



Evaluation of High Oxygen Saturation Status in Cirrhotic Patients

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Abstract

Background: Cirrhosis, as the end stage of a variety of chronic liver diseases, can affect oxygenation in patients and make them hypoxic through hepatopulmonary syndrome or portopulmonary hypertension. However, we observed that some patients referring to our center for liver transplantation had high arterial oxygen saturation.

Objectives: This study was designed to investigate the presence and association of hemoglobin oversaturation in cirrhotic patients candidate for liver transplantation.

Methods: In a cross-sectional study, cirrhotic patients referring to Shiraz Organ Transplantation Center were included from 2013 to 2015. The exclusion criteria were other disorders that might affect O₂ saturation and other causes of liver transplantation except for cirrhosis. Also, we excluded all patients with chest X-ray abnormality. Hemoglobin saturation was measured by arterial blood gas analysis. Patients were divided into two groups, oversaturated patients (Hb sat O₂ ≥ 98%) as the case group and patients with Hb sat O₂ < 98% as the control group. We compared the case and control groups for the cause of cirrhosis, sex, smoking status, age, spirometry, model for end-stage liver disease (MELD) score, and the place of residence's altitude. After univariate analysis, logistic regression models were used for multivariate analysis and adjusted for significant and near significant (P value < 0.2) covariates.

Results: Of 495 patients, 18.6% were oversaturated. Moreover, 64.5% of the control group patients were males versus 58.7% of the case group. The mean age of the control group (40.6 ± 14.7) was significantly higher than that of the case group (36.8 ± 15.7) in univariate analysis (P value = 0.02). Hemoglobin oversaturation was significantly higher in patients with auto-immune hepatitis (AIH) than in patients with other causes of cirrhosis (P value = 0.001). There was no significant difference between the case and control groups in other causes of cirrhosis or other factors. In multivariate analysis, just AIH remained statistically significant in the models (odds ratio = 2.03; 95% confidence interval = 1.13 - 3.65; P value = 0.01). After finding an association between AIH and oversaturation, the drugs routinely used for the treatment of AIH were compared between the case and control groups. No significant difference was found between them in using prednisone, azathioprine, and cyclosporine (P values = 0.5, 0.6, and 0.6, respectively).

Conclusions: Based on our research, there was an association between oversaturation in cirrhotic patients and AIH. The association was not related to the drugs used for the treatment of AIH.

Keywords: Cirrhosis, O₂ Saturation, Auto-immune Hepatitis

1. Background

Despite various etiologies of chronic liver disease, the final outcome is similar to some extent. Cirrhosis, as the end stage of most chronic liver diseases, accounts for high morbidity and mortality all over the world. The patients may suffer from other extra-hepatic organ complications. Widened alveolar-arterial oxygen difference (> 20 mmHg) is common and hypoxemia may occur in some cases (1). Respiratory failure and hypoxemia serve as the consequences of hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax among these patients (2). Hepatopulmonary syndrome (HPS) is

seen in 15% to 30% of cirrhotic patients (3).

Unexpectedly, some cirrhotic patients are oversaturated. During the routine workups before liver transplantation, in our referral center, we observe that some patients have high hemoglobin oxygen saturation levels without any oxygen therapy. This condition has not studied and focused yet.

2. Objectives

Thus, our study aimed to confirm and determine the association between some risk factors and related param-

ters of liver cirrhosis and high hemoglobin oxygen saturation in these patients.

3. Methods

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (ethics code: IR.sums.med.rec.1396.s03). The study participants included patients who were candidates for liver transplantation. In a cross-sectional study, we enrolled cirrhotic patients who referred to Shiraz Organ Transplantation Center from 2013 to 2015. The exclusion criteria were other disorders that might affect O₂ saturation, including intracardiac shunt, intrapulmonary shunt, pulmonary arterial hypertension, moderate to severe ascites, cystic fibrosis, and other causes of liver transplantation, except for cirrhosis. Moreover, we excluded patients with chest X-ray abnormality from this study. The patients' medical records were reviewed for data gathering. The participants were divided into case and control groups based on their arterial oxygen saturation (AOS) measured by arterial blood gas (ABG) sampling. The ABG sampling was performed in the outpatient clinic before admission for liver transplantation. The patients were in the sitting position for five minutes before sampling. Oxygen oversaturation was defined as an arterial oxygen saturation (AOS) equal to or more than 98%. The oversaturated patients (AOS \geq 98%) were regarded as the case group while the control group was defined as patients with AOS < 98%. We compared the case and control groups for causes of cirrhosis, age, sex, cigarette smoking status, simple spirometry, model of end-stage liver disease (MELD) score, and place of residence's altitude. The causes of cirrhosis were autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), cryptogenic, hepatitis B virus (HBV), hepatitis C virus (HCV), Wilson disease, primary biliary cirrhosis (PBC), alcoholic cirrhosis, Budd-Chiari syndrome, and biliary atresia.

