Role of Fatty Liver in Coronavirus Disease 2019 Patients' Disease Severity and Hospitalization Length: a Case-control Study

Arash Ziaee
Mashhad University of Medical Sciences
Ghodsiyeh Azarkar (gh.azarkar@yahoo.com)
Birjand University of Medical Sciences and Health Services https://orcid.org/0000-0003-2603-5255
masood ziaee
Birjand University of Medical Sciences

Research Article

Keywords: Fatty Liver, Coronavirus Disease 2019 (COVID-19), Illness Severity, Stay Length

Posted Date: August 6th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-773522/v1

Abstract

BACKGROUND AND PURPOSE

Fatty liver is one of the most common pre-existing illnesses; it can cause liver injury, leading to further complications for coronavirus disease 2019 patients. Our goal is to determine if pre-existing fatty liver is more prevalent in hospitalized COVID-19 patients compared to patients administrated before the SARS-CoV-2 pandemic and determine the severity of the disease among fatty liver patients.

EXPERIMENTAL APPROACH

This retro-perspective study involves a case and a control group consisting of 1162 patients; the case group contains hospitalized COVID-19 patients with positive PCR tests and available CT-scan; the control group contains patients with available imaging data previous to the COVID-19 pandemic. Patients' data such as liver Hounsfield unit, days of hospitalization, number of affected lobes, and total lungs involvement score were extracted and compared between the patients.

RESULTS

The findings indicate that 37.9% of hospitalized COVID-19 patients have a pre-existing fatty liver, which is significantly higher ($P < 0.001$) than the prevalence of pre-existing fatty liver in control group patients (9.02%). In comparison to hospitalized non-fatty liver COVID-19 patients, data from hospitalized COVID-19 patients with fatty liver indicates longer hospitalization length (6.81 ± 4.76 $P = 0.02$), a higher total lungs involvement score (8.73 ± 5.28 $P < 0.001$), and an increased number of affected lobes (4.42 ± 1.2 $P < 0.001$).

CONCLUSION

The statistical analysis shows fatty liver is much more prevalent among COVID-19 against non-COVID-19 patients, and they develop more severe disease and have to be hospitalized for more extended periods.

Introduction

There has been more than one year since December 29 that the first confirmed SARS-CoV-2 case emerged from Wuhan city of china, which after this long still has so many unknown characteristics. The head of the world health organization (WHO) On January 30, 2020, declared the outbreak of COVID-19 to be a public health emergency of international concern and issued a set of temporary recommendations, and at the point of writing this study, there is more than 100 million confirmed cases and more than two million global deaths. With 1.43 million confirmed cases and more than 58000 deaths, Iran seems to be an excellent candidate to analyze virus characteristics. Many researchers started testing different theories through this rough time to identify possible risk factors that affect this disease's severity and mortality, including analyzing pre-existing illnesses. These researches include systemic, respiratory, gastrointestinal, and cardiovascular symptoms (1); among these symptoms lays liver injury, that according to some

studies, has a noticeable prevalence in coronavirus disease 2019 (COVID-19) patients, COVID-19 positive patients had 45% mild, 21% moderate, and 6.4% severe liver injury" (2), Non-alcoholic fatty liver disease (NAFLD) is currently the most common form of chronic liver disease affecting both adults and children (3), these findings become more critical when we understand according to one study in China that up to 50 % of the people with SARS-CoV-2, had liver dysfunction at some point during their illness(4). the top significant modifiable risk factors for poor outcomes from COVID-19 are set to be obesity and metabolic disease (5, 6). these findings, such as that NAFLD causes the activation of inflammatory pathways (7), suggest that NAFLD can play a part as a risk factor in the severity and outcome of coronavirus disease 2019 patients. According to a meta-analysis conducted in 2016, the prevalence of NAFLD in Iran is 33.95% (8) and factoring in lifestyle changes, and the prevalence can be estimated to have increased in small amounts through past years. This study is conducted to give a more accurate understanding of disease outcome in one of the most common pre-existing illnesses.

