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Inhaling muscle spray: A rising trend of abuse

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Abstract

Ethyl chloride was popular as an inhalant recreational drug in the 1980s. It is easily available in pharmacies as well as sold online as a topical anesthetic spray for pain relief. In recent times, its use is gaining popularity again among the youth as an inhalant drug due to its neuro-stimulatory effects. To avoid the risks associated with use of illegal drugs, and ease of availability of ethyl chloride without restrictions, there is a rising trend to use it as a “substitute” drug of abuse. In this paper, we try to highlight to the critical care and emergency physicians that majority of these cases present with predominant neurological symptoms, with occasional involvement of the cardiovascular system. The diagnosis of ethyl chloride poisoning is primarily clinical and supportive care is the mainstay of treatment, along with subsequent counseling. Ethyl chloride abuse should be considered as a differential diagnosis in young patients presenting with predominant neurological symptoms. Alongside raising public awareness, the manufacturers and retail distributors of these products have an important role to play in reducing the risk of abuse.

Key Words: Ethyl chloride; Abuse; Inhalant; Neurological; Recreational; Counselling

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Core Tip: The purpose of this manuscript is to highlight to the critical care and emergency physicians regarding the rising trend of ethyl chloride spray as an inhalational drug of abuse, due to ease of availability as over-the-counter drug and its psychoactive effects. This manuscript emphasizes the need to consider ethyl chloride abuse in young patients presenting with predominant neurological symptoms. Also, raising public awareness and improving vigilance on the sale of these products will

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help in reducing the burden of abuse.

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INTRODUCTION

Volatile substance abuse comprises of inhalation of volatile compounds such as glue, paints, sprays and fuels due to their psychoactive effects. Ethyl chloride was popular as an inhalant recreational drug in the 1980s. It is a colorless, flammable hydrocarbon with a strong ether-like odour[1]. It was originally used as a general anesthetic, but its use was subsequently discontinued considering its safety profile, unpleasant recovery phase and availability of newer superior agents[2]. It is used for cryoanalgesia to drain small abscesses and as a solvent and refrigerant in chemical industries. It is easily available in pharmacies as an over-the-counter topical anesthetic spray and also sold online for pain-relief from muscle spasm in athletes and also during tattoo and piercings. It rapidly evaporates due to its boiling point of 12 °C, and hence produces a cold sensation and feeling of pain relief[3]. In recent times, its use is gaining popularity again among the youth as an inhalant drug to “feel high”.

DISCUSSION

Inhalants comprise of a broad range of volatile substances (Table 1). To avoid the risks associated with use of illegal drugs, and ease of availability of ethyl chloride without restrictions, there is a rising trend to use it as a “substitute” drug of abuse. The risk factors for potential abuse include male gender, low socio-economic status and middle-class youth.

People who “sniff” ethyl chloride inhale it directly from the container. During “huffing”, it is sprayed over the clothes or on a towel, and the evaporating fumes are then inhaled through the nose and the mouth. Chronic abusers use “bagging” as they can inhale higher concentration of the chemical.

The pathophysiology of ethyl chloride neurotoxicity is secondary to its rapid absorption in the blood from the lungs. Also, being lipophilic, it gets concentrated in the brain with subsequent development of a range of central nervous system effects. Acute solvent exposure appears to produce N-methyl-D-aspartate receptor inhibition, as well as it increases $\alpha 1\beta 1$ Gamma aminobutyric acid, $\alpha 1$ glycine and 5-hydroxy-tryptamine receptor activation[4].

They produce dose-related continuum of effects, ranging from motor excitation at low concentrations to central nervous system depression, seizures, coma and even cardiopulmonary arrest at higher concentrations. They can also sensitize the heart muscles and some people will develop fatal arrhythmias. The exact pharmacokinetics of ethyl chloride in humans is not known, but animal model studies suggest that its metabolism involves oxidation by cytochrome P-450 and NADPH- and O₂ dependant reaction to produce acetaldehyde. It may also undergo conjugation with glutathione via glutathione-S-transferase[1].

Majority of the cases have mild, short-lasting effects. The systemic effects of ethyl chloride are described in Table 2. Acute brief inhalation can result in feeling of drunkenness, euphoria, and hallucinations. Other acute effects include dizziness, confusion, impaired short-term memory, ataxia, lack of muscle coordination and even loss of consciousness[1,3]. Inhaling high dose of ethyl chloride has depressant effect on central nervous system. It is also used for chemsex[5]. Neurological symptoms secondary to chronic abuse result in ataxia, tremors, speech difficulties, decreased reflexes, hallucinations, involuntary eye movement/nystagmus and deranged liver function. It can also affect the cardiovascular system, predisposing the patient to various cardiac arrhythmias, like ventricular ectopy, atrio-ventricular conduction defects, brady-arrhythmias, and occasionally ventricular fibrillation or asystole leading to sudden cardiac death[6]. Data regarding severe toxicity secondary to ethyl chloride

Table 1 List of common volatile substances used as inhalants

| Classification | Inhalant compounds |
|------------------|---|
| Aerosols | Spray paints; hairspray; deodorant; vegetable oil spray; fabric protector spray; shoe-shine spray |
| Organic solvents | Glue; paint thinner; gasoline; nail polish remover; dry-cleaning fluid; correction fluid |
| Gases | Anesthetics (<i>e.g.</i> , ether, chloroform, halothane, ethyl chloride, nitrous oxide); propane; butane (cigarette lighter fluid); refrigerants; whipped cream dispensers |
| Nitrites | Amyl nitrite; video head cleaner; room odorizer; leather cleaner; liquid aroma |

Table 2 Systemic side-effects of ethyl chloride abuse

| System involved | Effects |
|------------------|---|
| Neurological | Euphoria; visual hallucinations; confusion; dizziness; impaired short-term memory; ataxia; nystagmus; dysarthria; lack of muscle coordination; grand mal seizure; unconsciousness |
| Respiratory | Respiratory paralysis (rare) |
| Cardiovascular | Cardiac depression; sensitization to endogenous and exogenous epinephrine; ventricular tachycardia; ventricular fibrillation; asystole |
| Gastrointestinal | Abdominal cramps; nausea/vomiting |
| Hematological | Cyanosis |
| Hepatic | Hepatomegaly; transient deranged liver function test; elevated serum alanine aminotransferase |
| Ocular | Mild eye irritation |
| Dermal | Contact dermatitis (rare) |

inhalation is rare, and few deaths have been reported till date. A patient developed cardiac arrhythmia along with neurological effects, subsequently leading to respiratory arrest[7].