Continuous variables were presented using means and standard deviations. Numbers and percentages were used for categorical variables. The chi-square test and independent *t*-test were used for univariate analysis. The *P* values of less than 0.05 were regarded as significant. Logistic regression models were used to calculate the odds ratio and 95% confidence interval (CI). Multivariate models were adjusted for significant and near significant (*P* value < 0.2) covariates. All statistical analyses were done using SPSS software (IBM SPSS, version 13).

4. Results

Of 495 participants, 92 (18.6%) had AOS \geq 98% as the case group and 403 (81.4%) as the control group. Moreover,

58.7% of the case group and 64.5% of the control group were males. The mean age of the case and control groups was 36.8 ± 15.7 years and 40.6 ± 14.7 years, respectively, with a statistically significant difference. The number of patients with the cause of AIH was significantly higher in the case group than in the control group. Table 1 shows the results of univariate analysis.

In the next step, the covariates including age, AIH, and PSC were put in the logistic regression models for multivariate analysis. After performing the analysis, AIH remained statistically significant in the models (odds ratio = 2.03; 95% CI = 1.31 - 3.65; *P* value = 0.01). The Hosmer and Lemeshow test confirmed the good fitness of the regression model (*P* value = 0.35). Table 2 shows the results of multivariate analysis.

After finding an association between AIH and oversaturation, drugs routinely used for the treatment of AIH was compared between the case and control groups. No significant difference was found between the groups in using prednisone (*P* value = 0.5), azathioprine (*P* value = 0.6), and cyclosporine (*P* value = 0.6).

5. Discussion

The results of our study showed that hemoglobin oversaturation was two times more common in cirrhotic patients with AIH than in patients with other causes of cirrhosis. The oxygen saturation level is an important predictive parameter in the pulmonary evaluation of cirrhotic patients since hypoxemia leads to a poor prognosis. Cirrhotic patients who undergo their first mechanical ventilation are prone to the increased risk of mortality (4).

It is found that the prognosis of patients with HPS that presents with severe hypoxemia is poor even after liver transplantation (5). Therefore, it is important to measure the patients' oxygen saturation level. Therefore, finding an etiology for oversaturation in some patients may help us find a way of managing hypoxemia in cirrhotic patients. Based on our search, there was no previous article focusing on oxygen oversaturation in cirrhosis.

ABG has more accuracy than pulse oximetry (6). Ghayumi et al. (7) found that pulse oximetry had enough accuracy (more than 94% equal to ABG sampling) for predicting hypoxemia in end-stage liver failure. However, the results of another study conducted by Forde et al. (8) revealed that pulse oximetry had low sensitivity (28%; 95% CI, 18% - 28%) to detect HPS in patients evaluated for liver transplantation. As the ABG remains the gold standard method, we decided to use this method for defining the case and control groups.

We excluded all patients with diseases other than cirrhosis like intracardiac shunt, intrapulmonary shunt,

Table 1. Some Factors Related to Cirrhosis Compared Between Oversaturated Patients ($\geq 98\%$ as the case group) and the Control Group in Univariate Analysis^a