It should be noted that it is not well understood if COVID-19 makes pre-existing liver disease worse, but during the course of the COVID-19 pandemic, many infected patients have been treated with antipyretic agents. Most of these medications contain acetaminophen, a drug recognized as being able to cause significant liver damage or induce liver failure (4). SARS-CoV-2 binds to target cells through angiotensin-converting enzyme II (ACE-2) and uses ACE-2 as the cellular entry receptor (9) ACE2 cellular receptor is highly expressed in human lung tissues, gastrointestinal tract, liver(10), and liver cells can act as a susceptible target for coronavirus disease 2019. However, it could not yet be fully confirmed or validated(11).

Attention was brought to this topic because of a high number of fatty liver patients while reporting and evaluating COVID-19 patients lungs involvement score; similar papers have studied severity and outcome of coronavirus disease 2019 using liver enzymes levels such as alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and viral shedding time(12); our study evaluated the severity of COVID-19 patients using different factors such as total lung involvement score and number of affected lobes, and hospitalization period. The hypothesis was tested to see if having pre-existing fatty liver can contribute to more susceptibility and a higher risk of severity and mortality of coronavirus disease 2019.

Materials And Methods

Ethics

This retro-perspective study tries to determine if there is a significant correlation between having fatty liver and being more susceptible to COVID-19 and developing a more severe form of the disease. The Ethics Committee of the Birjand University of Medical Sciences approved the study (IR.BUMS.REC.1399.187);

Study design

we selected patients from the Birajnd, South Khorasan's Vali-Asr hospital, which is the main hospital used for treating COVID-19 patients, and for the control group, data were also selected from the same hospital. Having a pre-existing fatty liver can be determined by measuring the patient's Liver Hounsfield unit (HU); HU reports radiodensity on a quantitative scale, and using patients' imaging data, HU can be measured. Hounsfield units are mainly used to report the fat content of the liver and diagnose fatty liver; according to references and protocols, patients with a HU of 40 or below are counted as fatty liver patients(13). Patients with a borderline score of 40 were evaluated twice to reduce the bias and develop more accurate results.

All COVID-19 patients had a positive Polymerase chain reaction (PCR) test. CT-scan images were taken by Siemens SOMATOM Emotion 16 Slice CT-Scan machine.

The data were extracted using the hospital picture archiving and communication system (PACS) system.

The study consists of the case (575) and the control (587) groups and a total of 1162 patients; the extracted data for each group are as follows:

Sex, Age, Date, Liver Hounsfield Unit was extracted for both case and control group; the additionally acquired data for the case group includes the number of affected lobes, Total Lungs Involvement, Days of Hospitalization, and Death.;

The severity of each patient's disease was evaluated by measuring the number of affected lobes and the total score of lungs involvement.

The severity of the disease was evaluated using three factors:

1. Days of hospitalization
2. The number of affected lobes ranges from 0 to 5
3. Total lungs involvement (chest severity) ranges from 0 to 20

Using Table 1. Information scores were calculated separately for upper, middle, lower lobes and separately for right and left lung; the sum of each lobe’s scores gives us total lungs involvement; this is on par with lungs involvement measurement protocols set by Iran Health Department and is the primary method used for evaluating lungs severity in Iran.

Table 1
Lobes Involvement score

Percentage of Lobe involvement	Score
< 25	1
25–49	2
50–75	3
> 75	4

For the primary analysis, the prevalence of fatty liver was measured and compared between hospitalized COVID-19 patients (case group) and non-COVID-19 patients (control group),

The case group

The case group is made up of hospitalized COVID-19 patients with and without fatty liver; they were chosen from March of 2020 through November of 2020

the evaluated data includes the prevalence of fatty liver in hospitalized COVID-19 patients; sex distribution difference between fatty liver and non-fatty liver patients;

Total lungs involvement, the number of affected lobes, and the hospitalization length were compared between different categories such as COVID-19 patients with and without fatty liver, sex and age groups, months of the year.

The mortality rate was also compared between COVID-19 fatty liver and non-fatty liver patients, sex, and age groups.

The control group

The Control group comprises non-COVID-19 patients with and without fatty liver; the control group patients were administrated before the coronavirus 2019 era and were selected from March of 2019 through the end of November 2019. the following items were measured:

Prevalence of fatty Liver among Non-COVID-19, sex, and age distribution was compared between fatty liver and non-fatty liver patients.

Inclusion criteria

All patients from the stated months were included in the study if they had the following features. For the case group: 1) Diagnosis with COVID-19 using PCR; 2) Hospitalization; 3) Available chest spiral CT-scan; and 4) Available access to patients' imaging data for liver HU measurement.