The diagnosis of ethyl chloride poisoning is primarily clinical, based on history, including a detailed social history, and physical examination. There are no definite investigations to check the level of ethyl chloride in blood or urine. Supportive care is the mainstay of management. The initial management entails removal of the patient from ongoing exposure, which includes removing patient's clothes as they usually spray it on their own clothes for inhalation. Patients need to be monitored for cardiac arrhythmias and neurological depression. Usually the neurological effects are transient, and resolve quickly. There are no known antidotes or any specific means to enhance elimination. Most neurological symptoms completely resolve in about a week following cessation of its inhalation[8]. Physicians should consider concomitant ingestion of alcohol or other drugs of abuse in patients who do not regain consciousness or recover rapidly in the emergency department[9]. Few patients require supplemental oxygen, and those who are unconscious and/or develop respiratory depression will require advanced airway and ventilatory support. Patients should also be specifically evaluated for traumatic injuries, which otherwise can be overlooked[6].

Once the patient is medically stable, he/she must be referred for counseling and an outpatient psychiatric evaluation, as these patients are typically young, and frequently suffer from underlying social or behavioral problems.

Also, the manufacturers and retail distributors of these products have an important role to play in reducing the risk of abuse. Similar to health hazard labelling on cigarette packets, these aerosol sprays as well as other volatile substances should have a warning logo to raise awareness among the public. Pharmacies as well as online retailers can play their part by allowing purchase of a single ethyl chloride canister. Staff at pharmacies should be trained to identify customers who look suspicious of misusing this product.

CONCLUSION

Propensity for addiction and adverse effects of ethyl chloride are underappreciated

due to lack of awareness in public and healthcare professionals. We wish to raise awareness among the physicians regarding its rising trend of abuse as an inhalation agent, due to ease of availability and neuro-stimulatory effects. Ethyl chloride abuse should be considered as a differential diagnosis in young patients presenting with predominant neurological symptoms. Raising public awareness as well as improving vigilance on the sale of these products will help in reducing the burden of abuse.

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Retrospective Cohort Study

Frequency of hepatic steatosis and its association with the pneumonia severity score on chest computed tomography in adult COVID-19 patients

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Abstract

BACKGROUND

Recent studies of the coronavirus disease 2019 (COVID-19) demonstrated that obesity is significantly associated with increased disease severity, clinical outcome, and mortality. The association between hepatic steatosis, which frequently accompanies obesity, and the pneumonia severity score (PSS) evaluated on computed tomography (CT), and the prevalence of steatosis in patients with COVID-19 remains to be elucidated.

AIM

To assess the frequency of hepatic steatosis in the chest CT of COVID-19 patients and its association with the PSS.

METHODS

The chest CT images of 485 patients who were admitted to the emergency department with suspected COVID-19 were retrospectively evaluated. The patients were divided into two groups as COVID-19-positive [CT- and reverse transcriptase-polymerase chain reaction (RT-PCR)-positive] and controls (CT- and RT-PCR-negative). The CT images of both groups were evaluated for PSS as the ratio of the volume of involved lung parenchyma to the total lung volume. Hepatic steatosis was defined as a liver attenuation value of ≤ 40 Hounsfield units (HU).

RESULTS

Of the 485 patients, 56.5% ($n = 274$) were defined as the COVID-19-positive group

study was retrospective in nature and no specific intervention is described in this article. The medical research center waived informed consent for this study.

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and 43.5% ($n = 211$) as the control group. The average age of the COVID-19-positive group was significantly higher than that of the control group (50.9 ± 10.9 years *vs* 40.4 ± 12.3 years, $P < 0.001$). The frequency of hepatic steatosis in the positive group was significantly higher compared with the control group (40.9% *vs* 19.4%, $P < 0.001$). The average hepatic attenuation values were significantly lower in the positive group compared with the control group (45.7 ± 11.4 HU *vs* 53.9 ± 15.9 HU, $P < 0.001$). Logistic regression analysis showed that after adjusting for age, hypertension, diabetes mellitus, overweight, and obesity there was almost a 2.2 times greater odds of hepatic steatosis in the COVID-19-positive group than in the controls (odds ratio 2.187; 95% confidence interval: 1.336-3.580, $P < 0.001$).

CONCLUSION

The prevalence of hepatic steatosis was significantly higher in COVID-19 patients compared with controls after adjustment for age and comorbidities. This finding can be easily assessed on chest CT images.

Key Words: Liver; Steatosis; COVID-19; Computed tomography; Pneumonia severity score

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Core Tip: We evaluated the frequency of hepatic steatosis in the computed tomography (CT) of coronavirus disease 2019 (COVID-19) patients and its association with the pneumonia severity score (PSS). We retrospectively evaluated the CTs of 485 patients with suspected COVID-19. Regression analysis showed that after adjusting for age and comorbidities there was almost a 2.2 times greater odds of hepatic steatosis in the COVID-19-positive group than in controls (odds ratio 2.187; 95% confidence interval: 1.336-3.580, $P < 0.001$). There was a positive correlation between hepatic steatosis and PSS. The study revealed a significantly higher prevalence of hepatic steatosis on CT in COVID-19 patients compared with controls.