Characteristics	All Participants	Case Group	Control Group	Unadjusted OR (95% CI)	P Values
Total	495	92 (18.6)	403 (81.4)		
Sex				1.27 (0.8 - 2.03)	0.29
Male	314 (63.4)	54 (58.7)	260 (64.5)		
Female	181 (36.6)	38 (41.3)	143 (35.5)		
Age, y	39.9 \pm 14.9	36.8 \pm 15.7	40.6 \pm 14.7	1.01 (1.002 - 1.03)	0.02
Smoking				1.08 (0.46 - 2.53)	0.85
Yes	40 (8.1)	7 (7.6)	33 (8.2)		
No	455 (91.9)	85 (92.4)	370 (91.8)		
AIH				2.57 (1.49 - 4.44)	0.001
Yes	76 (15.4)	25 (27.2)	51 (12.7)		
No	419 (84.5)	67 (72.8)	352 (87.3)		
PSC				1.8 (0.94 - 3.47)	0.07
Yes	98 (19.8)	12 (13)	86 (21.3)		
No	397 (80.2)	80 (87)	317 (78.7)		
Cryptogenic				1.23 (0.7 - 2.15)	0.45
Yes	94 (19)	20 (21.7)	74 (18.4)		
No	401 (81)	72 (78.3)	329 (81.6)		
HBV				1.43 (0.81 - 2.5)	0.21
Yes	122 (24.6)	18 (19.6)	104 (25.8)		
No	373 (75.4)	74 (80.4)	299 (74.2)		
HCV				1.26 (0.27 - 5.79)	0.76
Yes	13 (2.6)	2 (2.2)	11 (2.7)		
No	482 (97.4)	90 (97.8)	392 (97.3)		
Wilson disease				2.13 (0.63 - 7.18)	0.22
Yes	30 (6.1)	3 (3.3)	27 (6.7)		
No	465 (93.9)	89 (96.7)	376 (93.3)		
City altitude, km	1.117 \pm 0.599	1.125 \pm 0.578	1.115 \pm 0.605	0.97 (0.64 - 1.45)	0.89
FEV1 (predicted percent)	85.9 \pm 16.8	84.7 \pm 15.3	86.1 \pm 17.1	1.005 (0.99 - 1.01)	0.48
FVC (predicted percent)	85.4 \pm 15.7	84.3 \pm 15	85.6 \pm (15.9)	1.005 (0.99 - 1.02)	0.5
Meld score	20 \pm 5.3	20.4 \pm 5.6	19.9 \pm 5.2	0.98 (0.94 - 1.02)	0.39

^aValues are expressed as mean \pm SD or No. (%).

pulmonary arterial hypertension, and cystic fibrosis that could affect oxygenation. Also, patients with chest radiographic abnormalities were excluded from the study. It was done to prevent the concurrent effect of other situations on oxygenation.

As an unresolved inflammatory liver disease, AIH is associated with hypergammaglobulinemia and serum autoantibodies of unknown causes (9). The first - line treatment of AIH is combination therapy with prednisone and

azathioprine (10). We could not make an exact hypothesis of the association between AIH and oversaturation in cirrhotic patients. It was doubtful whether the treatment of AIH and taking corticosteroids for a long time may have caused this association. Thus, in the next step, the case and control groups were compared for using prednisone, azathioprine, and cyclosporine. There was no significant difference between the case and control groups.

As far as we know, some factors including tempera-

Table 2. Results of Multivariate Analysis After Adjusting Logistic Regression Models for Significant and Near Significant Factors in Univariate Analysis

Covariates	Odds Ratio	95% CI for Odds Ratio		P Values
		Lower	Upper	
Age	1.01	0.99	1.03	0.09
AIH	2.03	1.13	3.65	0.01
PSC	1.62	0.82	3.19	0.16

ture, PH, 2,3 - diphosphoglycerate concentration, and carbon dioxide concentration can affect the hemoglobin oxygen saturation (11). There might be some differences between AIH and other causes of cirrhosis in these factors, resulting in higher AOS. We did not include them in our study and it should be investigated in future studies. The level of 2, 3 - diphosphoglycerate, which affects the oxygen affinity of hemoglobin, is not the same in various types of liver diseases (12). The inverse association between altitude and blood oxygen saturation has been found previously (13). We compared the altitude of the patients' living area. However, we found no significant difference between the case and control groups.

Our study is the first study to date to specifically investigate hemoglobin oxygen oversaturation in a large population of cirrhotic patients candidate for liver transplantation. There were some limitations to this study. As stated above, we did not document or measure some other factors that might affect hemoglobin oxygen saturation. In this study, we did not analyze some causes of cirrhosis separately because of the very low number of participants. These causes were PBC, Alcoholic cirrhosis, Budd - Chiari syndrome, and biliary atresia. Thus, our findings cannot be generalized to the whole population of cirrhotic patients.

5.1. Conclusions

In conclusion, we found an association between AIH and HB oversaturation as a novel finding based on the results of our research in cirrhotic patients candidate for liver transplantation. Further studies are needed to document these findings and explore reasons for the HB oversaturation in AIH cirrhotic patients.