Control group inclusion criteria were: 1) Patients with available chest spiral CT-scan administrated before December 2019 2) available access to patient's imaging data for measuring liver HU

The exclusion criteria

Under 18 years old, patients were excluded from both study groups. If a hospitalized COVID-19 patient had two or more CT-scan, only the first imaging data were used to evaluate fatty liver scores.

Statistical analysis

In order to control and balance heterogenicity between the two groups, exclusion criteria were sought to be small so control and case group patients would have the same heterogenicity. For statistical analysis, patients were grouped into six different age groups: under 30; 30 to 40; 40 to 50; 50 to 60; 60 to 70; upper than 70

A comparison of categorical variables was performed using the Chi-squared test, and between-group comparisons were assessed using unpaired t-tests. Scatterplot Matrix was used to visualize and give a descriptive analysis of bivariate relationships between combinations of variables. Quantitative data were presented as mean, standard deviation (SD), or median with both a P-value of 0.05 and below being considered statistically significant. Statistical Package for the Social Sciences (SPSS) version 22 software was for data analysis. Statistical analysis was performed only on patients with a complete set of data; if the patient's data was incomplete, they were excluded from the analysis.

Results

Fatty liver Distribution

The study consists of 1162 patients; it includes a case group consisting of 575 patients hospitalized with confirmed COVID-19 infection, and the control group consisted of 587 patients with chest CT scans in the last year, and no patient had missing data. The prevalence of pre-existing fatty liver among hospitalized COVID-19 patients was significantly higher than the control group patients (37.9% vs. 9.02% $P < 0.001$). The percentage of male patients in COVID-19 patients who have fatty liver is noticeably higher than the percentage of male COVID-19 patients who do not have fatty liver (60.8 % vs. 50.7 %, $P = 0.02$), but there is no significant difference in male's sex distribution among non-COVID-19 patients (42.3% men vs. 44.8% men, $P = 0.77$). The distribution of fatty liver in the case group was much more focused in 51–60 years age group ($P = 0.01$)

COVID-19 Severity and Mortality

The severity of the disease was compared among COVID-19 patients with and without fatty liver; the virus seems to affect more lobes (4.42 ± 1.2 $P < 0.001$) and higher total lungs involvement score (8.73 ± 5.28 $P < 0.001$) among COVID-19 patients with fatty liver, COVID-19 patients with fatty liver are hospitalized for

more extended periods (6.81 ± 4.76 $P = 0.02$), multivariable analysis of 3 pervious factors showed total P-value < 0.001. interestingly while the results suggest that COVID-19 patients with fatty liver develop more severe coronavirus disease 2019 but the findings do not show a significantly higher risk of death for fatty liver patients (11.5 % vs. 10.1%, $P = 0.58$); however, deceased patients' lungs involvement score (11.9 ± 6.25 $P < 0.001$) and the number of affected lobes (4.52 ± 1.16 $P = 0.005$) are significantly higher than survived patients. The elderly patient's mortality rate was higher in hospitalized COVID-19 positive patients (74.56 ± 11.99 $P < 0.001$).

According to our result, there is not a significant difference between the male and female patient's disease severity and mortality; male patients total score of lungs involvement (7.4 ± 5.05 $P = 0.17$), number of affected lobes (4.01 ± 1.53 $P = 0.13$), and hospitalization period (6.39 ± 4.9 vs. 6 ± 4, $P = 0.32$) are not significantly higher than female patients; men are also not at a higher risk of coronavirus disease 2019 mortality (60.7%, $P = 0.31$).

Our Study shows the severity of the disease is increased in months of autumn in Iran (September – November) with a higher total score of lungs involvement (10.36 ± 4.94 $P < 0.001$) and a more significant number of affected lobes (4.79 ± 0.70 $P < 0.001$), in contrast, days of hospitalization is significantly higher in the first month of spring in Iran which is from March through April (8.9 ± 6.61 $P = 0.005$).

Factors correlation

Bivariate correlation between combinations of variables analysis (Fig. 1) that includes lungs involvement, number of affected lobes, and hospitalization period factors against age shows the following results 1) total score of lungs (r = 0.24, $P < 0.001$) and 2) number of affected lobes (r = 0.27, $P < 0.001$) 3) hospitalization period (r = 0.24, $P < 0.01$). The analysis shows elderly patients are more susceptible to be infected with COVID-19 and develop more severe disease with a higher total lungs involvement score and a more extended hospitalization period.