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INTRODUCTION

An unknown infection that first appeared as a pneumonia cluster in Wuhan, China was later found to be caused by a new betacoronavirus species, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease was named coronavirus disease 2019 (COVID-19)[1,2]. The infection rapidly spread in Japan, South Korea, and Thailand. The World Health Organization (WHO) declared a Public Health Emergency of International Concern for COVID-19, evaluating its pandemic potential[3]. SARS-CoV-2, which causes severe acute respiratory syndrome, has resulted in the death of nearly two million people worldwide within the last year, and continues to pose serious concerns[4]. Risk factors associated with severe infection and mortality in COVID-19 include hypertension, severe obesity, chronic obstructive pulmonary disease, asthma, diabetes, cardiovascular disease, chronic kidney and liver disease, male gender, and advanced age[5,6]. Obesity has also been shown to be associated with progression to severe pneumonia associated with SARS-CoV-2 infection, need for hospitalization and mechanical ventilation because of acute respiratory failure, diffuse coagulopathy, and increased mortality risk[7]. In fact, morbid obesity has been identified as one of the most important risk factors in young adults with COVID-19[8]. Obesity is considered to play an important role in the pathogenesis of COVID-19 as it increases vulnerability to infections and adverse effects of the chronic inflammation of adipose tissue on the immune system resulting from metabolic dysfunction[9]. Nonalcoholic fatty liver disease (NAFLD) caused by

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ongoing metabolic abnormalities appears to be a potential risk factor for developing SARS-CoV-2 infection and its associated complications[10]. NAFLD is considered a hepatic manifestation of metabolic syndrome, including obesity, diabetes, dyslipidemia, and insulin resistance. The risk of severe COVID-19 can thus also be attributed to impaired liver function as a result of NAFLD[10]. In this study, we aimed to investigate the possible relationship between hepatic steatosis and COVID-19 infection severity based on computed tomography (CT) to evaluate liver attenuation, which is a non-invasive approach that can be used to identify the presence of hepatic steatosis during pulmonary CT examinations without any additional procedures.

MATERIALS AND METHODS

This retrospective study was approved by the Clinical Research Ethics Committee of Harran University (date: 07.12.2020 and session: 20). Informed consent was waived given the retrospective nature and characteristics of the study.

Study population

Between September 1, 2020 and October 1, 2020, 1216 patients who were admitted to the emergency department of our hospital with the suspicion and symptoms of COVID-19 and underwent both chest CT and the reverse transcriptase-polymerase chain reaction (RT-PCR) test were retrospectively evaluated. Patients with motion and image artifacts (*e.g.*, due to not holding the arms overhead), those with chronic liver disease findings, and those without nonenhanced CT images, which would affect the density of the liver, were excluded from the study.

Patients with a positive RT-PCR test and involvement compatible with COVID-19 on CT following the proposed reporting criteria for CT findings related to COVID-19 by the Radiological Society of North America[11] were included in the COVID-19-positive group. Those who were negative for the RT-PCR test and had no lung lesions on CT were included in the control group. To avoid possible false negative and false positive results associated with the PCR test, we used both CT and RT-PCR results when creating the control and COVID-19-positive groups. We also checked all chest CT images of the patients, as there may have been early false negative RT-PCR results. Those with CT findings that were typical, atypical, or indeterminate were excluded, and the remaining patients were considered “negative”. According to these criteria, 62 patients were excluded from the control group. As a result, the study included a total of 485 consecutive presentations, of which 274 were COVID-19-positive (chest CT- and RT-PCR-positive) and 211 were COVID-19-negative controls (chest CT- and RT-PCR-negative). The flow diagram of the study population selection is shown in [Figure 1](#).

CT image acquisition

The chest CT scan was performed in all patients with a 16-detector multi-slice CT device (Siemens Healthineers; Erlangen, Germany). The CT room and scanner were sanitized using standard cleaning procedures and approved disinfectants after each procedure. CT images were obtained at end inspiration during a single breath-hold without using intravenous contrast material. The main scanning parameters were: Tube voltage, 120 kV; tube current-time product, 50-350 mAs; pitch, 1.25; matrix, 512 × 512; slice thickness, 10 mm; and reconstructed slice thickness, 0.625-1.250 mm.

CT evaluation

Several methods have been described in the literature to determine hepatic steatosis on noncontrast CT, including a liver attenuation value of 10 Hounsfield units (HU) that was less than the spleen attenuation, absolute liver attenuation of < 40 HU, and a liver-to-spleen attenuation ratio of < 1. For steatosis, unenhanced CT has a sensitivity ranging from 43% to 95% and a specificity of 90%-100%[12,13]. In this study, two radiologists reviewed the CT images and obtained the HU attenuation values of the liver using circular regions of interest with an area of approximately 10 cm². The measurements were made at the level of the porta hepatis, avoiding the right hepatic lobe (segments 6 and 7), as well as vessels, calcifications, and biliary structures when possible ([Figure 2](#)). The chest CT images were evaluated by two thoracic radiologists with 8 and 9 yr of experience. They agreed on the results of each measurement and were blinded to the patient information. To prevent bias, the CT images were evaluated for steatosis in the abdominal window before the result of the RT-PCR test was known. Then, the lung window, with a center of -500 HU and a width of 1500 HU was examined for COVID-19 involvement. The RT-PCR test results were recorded

