

STUDY OF THORACIC COMPLICATIONS IN PATIENTS WITH LIVER CIRRHOSIS

By

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ABSTRACT

Background: Liver cirrhosis and its complications are a leading cause of death among adults. The diseased liver leads to many deleterious effects on multiple organ systems, including the pulmonary system.

Objective: To determine the types and frequency of pulmonary complications in patients with liver cirrhosis and to assess the relation between the incidence of pulmonary complications and severity of liver cirrhosis according to Child-Pugh Score.

Patients and Methods: This was a prospective cohort study that conducted on 100 cirrhotic patients. The study was carried in the period from January 2018 till February 2019, Patients included in this study were classified according to their Pugh score into class A with 71 patients, class B with 15 patients and class C with 14 patients. This study was conducted in Dekernes general hospital and Dekernes chest hospital/ Dakahlia Governorate.

Results: 58% of the included patients were females and 42% of them were males. Their ages ranged from 38 to 77 years with a mean age of 56.24 ± 9.39 years. The main findings of this study were that 65% of the liver cirrhosis patients had associated co-morbidities. Pulmonary complications in these patients were presented as cough, dyspnea, fever and dyspnea with wheezes. Hospitalization was needed in 12% of them for management of pneumonia, bronchitis, bronchial asthma and pleural effusion. 100% of the patients were HCV positive and by the end of the study 100% of the patients survived. When patients were classified based on Pugh score, those groups showed statistically significant differences as regards associated co-morbidities, incidence of jaundice at presentation, degree of ascites, results of investigations as well as incidence of different types of pulmonary complications.

Conclusion: Liver cirrhosis was associated with unique pulmonary complications, which differ in incidence with progression of the disease.

Keywords: Liver cirrhosis, Complications, Pulmonary, Pugh classification.

INTRODUCTION

Cirrhosis is a complication of many liver diseases characterized by abnormal structure and function of the liver. The diseases that lead to cirrhosis do so because they injure and kill liver cells,

after which the inflammation and repair that is associated with the dying liver cells causes, scar tissue to form. The liver cells that do not die multiply in an attempt to replace the cells that have died. This results in clusters of newly-formed liver cells (regenerative nodules) within the

scar tissue (*Montano-Loza, 2013*). There are many causes of cirrhosis including chemicals (such as alcohol, fat, and certain medications), viruses (Chronic infection with hepatitis B virus, hepatitis C virus), toxic metals (such as iron and copper that accumulate in the liver as a result of genetic diseases), and autoimmune liver disease in which the body's immune system attacks the liver (*Aliannejad and Ghanei, 2011*).

The liver plays a key role in homeostasis. A diseased liver leads to deleterious effects on multiple organs, including the lungs. Pulmonary complications may occur as a result of hepatic disease from any cause and embrace a wide and heterogeneous spectrum of conditions involving diverse pathogenetic mechanisms (*Machicao et al., 2014*). There are many studies include the frequency of pulmonary complications in patients with liver cirrhosis as pleural effusion, interstitial lung disease, pneumonia, lung abscess, obesity hypoventilation syndrome, chronic obstructive pulmonary diseases, bronchiectasis, pulmonary embolism, pyopneumothorax, asthma and pulmonary TB (*Banerjee, 2017*).

The present work was to determine the types and frequency of pulmonary complications in patients with liver cirrhosis and to assess the relation between the incidence of pulmonary complication and severity of liver cirrhosis according to Child-Pugh Score.

PATIENTS AND METHODS

This study was a prospective cohort study that was conducted in Dekernes general hospital and Dekernes chest

hospital/ Dakahlia Governorate on liver cirrhotic patients who arrived to the outpatient clinics at the study hospitals with pulmonary complications as Pleural effusion, interstitial lung disease, pneumonia, lung abscess, obesity hypoventilation syndrome, chronic obstructive pulmonary disease, bronchiectasis, pulmonary embolism, pyopneumothorax, asthma, pulmonary TB from January 2019 to the end of December 2019. This study included 100 liver cirrhotic patients with pulmonary complications who were classified according to their Pugh score into: Class A (71 patients), class B (15 patients) and class C (14 patients).