Sex distribution

The percentage of male patients in the case group is much higher than the control group (54.5% male vs. 44.5% male, P 0.001. Males have higher average age among non-fatty liver non-COVID-19 patients (59.15 ± 18.91, $P = 0.03$) (Table 2.).

Table 2
Comparison of Sex Distribution in the control group. Average Age, Average Hounsfield Unit

The Control Group Total Number of Patients = 587		**Non-COVID-19 Fatty Liver Patients**	**Non-Fatty Liver Non-COVID-19 Patients**
The Average Age	Male	55.14 ± 18.41	59.15 ± 18.91
	Female	56.43 ± 15.20	55.71 ± 17.45
	P Value	0.78	0.03
The Average Liver Hounsfield Unit	Male	33.18 ± 7.90	56.21 ± 7.52
	Female	35.37 ± 5.22	57.63 ± 7.99
	P Value	0.23	0.04

Females have higher average age among COVID-19 Patients with Fatty Liver (59.29 ± 13.45, $P = 0.03$), however in COVID-19 Patients without fatty liver, the average female age is not significantly higher than males. The number of affected lobes (4.61 ± 1.09, $P = 0.05$) and total score of lungs involvement (9.68 ± 5.70, $P = 0.04$) are noticeably higher among female COVID-19 Patients with Fatty Liver. There is no significant difference between each sex's mortality rate among COVID-19 Patients with Fatty Liver; in contrast, the male mortality rate is higher in COVID-19 patients without fatty liver (69.4%, $P = 0.02$) (Table 3).

Table 3
Comparison of Sex Distribution in the case group. Average Age, Average Liver Hounsfield Unit, Average Number Of Involved Lobes, Average Score Of Lungs Involvement, And Mortality Among Patients are included and compared

The Case Group Total Number of Patients = 575		**COVID-19 With Fatty Liver Patients**	**COVID-19 Without Fatty Liver COVID-19 Patients**
The Average Age	Male	54.53 ± 18.85	58.31 ± 20.41
	Female	59.29 ± 13.45	57.77 ± 17.67
	P Value	0.03	0.79
The Average Hounsfield Unit	Male	32.64 ± 7.89	50.49 ± 6.03
	Female	30.99 ± 8.88	51.30 ± 6.72
	P Value	0.16	0.23
The Average Days Of Hospitalization	Male	6.83 ± 4.98	6.07 ± 4.87
	Female	6.77 ± 4.44	5.63 ± 3.74
	P Value	0.93	0.36
The Average Number Of Affected Lobes	Male	4.29 ± 1.25	3.81 ± 1.67
	Female	4.61 ± 1.09	4.01 ± 1.55
	P Value	0.05	0.25
The Average Total Score Of Lungs Involvement	Male	8.11 ± 4.91	6.90 ± 5.11
	Female	9.68 ± 5.70	7.20 ± 5.22
	P Value	0.04	0.57
Deceased	Male	48%	69.4%
Total: 62	Male	48%	69.4%
	Female	52%	30.6%
	P Value	0.16	0.02

Discussion

Our results showed that fatty liver is much more prevalent in COVID-19 patients, which is on par with other studies stating that fatty liver has a higher percentage among COVID-19 patients in comparison

with non-COVID-19 patients (7, 12). The fatty liver prevalence among hospitalized COVID-19 patients is higher than the calculated prevalence of NAFLD in Iran from 2016 (37.84% vs. 33.95%). Other study findings state that increased liver fibrosis in NAFLD might affect COVID-19 outcome (3). Our result is also supported by Bramante et al. study indicating Fatty liver patients have a much higher risk of COVID-19 hospitalization; their study suggests metabolic syndrome and NAFLD/NASH available treatments significantly mitigated risks from COVID-19 those with home metformin glucagon-like-peptide 1 receptor agonist (GLP-1 RA) use has a non-significantly reduced odds of hospitalization(6).

Our study demonstrates that COVID-19 patients who suffer from fatty liver have to be hospitalized for more extended periods, which is confirmed by the study of Dong Ji and colleagues(12). The data analysis also shows that patients with fatty liver experience more severe symptoms during the course of the disease; the number of involved lobes and total involvement of lugs are higher in fatty liver patients, which can be attributed to the findings of the extended period of hospitalization data. A higher risk of disease progression is also suggested by another study that evaluated the disease severity by different factors(12), and another study also suggests fatty liver patients experience a more severe form of the disease(14).