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Footnotes

Authors' Contribution: Study concept and design: Seiyed Mohammad Ali Ghayumi and Ali Adib. Acquisition of data, analysis, and drafting of the manuscript: Ali Adib, Mohammad Javad Fallahi, and Peyman Arasteh. All authors read and signed the final paper.

Conflict of Interests: The authors declare that they have no conflict of interest.

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References

- Ghayumi SM, Mehrabi S, Zamirian M, Haseli J, Bagheri Lankarani K. Pulmonary complications in cirrhotic candidates for liver transplantation. *Hepat Mon.* 2010;**10**(2):105-9. [PubMed: 22312382]. [PubMed Central: PMC3270352].
- Hemprich U, Papadakos PJ, Lachmann B. Respiratory failure and hypoxemia in the cirrhotic patient including hepatopulmonary syndrome. *Curr Opin Anaesthesiol.* 2010;**23**(2):133-8. doi: 10.1097/ACO.0b013e328335f024. [PubMed: 20019600].
- Surani SR, Mendez Y, Anjum H, Varon J. Pulmonary complications of hepatic diseases. *World J Gastroenterol.* 2016;**22**(26):6008-15. doi:10.3748/wjg.v22.i26.6008. [PubMed: 27468192]. [PubMed Central: PMC4948262].
- Lai CC, Ho CH, Cheng KC, Chao CM, Chen CM, Chou W. Effect of liver cirrhosis on long-term outcomes after acute respiratory failure: A population-based study. *World J Gastroenterol.* 2017;**23**(12):2201-8. doi:10.3748/wjg.v23.i12.2201. [PubMed: 28405148]. [PubMed Central: PMC5374132].
- Nayyar D, Man HS, Granton J, Gupta S. Defining and characterizing severe hypoxemia after liver transplantation in hepatopulmonary syndrome. *Liver Transpl.* 2014;**20**(2):182-90. doi: 10.1002/lt.23776. [PubMed: 24142412].
- Olive S, Twentyman O, Ramsay C. Comparison of fingertip and earlobe pulse oximetry with arterial blood gas results. *Eur Respiratory Soc.* 2016:PA3702. doi: 10.1183/13993003.congress-2016.PA3702.
- Ghayumi SM, Khalafi-Nezhad A, Jowkar Z. Pulse oximeter oxygen saturation in prediction of arterial oxygen saturation in liver transplant candidates. *Hepat Mon.* 2014;**14**(4). e15449. doi: 10.5812/hepatmon.15449. [PubMed: 24748894]. [PubMed Central: PMC3989597].
- Forde KA, Fallon MB, Krowka MJ, Sprys M, Goldberg DS, Krok KL, et al. Pulse oximetry is insensitive for detection of hepatopulmonary syndrome in patients evaluated for liver transplantation. *Hepatology.* 2019;**69**(1):270-81. doi: 10.1002/hep.30139. [PubMed: 30070715]. [PubMed Central: PMC6652183].
- Doycheva I, Watt KD, Gulamhusein AF. Autoimmune hepatitis: Current and future therapeutic options. *Liver Int.* 2019;**39**(6):1002-13. doi: 10.1111/liv.14062. [PubMed: 30716203].
- Santiago P, Schwartz I, Tamariz L, Levy C. Systematic review with meta-analysis: Mycophenolate mofetil as a second-line therapy for autoimmune hepatitis. *Aliment Pharmacol Ther.* 2019;**49**(7):830-9. doi: 10.1111/apt.15157. [PubMed: 30761563].
- Dash RK, Korman B, Bassingthwaite JB. Simple accurate mathematical models of blood HbO2 and HbCO2 dissociation curves at varied physiological conditions: evaluation and comparison with other models. *Eur J Appl Physiol.* 2016;**116**(1):97-113. doi: 10.1007/s00421-015-3228-3. [PubMed: 26298270]. [PubMed Central: PMC4699875].

12. Nakano T, Fujioka H, Tamura S, Amuro Y, Nabeshima K, Hada T, et al. Erythrocyte 2,3-diphosphoglycerate in liver diseases. *Am J Gastroenterol.* 1987;**82**(12):1283-6. [PubMed: [2825516](#)].
13. Radak Z, Acs Z, Bori Z, Taylor AW, Yang H. The effects of high-altitude exposure on reactive oxygen and nitrogen species. *Sys Biol Free Radicals Antioxid.* 2014:407-16. doi: [10.1007/978-3-642-30018-9_28](#).