Liver cirrhotic patients with pulmonary complications, but pregnant or lactating women, patients who were non-resident in the region due to difficulties in follow up, handicapped patients, patients with hepato-cellular carcinoma, patients with any type of malignancy and patients who were unable to perform the required tests were excluded from the study.

All patients included in this study were subjected to:

Full history taking, detailed clinical examination, routine laboratory investigations: (including CBC, liver functions, bilirubin, albumin, PT, INR), plain chest X-Ray as a part of regular follow-up, electrocardiography and liver ultrasound.

Study protocol received approval from Institutional Review Board (IRB) – Al-Azhar Faculty of Medicine, administrative approval and official permissions were obtained from the managers of the study hospitals and informed consent were

obtained from patients included in the study.

Statistical Analysis:

The collected data was revised, coded, processed and analyzed using SPSS program (Statistical Package for the Social Sciences) for windows version 20 (SPSS Inc., Chicago, IL, USA). The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data. The appropriate tests of significance

were conducted. Chi-square test was used in the comparison between the groups with qualitative data and Fisher exact test was used instead of the Chi-square test when the expected count in any cell found less than 5. One Way ANOVA was used in the comparison between the groups with quantitative data. Followed by post-hot test. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

RESULTS

As regard the classification according to Pugh score, 71% of the included patients were class A, 15% of them were class B and 14% of them were class C. Furthermore, 100% of the included patients were HCV positive.

According to the gender distribution in the three classes, no statistically significant differences were found among

the three classes as regards gender distribution as showed in this study as regard the demographic data, 58% of the included patients were females and 42% of them were males. Their ages ranged from 38 to 77 years with a mean age of 56.24 ±9.39 years. 66% of the included patients were not smokers and 34% of them were smokers (**Table 1**).

Table (1): Gender distribution of patients in the three classes

Gender Class	Female (No.=58)		Male (No.=42)		P value
	Number	%	Number	%	
A	42	72.4%	29	69.0%	0.915
B	8	13.8%	7	16.7%	
C	8	13.8%	6	14.3%	

As regard the associated comorbidities, showed there were statistically significant differences existed among the three classes as regards the associated comorbidities. As regard the comorbidity, 21% of the included patients had diabetes mellitus; 14% of them had hypertension; 16% of them had hypertension and heart failure; 9% of them had diabetes mellitus

and hypertension; 4% of them had diabetes mellitus, hypertension and heart failure; 1% of them had heart failure and 35% of them did not have ant-associated co-morbidities. Gender differences did not result in statistically significant differences in the associated co-morbidity (**Table 2**).

Table (2): Associated co-morbidity in the three classes

Classes Co-morbidity	A (No.=71)		B (No.=15)		C (No.=14)		P value
	No.	%	No.	%	No.	%	
D.M	19	26.8%	0	0.0%	2	14.3%	<0.001
HTN	10	14.1%	3	20.0%	1	7.1%	
HTN/HF	10	14.1%	0	0.0%	6	42.9%	
D.M/HTN	0	0.0%	7	46.7%	2	14.3%	
D.M/HTN/HF	2	2.8%	0	0.0%	2	14.3%	
HF	1	1.4%	0	0.0%	0	0.0%	
No	29	40.8%	5	33.3%	1	7.1%	

Regarding the symptoms at presentation in the three classes, no statistically significant differences was found among the three classes as regards symptoms at presentation including

abdominal pain, loss of appetite, fatigue or itching. However, a highly statistically significant difference was found among the three groups as regards presence of jaundice at presentation (**Table 3**).

