and internalization of the SARS-CoV-2 virus.[24,25]

Whether the use of e-cigarettes predisposes to COVID-19 infection or worsens the clinical course is still not well defined, but there are several potential mechanisms by which e-cigarette use and vaping may influence the development of acute lung injury in COVID-19 infection. In the early stages of COVID-19 infection, the virus undergoes local replication and propagation, and elicits an immune response that is usually relatively contained.[26,27] Most infected patients will have symptoms, but the majority have relatively mild infection that is self-limiting. Approximately 15% to 20% of all infected adults develop more severe illness with pneumonia and systemic as well as severe lung inflammation and associated lung infiltrates.[28] Key events in the pathophysiology of the more severe illness include the invasion and injury of type 2 alveolar epithelial cells that abundantly express the ACE-2 receptor.[29] This injury is likely a critical aspect of the pathogenesis, as these type 2 cells produce surfactant which is essential for maintaining alveolar integrity and function, and these cells also serve as precursor cells required to regenerate new type 1 alveolar epithelial cells.[30] In addition, type 2 alveolar epithelial cells also release cytokines and inflammatory mediators that, in tandem with alveolar macrophage activation and cytokine generation, create a local cytokines surge in the lung.[31] These cells are responsible for fighting off the virus, but in doing so are responsible for the subsequent inflammation and lung injury. Cytotoxic effects of Vitamin E acetate on macrophage and epithelial cell functions in the lung may have additive or synergistic effects with the SARS-CoV-2 virus, and further amplify lung injury and inflammation in vapers. The increased inflammation promoted by combined injury from the SARS-Co-V-2 cytokine release and inflammation induced by vaping induced epithelial cell injury in the lung may worsen the likelihood of cytokine release and systemic inflammation with an associated increase in systemic manifestations such as fever, myalgias, fatigue, and headache.

There are both strengths and weaknesses to this retrospective study of Covid-19 experience in concurrent vapers. The greatest strength is the inclusion of a relatively large group of vapers whose demographics were very closely matched in a 5:1 ratio to a control group of non-vapers and non-smokers. However, it should be noted that the non-users selected for the matched analysis are not a random sample of all non-users (Supplemental Table 1). In addition, due to the nature of this being a retrospective study of clinical experiences, we could only include patients who had previously provided the Minnesota Research Authorization (a priori consent to allow researchers to use clinical data) and therefore also limit the study inclusion to adults (18 years of age or older). In addition, we did not collect details of the patients' vaping history, such as frequency and duration of vaping and type/brand and content of material vaped. Our study cohort included only 46 patients who were dual users (both vapers and smokers). Given this limited number of dual users our finding that the frequency of any ED visit for this group was significantly higher than that observed for matched non-users should not be interpreted as suggestive and not definitive. Finally, the data set did not include clinical information which occurred after March 2021, available thus limiting conclusions regarding outcomes.

Conclusion

Whereas no evidence has been shown that vapers are at greater risk for contracting COVID-19, this analysis has shown that vapers who contract COVID-19 experience higher frequency of covid-19 related symptoms when compared with age and gender matched non-vapers. COVID-19 positive patients who were both smokers and vapers complained of dyspnea and had more frequent ER visits than non-users. Further work should examine further the impact vaping has on recovery from COVID-19 and post-covid-19 symptoms.

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Author Contributions

All the authors participated in the study concept and design, analysis and interpretation of data, drafting and revising the paper, and have seen and approved the final version of the manuscript.

Availability of Data and Materials

All data supporting the study findings are contained within this manuscript.

Declaration of Conflicting Interests

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Ethical Standards

All authors assert that all procedures contributing to this work comply with the ethical standards of the Mayo Clinic.

Ethics and Consent to Participate

In accordance with the Declaration of Helsinki, this study was reviewed by The Mayo Clinic Institutional Review Board (IRB) and determined to be exempt under section 45 CFR 46.101, item 2. Mayo Clinic IRB approved waiver of informed consent for all study participants prior to study participation. Participants included in this report approved use of their clinical data for the purposes of research (Minnesota authorization for research).

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Supplemental Material

Supplemental material for this article is available online.