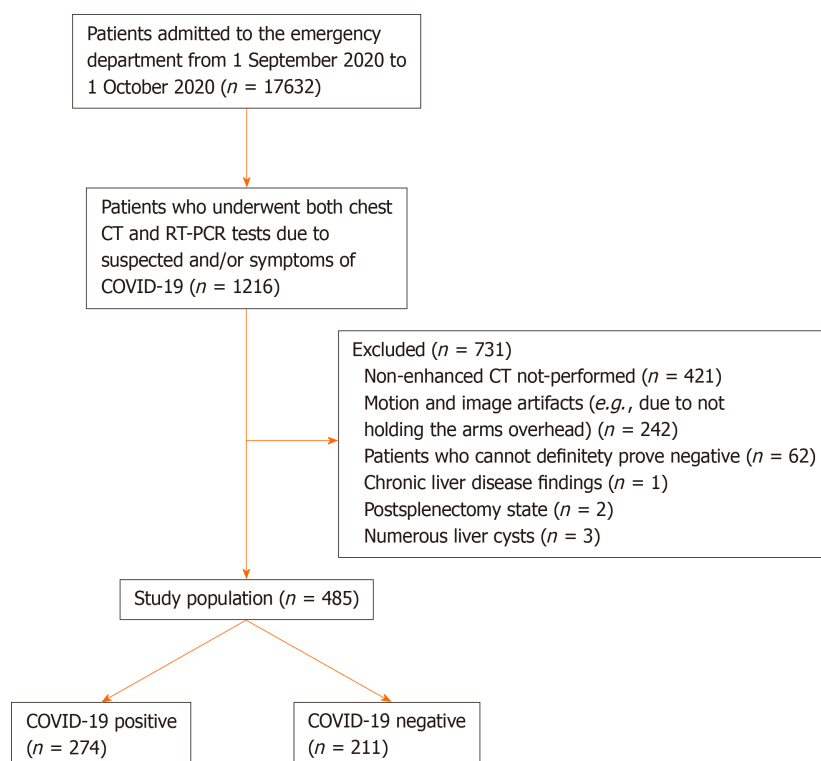


Figure 1 Flow diagram of the study population. COVID-19: Coronavirus disease; 2019; CT: Computed tomography; RT-PCR: Reverse transcription-polymerase chain reaction.

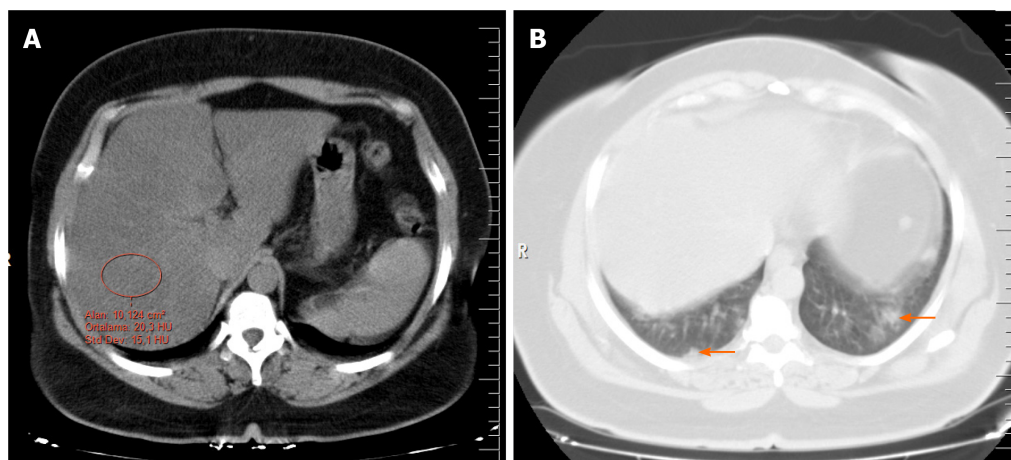


Figure 2 Noncontrast computed tomography of a patient with coronavirus disease 2019 accompanied by hepatic steatosis. A: The abdominal window shows the determination of the attenuation value with the measurement of a single region of interest (an area of approximately 10 cm²) from the right liver lobe (segment 7); B: Lung window demonstrating lesions (orange arrows) compatible with coronavirus disease 2019.

after all the CT images were evaluated.

In this study, the definition of hepatic steatosis was accepted as a liver attenuation value of < 40 HU. Spleen attenuation values were not measured as the detection of steatosis by comparing the attenuation of the liver and spleen is more complex, requires more effort and time, and does not contribute to the diagnosis. All measurements were performed from a single section using the same method, which is supported by previous data showing that fat deposition in the liver is relatively homogeneous and most of the variation in the measurement of attenuation in that organ can be captured by measuring it in just one slice[14].

The COVID-19 pneumonia severity score (PSS), a semiquantitative method employed in previous studies, was used to measure the severity of lesions on chest CT[15,16]. First, the scope of the lesions in each lobe was estimated, and a score of 0 (none), 1 (affecting less than 5% of the lobe), 2 (affecting 5%-25% of the lobe), 3

(affecting 26%-49% of the lobe), 4 (affecting 50%-75% of the lobe), or 5 (affecting more than 75% of the lobe) was assigned. Second, the CT score was obtained by adding up the scores of the five lobes. For each patient, the CT score was in the range of 0 to 25.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, United States). Variables were divided into two groups, categorical and continuous. Frequency (percentage) values were used to report categorical variables, which were compared using the χ^2 test. means \pm SD were used to compare continuous variables. The Kolmogorov-Smirnov test was used to determine whether continuous data were normally distributed. Normally distributed continuous variables were compared using Student's *t*-test, and continuous variables without normal distribution were compared using the Mann-Whitney *U*-test. Statistical significance was defined as a *P* value of < 0.05 for all comparisons. Binominal logistic regression analysis was performed with significant variables. Spearman's correlation was used to evaluate the relationships between continuous variables.

RESULTS

Of the 485 participants included in the study, 56.5% ($n = 274$) were included in the COVID-19-positive group and 43.5% ($n = 211$) in the control group. There was no significant difference between the COVID-19-positive and control groups in gender distribution (52.6% male, 47.4% female in the COVID-19-positive group and 53.6% male, 46.4% female in the control group; $P = 0.450$). The average age of the COVID-19-positive group was significantly higher than that of the control group (50.9 ± 10.9 years *vs* 40.4 ± 12.3 years, $P < 0.001$). The frequency of accompanying hepatic steatosis in the COVID-19-positive group was significantly higher compared with the control group (40.9% *vs* 19.4%, $P < 0.001$). The average hepatic attenuation value was significantly lower in the COVID-19-positive group compared with the control group (45.7 ± 11.4 HU *vs* 53.9 ± 15.9 HU, $P < 0.001$). The average PSS value of the COVID-19-positive group was 7.5 ± 3.4 (range: 2-18). The numbers of patients with obesity, overweight, diabetes mellitus, and hypertension were significantly higher in the COVID-19-positive group compared than in the control group ($P = 0.001$, $P < 0.001$, $P = 0.003$, and $P < 0.001$ respectively; Table 1).