Table (3): Symptoms at presentation in the three classes

Classes Symptoms	Class A (No.=71)		Class B (No.=15)		Class C (No.=14)		P value
	No.	%	No.	%	No.	%	
Abdominal pain	18	25.4%	2	13.3%	1	7.1%	0.227
Loss of appetite	25	35.2%	3	20.0%	3	21.4%	0.361
Fatigue	13	18.3%	5	33.3%	2	14.3%	0.353
Itching	15	21.1%	1	6.7%	4	28.6%	0.306
Jaundice	0	0.0%	4	26.7%	4	28.6%	0.001

No statistically significant differences were found among patients in the three classes as regards presenting symptoms of pulmonary complications. Pulmonary complications in the included patients

were 45% of patients had cough, 29% of them had dyspnea, 14% of them had fever and 12% of them had dyspnea and wheezes as a presentation of pulmonary complications (**Table 4**).

Table (4): Presentation of pulmonary complications in the three classes

Classes Presentation of pulmonary	Class A (No.=71)		Class B (No.=15)		Class C (No.=14)		P value
	No.	%	No.	%	No.	%	
Cough	15	35.7%	18	85.7%	12	36.4%	0.057
Dyspnea	5	28.6%	11	92.9%	13	48.5%	
Fever	5	11.9%	6	21.4%	3	9.0%	
Dyspnea/wheezes	10	23.8%	0	14.2%	2	6.1%	

None of the patients in the three classes had encephalopathy and that a very highly

statistically significant difference existed among the three classes as regards the

degree of ascites as 100% of class A patients and 73.3% of class B patients had no ascites whereas 50% of class c patients had moderate ascites (Table 5).

Table (5): Examination findings in the three classes

Findings \ Classes		Class A (No.=71)		Class B (No.=15)		Class C (No.=14)		P value
		No.	%	No.	%	No.	%	
Encephalopathy	NO	71	100.0%	15	100.0%	14	100.0%	NA
	Mild	0	0.0%	4	26.7%	5	35.7%	
Ascites	Moderate	0	0.0%	0	0.0%	7	50.0%	<0.001
	NO	71	100.0%	11	73.3%	2	14.3%	

Regarding the results in the three classes, there were statistically significant differences among the three classes as regards results of investigations. Class C patients had the highest levels of mean serum bilirubin, mean INR and mean PUGH score whereas class A patients had the highest mean albumin level. According to the laboratory investigations, the serum bilirubin in the included patients ranged from 1 to 4 mg/dL with a mean of 1.61 ± 0.95 mg/dL, their albumin level ranged from 2 to 4 g/dL with a mean of 3.57 ± 0.69 g/dL,

their INR ranged from 0 to 3 with a mean of 1.48 ± 0.58 and their Pugh score ranged from 5 to 12 with a mean of 6.62 ± 1.99 . None of the included patients had encephalopathy, 84% of them did not have ascites, 9% of them had mild ascites and 7% of them had moderate ascites. Hospitalization was needed in 12% of the included patients whose hospitalization days had a median of 7 days with an IQR of 6 to 7 days. By the end of the study, 100% of the patients had survived (Table 6).

Table (6): Results of investigations in the three classes

Investigations \ Classes	Class A (No.=71)	Class B (No.=15)	Class C (No.=14)	P value
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
S. Bilirubin (mg/dL)	1.19 ± 0.49	2.00 ± 0.85	3.29 ± 0.73	<0.001
Albumin (g/dL)	3.86 ± 0.39	3.27 ± 0.70	2.43 ± 0.51	<0.001
INR	1.25 ± 0.50	1.93 ± 0.26	2.14 ± 0.36	<0.001
PUGH Score	5.52 ± 0.50	7.87 ± 0.64	10.86 ± 0.86	<0.001

No statistically significant differences among patients in the three classes as regards the need for hospitalization (Table 7).