In addition, the results suggest that social awareness should be gained regarding the negative impact of metabolic diseases such as fatty livers on patients with COVID-19 and that health policymakers should promote the use of preventive measures to prevent obesity and fatty liver.

With increased disease severity, the coronavirus disease 2019 mortality rate was expected to be noticeably higher among fatty liver patients. However, data analysis showed it could not be concluded that fatty liver is linked to a higher COVID-19 mortality rate, which is in contrast to another study that concludes liver injury is strongly associated with the COVID-19 mortality risk(6, 14).

According to our findings, the severity of COVID-19 is increased in Iran's autumn months, which is from September through October. It can be confirmed by other studies that suggest the emergence of virus mutations could have made the COVID-19 virus more transmissible and infectious (15). COVID-19 hospitalization length was not linked to autumn; however, it was much higher at the beginning of the COVID-19 pandemic; it can be speculated that patients used to be hospitalized for more extended periods because of not fully understood treatment and hospitalization protocols. We suggest coronavirus disease 2019 had higher severity in autumn; however, it should also be noted that during the autumn number of patients drastically increased; therefore, hospitals could only administrate patients with more severe symptoms. A newly conducted study also suggests that an increase in the number of COVID-19 patients and severity could be related to the decrease in the amount of individual vitamin D in the autumn and winter season (16). The previous studies give a clear understanding that there is an essential and direct role for vitamin D in modulating liver inflammation and fibrogenesis (17, 18). Other studies show a clear correlation between COVID-19 and vitamin D deficiency (19, 20), which indicates that treating fatty liver patients' vitamin D deficiency can reduce the chance of liver injury(20) and ultimately decrease coronavirus disease 2019 severity and mortality(6, 21).

According to our study and similar studies, the percentage of male patients is more significant than women in COVID-19 (22); our findings cannot validate the theory that male patients are also more prone to more severe forms of the disease, which is, in contrast, to study of Kuno et al.(23) Scatterplot Matrix data analysis showed that older adults are more susceptible to develop a more severe form of disease according to our data elderly patients have to hospitalized for more extended periods. The total score of lungs involvement is significantly higher, which is validated by previous studies; it can also be attributed to pre-existing illnesses (24). The elderly male mortality rate is higher than expected, and it is validated by other studies(25).

Limitations

Deceased patients' data could only be collected from June through August and October through November of 2020, so the number of deceased patients could not be compared between different months of the year; the deceased patients' data was only used to compare mortality between the COVID-19 patients with and without fatty liver and if one sexuality has a higher risk of mortality. We did not have access to each patient's past medical history, so patients could not be accurately categorized into Non-alcoholic fatty liver disease patients; instead, the selected used term was fatty liver patients.

Conclusion

The study concludes that fatty liver can play an important role in susceptibility to being infected with SARS-CoV-2 and the severity of COVID-19 patients; the prevalence of fatty liver patients in COVID-19 is much higher than patients that do not have pre-existing fatty liver. COVID-19 patients with fatty liver are hospitalized for more than extended periods and have a higher total lungs involvement score.

The results also further confirm findings from previous studies that male and elderly patients are more prone to coronavirus disease 2019 infection. In contrast to other studies' findings, male and elderly patients are not at a higher risk of disease severity and mortality.

Treatment for obesity and pre-existing metabolic disease should be a priority while knowing this significantly higher risk. Therefore, it is necessary to investigate future prospective studies to determine the exact cause and effect correlation between SARS-CoV-2 and fatty liver.

Abbreviations

HU, Hounsfield Unit; COVID-19, coronavirus disease 2019; WHO, world health organization; NAFLD, Non-alcoholic fatty liver disease; ACE-2, angiotensin-converting enzyme II; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PACS, picture archiving and communication system; PCR, Polymerase chain reaction; NASH, Non-alcoholic steatohepatitis; GLP-1 RA, glucagon-like-peptide 1 receptor agonist.

Declarations

Ethics

The Ethics Committee of the Birjand University of Medical Sciences approved the study (IR.BUMS.REC.1399.187)

Conflict of Interests

The authors declare no conflict of interest.