Logistic regression analysis (Table 2) showed that after adjusting for age, hypertension, diabetes mellitus, overweight, and obesity there odds of hepatic steatosis was nearly 2.2 times greater in the COVID-19 positive group compared with the controls [odds ratio (OR) 2.187; 95% confidence interval (CI): 1.336-3.580, $P < 0.001$].

The characteristics of COVID-19 patients with and without the presence of hepatic steatosis are shown in Table 3. PSS was significantly higher in COVID-19 patients with hepatic steatosis than it was in those without steatosis (8.6 ± 3.5 *vs* 6.8 ± 3.2 , $P < 0.001$). Similarly, obesity (25.0% *vs* 10.5%, $P = 0.001$), overweight (61.6% *vs* 40.6%, $P < 0.001$) and alcohol usage (3.6% *vs* 0%, $P = 0.015$) were significantly higher in those with hepatic steatosis.

The results of the correlation analyses are shown in Table 4. There was a weakly negative correlation between the hepatic attenuation value and PSS ($r = -0.305$, $P < 0.001$; Figure 3). There was a weakly positive correlation between PSS and age ($r = 0.329$, $P < 0.001$; Figure 4), and a weakly negative correlation was found between hepatic attenuation and age ($r = -0.242$, $P < 0.001$; Figure 5).

DISCUSSION

Following studies revealing the relationship between obesity and COVID-19[5,7], researchers focused on more specific issues related to metabolic disorders. A study suggested a possible association between hepatic steatosis and COVID-19 infection and showed that the frequency of this liver disorder was increased in COVID-19-positive patients[9]. That study, conducted in Brazil, included 316 patients (204 RT-PCR-positive; 112 RT-PCR-negative and chest CT-negative) who were evaluated retrospectively, the frequency of hepatic steatosis was found to be higher in the RT-PCR-positive group compared to the control group (31.9% *vs* 7.1%, $P < 0.001$)[9]. In this study, the CT results of 485 people (274 RT-PCR- and CT-positive and 211 RT-

Table 1 Comparison of patient variables in the coronavirus disease 2019-positive and control groups

| | | COVID-19 ⁺ , n = 274 (56.5%) | COVID-19 ⁻ , n = 211 (43.5%) | Total, n = 485 | P value |
|---|----------|---|---|----------------|----------------------|
| Age (yr) | | 50.9 ± 10.9 | 40.4 ± 12.3 | 46.4 ± 12.7 | < 0.001 ^c |
| Male gender, n (%) | | 144 (52.6) | 113 (53.6) | 257 (53.0) | 0.450 |
| Hepatic steatosis, n (%) | Presence | 112 (40.9) | 41 (19.4) | 153 (31.5) | < 0.001 ^c |
| | Absence | 162 (58.1) | 170 (80.6) | 332 (68.5) | |
| Liver's attenuation (HU) | | 45.7 ± 11.4 | 53.9 ± 15.9 | 49.3 ± 14.2 | < 0.001 ^c |
| Comorbidities | | | | | |
| Obesity (BMI ≥ 30 kg/m ²) | | 45 (16.4) | 13 (6.2) | 58 (12.0) | 0.001 ^b |
| Overweight (BMI 25–29.9 kg/m ²) | | 153 (55.8) | 55 (26.1) | 208 (42.9) | < 0.001 ^c |
| Diabetes mellitus | | 68 (24.8) | 29 (13.7) | 97 (20.0) | 0.003 ^b |
| Hypertension | | 107 (39.1) | 37 (17.5) | 144 (29.7) | < 0.001 ^c |
| Cardiac disease | | 36 (13.1) | 23 (10.9) | 59 (12.2) | 0.455 |
| Chronic lung disease | | 29 (10.6) | 24 (13.7) | 53 (10.9) | 0.896 |
| No comorbidity ¹ | | 136 (49.6) | 129 (61.1) | 265 (54.6) | 0.012 ^a |
| Smoking history | | 57 (20.8) | 56 (26.1) | 112 (23.1) | 0.110 |
| Alcohol usage | | 4 (1.5) | 4 (1.9) | 8 (1.6) | 0.709 |

¹Includes obesity, overweight, diabetes mellitus, hypertension, smoking history, heart and lung diseases.^aP < 0.05.^bP < 0.01.^cP < 0.001.

BMI: Body mass index; COVID-19: Coronavirus disease 2019; HU: Hounsfield unit. Data are means ± SD or n (%).

Table 2 Binominal logistic regression analysis of statistically significant data in univariate analysis of patients with coronavirus disease 2019

| Variable | OR | 95%CI | P-value |
|---|-------|--------------|----------------------|
| Age | 1.074 | 1.052-1.097 | 0.002 ^b |
| Hepatic steatosis | 2.187 | 1.336-3.580 | < 0.001 ^c |
| Obesity (BMI ≥ 30 kg/m ²) | 4.810 | 2.269-10.195 | 0.001 ^b |
| Overweight (BMI 25–29.9 kg/m ²) | 3.573 | 2.181-5.853 | < 0.001 ^c |
| Diabetes mellitus | 0.396 | 0.213-0.736 | 0.003 ^b |
| Hypertension | 1.455 | 0.867-2.442 | 0.156 |

^bP < 0.01.^cP < 0.001.

BMI: Body mass index; CI: Confidence interval; OR: Odds ratio.