References

1. Winnicka L, Shenoy MA. EVALI and the pulmonary toxicity of electronic cigarettes: a review. *J Gen Intern Med*. 2020;35(7):2130-2135.
2. Harrill WC. Vaping during the COVID-19 pandemic: NOT GOOD!! *Laryngoscope Investig Otolaryngol*. 2020;5(3):399-400.
3. Creamer MR, Everett Jones S, Gentzke AS, Jamal A, King BA., Tobacco product use among high school students - youth risk behavior survey, United States, 2019. *MMWR Suppl*. 2020;69(Suppl 1):56-63.
4. McAlinden KD, Eapen MS, Lu W, Sharma P, Sohal SS. The rise of electronic nicotine delivery systems and the emergence of electronic-cigarette-driven disease. *Am J Physiol Lung Cell Mol Physiol*. 2020;319(4):L585-l595.
5. Pitlick MM, Lang DK, Meehan AM, McCoy CP. EVALI: a mimicker of COVID-19. *Mayo Clin Proc Innov Qual Outcomes*. 2021;5:682-687.
6. Kazachkov M, Pirzada M. Diagnosis of EVALI in the COVID-19 era. *Lancet Respir Med*. 2020;8(12):1169-1170.
7. Darmawan DO, Gwal K, Goudy BD, Jhawar S, Nandalike K. Vaping in today's pandemic: E-cigarette, or vaping, product use-associated lung injury mimicking COVID-19 in teenagers presenting with respiratory distress. *SAGE Open Med Case Rep*. 2020;8:2050313x20969590.
8. Marques P, Piqueras L, Sanz MJ. An updated overview of e-cigarette impact on human health. *Respir Res*. 2021;22(1):151.
9. Kale D, Herbec A, Perski O, Jackson SE, Brown J, Shahab L. Associations between vaping and covid-19: cross-sectional findings from the HEBECO study. *Drug Alcohol Depend*. 2021;221:108590.
10. Majmundar A, Allem JP, Cruz TB, Unger JB. Public health concerns and unsubstantiated claims at the intersection of vaping and COVID-19. *Nicotine Tob Res*. 2020;22(9):1667-1668.
11. Axelsson GT, Eythorsson ES, Hardardottir H, Gudmundsson G, Hansdottir S. [The impact of lung diseases, smoking and e-cigarette use on the severity of COVID-19 illness at diagnosis]. *Laeknabladid*. 2020;106(12):574-579.
12. Pino LE, Triana I, Pérez C, et al. Electronic nicotine delivery systems (ECs) and COVID-19: the perfect storm for young consumers. *Clin Transl Oncol*. 2021;23(1):5-9.
13. Gaiha SM, Cheng J, Halpern-Felsher B. Association between youth smoking, electronic cigarette use, and COVID-19. *J Adolesc Health*. 2020;67(4):519-523.
14. Jose T, Croghan IT, Hays JT, Schroeder DR, Warner DO. Electronic cigarette use is not associated with COVID-19 diagnosis. *J Prim Care Community Health*. 2021;12:21501327211024391.
15. Camacho OM, Murphy JJ. In response to "Association Between Youth Smoking, Electronic Cigarette Use, and COVID-19". *J Adolesc Health*. 2021;68(1):214.
16. Farsalinos K, Niaura R. E-Cigarette use and COVID-19: questioning data reliability. *J Adolesc Health*. 2021;68(1):213.
17. Sifat AE, Nozohouri S, Villalba H, Vaidya B, Abbruscato TJ. The role of smoking and nicotine in the transmission and pathogenesis of COVID-19. *J Pharmacol Exp Ther*. 2020;375(3):498-509.
18. Lallai V, Manca L, Fowler CD. E-cigarette vape and lung ACE2 expression: implications for coronavirus vulnerability. *Environ Toxicol Pharmacol*. 2021;86:103656.
19. Chen DT, Kyriakos CN. Cigarette and E-cigarettes dual users, exclusive users and COVID-19: findings from four UK birth cohort studies. *Int J Environ Res Public Health*. 2021;18(8):3935.

20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
21. Consort: Transparent Reporting of Trials. Accessed August 15, 2016. www.consort-statement.org/consort-statement/flow-diagram
22. Callahan SJ, Harris D, Collingridge DS, et al. Diagnosing EVALI in the time of COVID-19. *Chest*. 2020;158(5):2034-2037.
23. Habashi NM, Camporota L, Gatto LA, Nieman G. Functional pathophysiology of SARS-CoV-2-induced acute lung injury and clinical implications. *J Appl Physiol*. 2021;130(3):877-891.
24. Naidu V, Zeki AA, Sharma P. Sex differences in the induction of angiotensin converting enzyme 2 (ACE-2) in mouse lungs after e-cigarette vapor exposure and its relevance to COVID-19. *J Investig Med*. 2021;69(5):954-961.
25. Purkayastha A, Sen C, Garcia G Jr, et al. Direct exposure to SARS-CoV-2 and cigarette smoke increases infection severity and alters the stem cell-derived airway repair response. *Cell Stem Cell*. 2020;27(6):869-875.e4.
26. Ahn JH, Kim J, Hong SP, et al. Nasal ciliated cells are primary targets for SARS-CoV-2 replication in the early stage of COVID-19. *J Clin Investig*. 2021;131(13):e148517.
27. Zhao Y, Qin L, Zhang P, et al. Longitudinal COVID-19 profiling associates IL-1RA and IL-10 with disease severity and RANTES with mild disease. *JCI Insight*. 2020;5(13):e139834.
28. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395(10239):1763-1770.
29. Bösmüller H, Matter M, Fend F, Tzankov A. The pulmonary pathology of COVID-19. *Virchows Arch*. 2021;478(1):137-150.
30. Katsura H, Sontake V, Tata A, et al. Human lung stem cell-based alveolospheres provide insights into SARS-CoV-2-mediated interferon responses and pneumocyte dysfunction. *Cell Stem Cell*. 2020;27(6):890-904.e8.
31. Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. *Am J Pathol*. 2021;191(1):4-17.