Consent to Publish

All authors, including Ghodsiyeh Azarkar, Arash Ziaee, and Masood Ziaee, give their full consent regarding the publishing of Role of Fatty Liver In Coronavirus Disease 2019 Patients' Disease Severity and Hospitalization Length: A Case-Control Study.

Financial support statement

Vice-Chancellor for Research and Technology of the Birjand University of Medical Sciences supported this study (No.: 5467).

Authors' Contribution

GA presented the study's main idea, AZ constructed the theory, evaluated needed data, and contributed to the statistical analysis. MZ contributed to granting access to patient data and planning study procedures and study coherence; GA and AZ contributed to data extraction. All authors contributed to data evaluation and interpretation. The study's final approval and review procedure was done under the contribution of all authors.

Acknowledgment

We would like to acknowledge the Vice-Chancellor of Research and Technology of the Birjand University of Medical Science for their support and thank the Infectious Diseases Research Institute for their data analysis.

Data Availability

All of the authors of “Role of Fatty Liver In Coronavirus Disease 2019 Patients' Disease Severity and Hospitalization Length: A Case-Control Study” confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Complete set of data will be provided upon request to the reviewers if it’s necessary but due to the fact that COVID-19 is still not a well-known disease there are confidential concerns around COVID-19 patients’ data, therefore the data cannot openly be deposited in repositories and supporting data cannot be made openly available.

References

1. Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. Cochrane Database of Systematic Reviews. 2020(7).
2. Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, et al. Acute liver injury in COVID-19: prevalence and association with clinical outcomes in a large US cohort. Hepatology. 2020;72(3):807-17.
3. Fricker ZP, Pedley A, Massaro JM, Vasan RS, Hoffmann U, Benjamin EJ, et al. Liver fat is associated with markers of inflammation and oxidative stress in analysis of data from the Framingham heart study. Clinical Gastroenterology and Hepatology. 2019;17(6):1157-64. e4.
4. Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, et al. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. J Clin Transl Hepatol. 2020;8(1):18-24.
5. Yang J, Hu J, Zhu C. Obesity aggravates COVID-19: a systematic review and meta-analysis. Journal of medical virology. 2021;93(1):257-61.
6. Bramante C, Tignanelli CJ, Dutta N, Jones E, Tamariz L, Clark JM, et al. Non-alcoholic fatty liver disease (NAFLD) and risk of hospitalization for Covid-19. medRxiv. 2020.
7. Portincasa P, Krawczyk M, Smyk W, Lammert F, Di Ciaula A. COVID-19 and non-alcoholic fatty liver disease: Two intersecting pandemics. Eur J Clin Invest. 2020;50(10):e13338.
8. Moghaddasifar I, Lankarani KB, Moosazadeh M, Afshari M, Ghaemi A, Aliramezany M, et al. Prevalence of Non-alcoholic Fatty Liver Disease and Its Related Factors in Iran. Int J Organ Transplant Med. 2016;7(3):149-60.
9. Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J. 2020;55(5).
10. Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, et al. The ACE2/Angiotensin-(1-7)/MAS Axis of the Renin-Angiotensin System: Focus on Angiotensin-(1-7). Physiol Rev. 2018;98(1):505-53.
11. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. biorxiv. 2020.
12. Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. J Hepatol. 2020;73(2):451-3.
13. Graffy PM, Sandfort V, Summers RM, Pickhardt PJ. Automated Liver Fat Quantification at Nonenhanced Abdominal CT for Population-based Steatosis Assessment. Radiology. 2019;293(2):334-42.
14. Pan L, Huang P, Xie X, Xu J, Guo D, Jiang Y. Metabolic associated fatty liver disease increases the severity of COVID-19: A meta-analysis. Dig Liver Dis. 2021;53(2):153-7.

15. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell. 2020;182(4):812-27. e19.
16. Walrand S. Autumn COVID-19 surge dates in Europe correlated to latitudes, not to temperature-humidity, pointing to vitamin D as contributing factor. Scientific reports. 2021;11(1):1-9.
17. Eliades M, Spyrou E. Vitamin D: a new player in non-alcoholic fatty liver disease? World J Gastroenterol. 2015;21(6):1718-27.
18. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J Infect Public Health. 2020;13(10):1373-80.
19. Zemb P, Bergman P, Camargo CA, Jr., Cavalier E, Cormier C, Courbebaisse M, et al. Vitamin D deficiency and the COVID-19 pandemic. J Glob Antimicrob Resist. 2020;22:133-4.
20. Barchetta I, Cimini FA, Cavallo MG. Vitamin D Supplementation and Non-Alcoholic Fatty Liver Disease: Present and Future. Nutrients. 2017;9(9).
21. Mercola J, Grant WB, Wagner CL. Evidence Regarding Vitamin D and Risk of COVID-19 and Its Severity. Nutrients. 2020;12(11).
22. Abate BB, Kassie AM, Kassaw MW, Aragie TG, Masresha SA. Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis. BMJ Open. 2020;10(10):e040129.
23. Ueyama H, Kuno T, Takagi H, Krishnamoorthy P, Vengrenyuk Y, Sharma SK, et al. Gender difference is associated with severity of coronavirus disease 2019 infection: an insight from a meta-analysis. Critical care explorations. 2020;2(6).
24. Team CC-R, Team CC-R, Team CC-R, Bialek S, Boundy E, Bowen V, et al. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–March 16, 2020. Morbidity and mortality weekly report. 2020;69(12):343-6.
25. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-5.

Figures

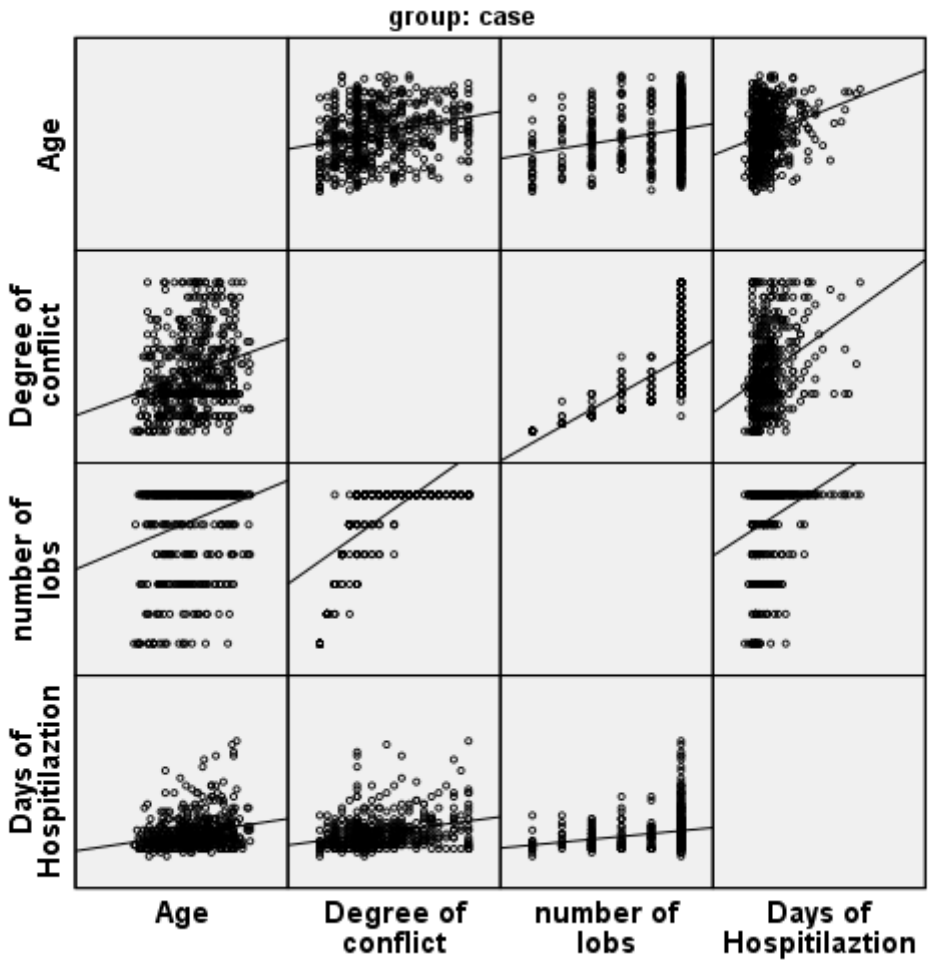

Figure 1

Scatterplot Matrix Analysis shows the correlation of Lungs Involvement, Number of Affected Lobes and Hospitalization Period with each other