PCR- and CT-negative), also found a significantly higher frequency of hepatic steatosis in the COVID-19 group than in the control group [40.9% (112 of 274 patients) *vs* 19.4% (41 of 211 patients)]. In the previous study, the COVID-19-positive group had an almost 4.7 times higher probability of steatosis (OR: 4.698) compared with the controls. In our study, the odds were approximately 2.2 higher (OR: 2.187). The difference might be related to the greater prevalence of hepatic steatosis in Turkey. Unlike the Brazilian study, we evaluated comorbidities such as obesity, overweight, diabetes mellitus, and hypertension. The results of our study revealed that the incidence of hepatic steatosis remained increased in COVID-19 patients even after adjustment for age and comorbidities. In addition, in our study, the rates of hepatic steatosis in both the COVID-19 and control groups were higher than those of the Brazilian study, which may be related to nutritional, genetic or other regional differences. The prevalence of

Table 3 Comparison of patient variables in those with coronavirus disease 2019 and with or without hepatic steatosis

| Variable | Steatosis ⁺ , n = 112 | Steatosis ⁻ , n = 162 | Total, n = 284 | P value |
|---|----------------------------------|----------------------------------|----------------|----------------------|
| Age (yr) | 51.2 ± 9.2 | 50.7 ± 10.1 | 50.9 ± 10.9 | 0.321 |
| Male gender, n (%) | 65 (58.0) | 79 (48.8) | 144 (52.6) | 0.131 |
| Liver's attenuation, Hounsfield unit | 34.2 ± 4.8 | 53.6 ± 7.2 | 45.7 ± 11.5 | < 0.001 ^c |
| Pneumonia severity score | 8.6 ± 3.5 | 6.8 ± 3.2 | 7.5 ± 3.4 | < 0.001 ^c |
| Comorbidities | | | | |
| Obesity (BMI ≥ 30 kg/m ²) | 28 (25.0) | 17 (10.5) | 45 (16.4) | 0.001 ^b |
| Overweight (BMI 25-29.9 kg/m ²) | 69 (61.6) | 65 (40.6) | 134 (48.9) | < 0.001 ^c |
| Diabetes mellitus | 33 (29.5) | 35 (21.6) | 68 (24.8) | 0.139 |
| Hypertension | 42 (37.5) | 65 (40.1) | 107 (39.1) | 0.662 |
| Cardiac disease | 13 (11.6) | 23 (14.2) | 36 (13.1) | 0.533 |
| Chronic lung disease | 12 (10.7) | 18 (11.1) | 30 (10.9) | 0.918 |
| No comorbidity ¹ | 54 (48.2) | 82 (50.6) | 136 (49.6) | 0.696 |
| Smoking history | 18 (16.1) | 39 (24.1) | 57 (20.8) | 0.109 |
| Alcohol usage | 4 (3.6) | 0 (0) | 4 (1.5) | 0.015 ^a |

¹Includes obesity, overweight, diabetes mellitus, hypertension, smoking history, and heart and lung diseases.^aP < 0.05.^bP < 0.01.^cP < 0.001.

BMI: Body mass index. Data are means ± SD or n (%)

Table 4 Correlation between hepatic attenuation value, coronavirus disease 2019 pneumonia severity score, and age

| | | Liver attenuation value | Pneumonia severity score | Age |
|--------------------------|---------|-------------------------|--------------------------|----------------------|
| Liver attenuation value | r | 1 | -0.305 ¹ | 0.242 ¹ |
| | P value | | < 0.001 ^c | < 0.001 ^c |
| Pneumonia severity score | r | -0.305 ¹ | 1 | 0.329 ¹ |
| | P value | < 0.001 ^c | | < 0.001 ^c |
| Age | r | -0.242 ¹ | 0.329 ¹ | 1 |
| | P value | < 0.001 ^c | < 0.001 ^c | |

¹Correlation is significant at the 0.01 level (2-tailed).^cP < 0.001.

NAFLD worldwide is estimated to be approximately 25% [17]. In a 2016 study conducted in Brazil in an age group similar to our study, a total of 800 people (561 women and 239 men) were examined, and the prevalence of steatosis was found to be 29.1% and higher in men than in women [18]. According to 2016 data published by WHO, Turkey is the country with the highest obesity prevalence (32.1%) in Europe [17]. A comprehensive review published in 2019, included studies reporting that the NAFLD prevalence in Turkey was between 47.9% and 54.4% in age groups similar to those in our study [17]. In a previous study conducted in our hospital population, it was found that men were most affected by NAFLD in the third and fourth decades of age [19]. Despite early studies reporting a higher risk of NAFLD in women, a large body of evidence now shows that the prevalence of NAFLD is higher in men than women, with gender-specific differences by age [20].

A systematic literature review of the association between NAFLD and severe COVID-19 regardless of obesity, which is considered the most important risk factor for both NAFLD and COVID-19, concluded that NAFLD might be a determining factor for severe COVID-19 even after adjusting for the presence of obesity (OR: 2.358, P <

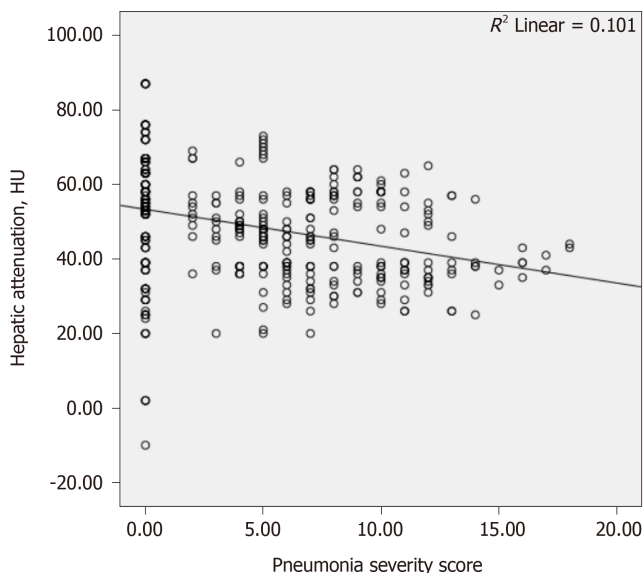


Figure 3 Scatter graph showing a negative correlation between the hepatic attenuation value and pneumonia severity score measured on computed tomography (Spearman's correlation coefficient, $r = -0.357$ and $P < 0.001$). The mean pneumonia severity score of the coronavirus disease 2019-positive group was 7.6 (4.2-11; minimum 2, maximum 18). HU: Hounsfield unit.

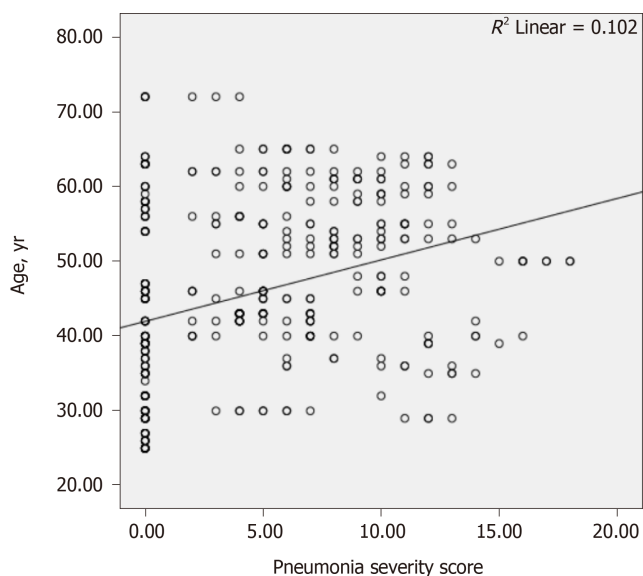


Figure 4 Scatter graph showing a positive correlation between age and the pneumonia severity score measured on computed tomography (Spearman's correlation coefficient, $r = 0.371$ and $P < 0.001$).

0.001)[5]. However, a direct comparison and correlation analysis between hepatic steatosis and disease severity has not previously been published. In patients with COVID-19 requiring intensive care, new parameters such as invasive mechanical ventilation, nosocomial infections, acute respiratory distress syndrome, coagulopathy, and acute kidney injury are added to the main comorbidities, including male gender, advanced age, hypertension, coronary heart disease, chronic obstructive pulmonary disease, obesity, and chronic kidney disease, which further complicates the investigation of factors affecting disease progression[7,21,22]. In this study, we examined the relationship between PSS and hepatic steatosis in patients with symptomatic infection. We found that the PSS was significantly increased in COVID-19 patients with hepatic steatosis (8.6 ± 3.5 vs 6.8 ± 3.2 , $P < 0.001$). That may indicate that comorbidities may accompany in patients with severe pneumonia. In addition, we showed a moderate correlation between hepatic steatosis with age and PSS. We consider that our results are the first data to directly demonstrate that relationship.

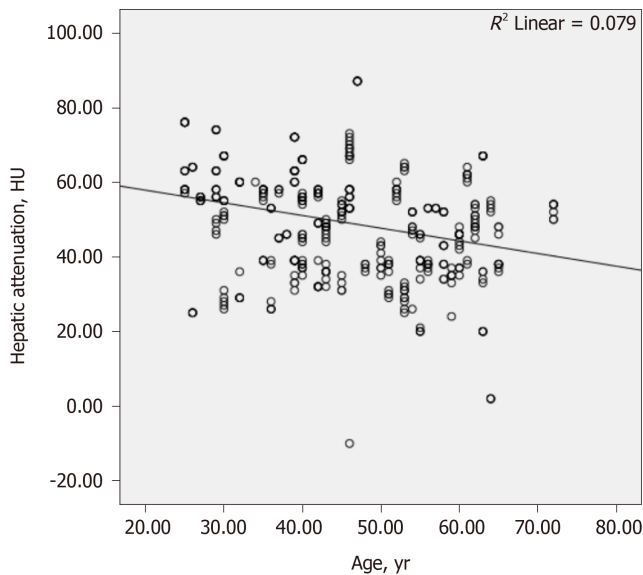


Figure 5 Scatter graph showing a negative correlation between the hepatic attenuation value and age (Spearman's correlation coefficient, $r = -0.303$ and $P < 0.001$). HU: Hounsfield unit.

According to the Centers for Disease Control and Prevention, having a chronic liver disease such as alcohol-related liver disease, NAFLD, and especially cirrhosis, can increase the risk of severe COVID-19[23]. In a retrospective study conducted in China including 202 COVID-19 patients, the prevalence of metabolic associated fatty liver disease (MAFLD) was 37.6%, and the risk of disease progression was increased in that group[24]. Various articles attempting to explain that possible relationship emphasize that MAFLD (defined as NAFLD in some articles) is a liver symptom of metabolic syndrome, is associated with chronic inflammation, and contributes to the interaction in the cytokine storm described in COVID-19 patients, causing disease progression, complications, and fatal consequences[9,10,24]. In support of those studies, we found that the radiological severity of pneumonia was higher in COVID-19 patients with steatosis than without steatosis. Our study, which investigated the relationship between hepatic steatosis and the severity of COVID-19 disease in patients according to tomographic criteria, provides valuable data to guide further study.

This study had several limitations. It was conducted retrospectively in a single tertiary university hospital, and all patients were from a single geographic region. The prevalence of hepatic steatosis may differ in different populations and regions. A strength of our study, is that to the best of our knowledge, it is the first to investigate the relationship between CT-assessed steatosis and PSS in adult COVID-19 patients.

CONCLUSION

The current study revealed a significantly higher prevalence of hepatic steatosis on CT in COVID-19 patients compared with controls after adjustment for age and comorbidities. In addition, it found a correlation between the severity of pneumonia measured on CT and liver density. Therefore, liver density measurement can be considered as a new parameter in the risk analysis of infected patients. This evaluation can be quickly and easily performed using already available CT data without the need for an additional examination. Further study is needed to confirm the presence of such an association after considering and minimizing multiple variables that can affect hepatic steatosis.

ARTICLE HIGHLIGHTS

Research background

Recent studies on coronavirus disease 2019 (COVID-19) demonstrated that obesity is significantly associated with increased disease severity, clinical outcome, and

mortality.

Research motivation

The association between hepatic steatosis, which frequently accompanies obesity, the pneumonia severity score (PSS) evaluated by computed tomography (CT), and the prevalence of steatosis in patients with COVID-19 remains to be elucidated.

Research objectives

The study objective was to assess the frequency of hepatic steatosis in the chest CT of COVID-19 patients and its association with the PSS.

Research methods

This was a retrospective study evaluating the CT of COVID-19 positive and negative patients in a tertiary hospital.

Research results

Of the 485 patients, 274 (56.5%) were defined as the COVID-19-positive group and 211 (43.5%) as the control group. The frequency of hepatic steatosis was significantly higher in the positive group than in the control group (40.9% *vs* 19.4%, $P < 0.001$). The average hepatic attenuation values were significantly lower in the positive group than in the control group (45.7 ± 11.4 HU *vs* 53.9 ± 15.9 HU, $P < 0.001$). Logistic regression analysis showed that after adjusting for age, hypertension, diabetes mellitus, overweight, and obesity there was almost a 2.2 times greater odds of hepatic steatosis in the COVID-19-positive group than in the controls (odds ratio 2.187; 95% confidence interval: 1.336-3.580, $P < 0.001$).

Research conclusions

The current study revealed a significantly higher prevalence of hepatic steatosis on CT in COVID-19 patients compared with controls after adjusting for age and comorbidities.

Research perspectives

Liver density and PSS can be easily examined on CT images of COVID-19 patients and the relationship between tomographic severity and steatosis can be evaluated.

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Patient-ventilator asynchrony in Saudi Arabia: Where we stand?

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Abstract

Patient-ventilator asynchrony in Saudi Arabia practices is common, and more emphasis on how to mitigate such a clinical problem is needed. This letter is intended to shed the light on the current national evidence of patient-ventilator asynchrony and how to step ahead for better patients' ventilation management.

Key Words: Ventilator; Asynchrony; Critical care; Saudi Arabia; Double triggering; Respiratory

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Core Tip: Our Saudi national findings have questioned the effectiveness of the current education and training approaches on mechanical ventilation subject and its related management such as patient-ventilator asynchrony detection. Therefore, “keep calm and carry on strategy” is no longer effective; hence keep research with training and carry on strategy is indeed what we need to improve patient's outcomes.

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TO THE EDITOR

In acute and chronically ill patients, mechanical ventilation is used to improve oxygenation and reduce the load on respiratory muscles, ultimately preventing acute respiratory failure. The optimum interaction between the patient and the ventilator

Grade B (Very good): 0
 Grade C (Good): 0
 Grade D (Fair): 0
 Grade E (Poor): 0

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can help avoid unnecessary sedation, anxiety, discomfort, ventilator fighting events, diaphragm dysfunction and disuse atrophy, potentially cognitive changes, continued ventilation support and additional pulmonary complications[1,2]. Patient-ventilator asynchrony (PVA) is described as a lack of agreement between what is delivered from the ventilator and what patient's needs, which about 25% of those patients who ventilated for more than 24 h had a high rate of PVAs throughout the ventilation support. Indeed, when the incidence of PVAs is greater than 10%, the time interval of invasive ventilation support and the chance of developing tracheostomy are significantly increased[3].

The most common asynchronies in mechanical ventilation process are infective triggering, followed by double triggering, with slight variations between day and night[3,4]. For successful management, it is important to recognise the nature and triggers of the asynchrony. Several techniques were used to identify PVAs, including measurements of electrical diaphragm movement and oesophageal pressure. Such techniques are invasive, costly and require cumbersome equipment, which reduce their daily clinical practice usage[3,5,6]. A non-invasive and accurate method – namely, waveform analysis – would more certainly be effective for identifying and minimising PVAs[3]. However, it is no wonder that most critical care practitioners fail to manage interactions between patient and ventilator and even do not recognise common forms of PVAs[6].

Our recent work badged 'Saudi' in this area has included an attempt to use ventilator waveform analysis to detect common PVAs[7]. To assess the competence of intensive care clinicians to recognise different PVAs, Alqahtani *et al*[7] used a validated assessment approach. This tool included three videotapes for the most popular PVAs, such as auto-triggering. Remarkably, in critical care settings detection of PVAs were found low, with about 25% of PVAs being unnoticed by critical care practitioners. Only 10% of the respiratory therapists, nurses and physicians correctly detected all types, while only 22% correctly found two of these asynchronies. When we investigated the impact of previous training in mechanical ventilation on detection of PVAs, there were significant findings between trained and untrained clinicians. Those who were trained on ventilator waveforms analysis detected more asynchronies compared to not trained (identified three types 19% *vs* 3%, $P < 0.001$; identified two types, 30% *vs* 16%, $P = 0.001$). In accordance with the literature, the present research also established prior training as an independent factor of the proper recognition of the PVAs[6,8]. Such factor is not only required in the detection of asynchronies but also in the management of all invasive and non-invasive ventilation modalities[4,9,10]. We did not find any correlation between years of experience and PVAs recognition. It seems that people with expertise may be overconfidence to their information and in effect, discourage them from honing their skills in the detection to PVAs. Double-triggering was commonly detected among clinicians, which about 49% of the clinicians correctly identified, indicating how easy to identify it. The positive effects of female gender were also associated, which we found female gender as an independent and significant factor to better identify two or more PVAs (odd ratio 1.93; 1.07-3.49). Altogether, though, all clinicians showed a poor level of PVA detection. Such findings could be attributed to the lack of adequate training in mechanical ventilation. Adequate education and training are vital in reducing failures and in alleviating otherwise non-invasive and invasive mechanical ventilation complications[10,11]. All things considered, establishing a clinical audit at intensive care level would improve patient care and outcomes.

The clinical and research implications of our findings are crucial. They confirm that the primary and only modifiable factor to help in the proper recognition of PVAs is prior training on ventilator graphics, irrespective of expertise. This will help to advise hospital policymakers as to create PVA identification policies and provide systematic PVA management guidance. To improve the capacity to identify PVAs further, each hospital can perform more regular training and guidance on ventilator graphics for all critical care clinicians who handle patients with mechanical ventilation. In future studies, the experience and application of PVAs should be investigated before and after education and training sessions to assess the short and long-standing impact on outcomes. Our result has questioned the effectiveness of the current education and training approaches on mechanical ventilation subject and its related management such as PVAs detection. Therefore, "keep calm and carry on strategy" is no longer effective; hence keep research with training and carry on strategy is indeed what we need to improve patient's outcomes.

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