Table (7): Hospitalization in the three classes

Classes Need for hospitalization	Class A (No.=71)		Class B (No.=15)		Class C (No.=14)		P value
	No.	%	No.	%	No.	%	
No	66	93.0%	11	73.3%	11	78.6%	0.053
Yes	5	7.0%	4	26.7%	3	21.4%	

According to the pulmonary complications in the three classes, there was a highly statistically significant difference among patients in the three classes as regards the incidence of

pulmonary complications as the highest percentage of patients with no complications was in class A followed by class B (Table 8).

Table (8): Pulmonary complications in the three classes

Classes Pulmonary Complications	Class A (No.71)		Class B (No.15)		Class C (No.14)		Total		P value
	No.	%	No.	%	No.	%	No	%	
Bronchial Asthma	3	4.2%	4	26.7%	4	28.6%	11	11.5%	0.001
Bronchitis	3	4.2%	0	0.0%	4	28.6%	7	3.1%	
Lung abscess	0	0.0%	0	0.0%	1	7.1%	1	1.0%	
Pneumonia	6	8.5%	5	33.3%	2	14.3%	13	13.5%	
RT. Pleural Effusion	4	5.6%	5	33.3%	7	50%	16	16.7%	
No Complications	51	77.8%	1	6.7%	0	0.0%	52	54.2%	

DISCUSSION

The present study revealed that 58% of the included patients were females and 42% of them were males and that their ages ranged from 38 to 77 years with a mean age of 56.24 ± 9.39 years. These findings were more or less comparable to those published by *Sajja et al. (2014)* who found that ages of patients ranged from 19 to 94 with a mean of 51.5 ± 10.7 years and this difference in age range and mean might be explained by the larger sample size in their study. For the influence of gender on the epidemiology of liver cirrhosis, findings of the present study came in line with what was published by *Guy and Peters (2013)* as they mentioned

that women more commonly present with acute liver failure, autoimmune hepatitis, benign liver lesions, primary biliary cirrhosis, and toxin-mediated hepatotoxicity and they attributed this gender difference to various potential mechanisms which include the effect of sex hormones on oxidative and metabolic pathways, differential gene transcription in response to injury in women compared with men and sex differences in immune regulation. However, a different result with male preponderance was reported by *Sagnelli et al. (2017)* who performed their study patients with chronic liver and found that the male to female ratio was 1.4 this difference might be explained by

the different ethnicity with different proportion of alcohol-related aetiology which is commonly higher among males.

The present study revealed that 66% of the included patients were not smokers and 34% of them were smokers and smoking can increase the risk of liver cirrhosis. Moreover, smoking promotes the production of cytokines that cause even more inflammation and damage to liver cells (*Gardner, 2017*).

Dam et al. (2013) found that cases of alcoholic liver cirrhosis and cases of liver cirrhosis occurred during follow-up and calculated the hazard ratio for men smoking >10 g of tobacco per day compared with never-smokers to be 3. They concluded that smoking was associated with an increased risk of liver cirrhosis independent of alcohol intake.

The present study revealed that in patients with cirrhosis, diabetes can be either a classical type 2 diabetes mellitus or the so-called hepatogenous diabetes which is a consequence of liver insufficiency and portal hypertension (*Elkrief et al., 2016*). So, the prevalence of diabetes mellitus in cirrhotic patients is much higher than that in the general population (*Kumar et al., 2018*). A higher percentage of diabetes in cirrhotic patients was reported by *Lunati et al. (2013)* as 41.7% of the patients were diabetic and this difference might be explained by the different ethnicity. Meanwhile, a nearly similar percentage of cirrhosis patients with diabetes mellitus were reported in the study published by *Grancini et al. (2015)* who performed their study on cirrhotic patients and found that 27.4% of patients had diabetes mellitus based upon their fasting blood glucose and HbA1C results,

but when oral glucose tolerance test was performed. This percentage became 47.2% of the patients.

As regards the presentation of pulmonary complications in the studied patients, the present study revealed that 45% of the patients had cough, 29% of them had dyspnea, 14% of them had fever and 12% of them had dyspnea and wheezes. These findings come in line with what was mentioned by *Kwo (2012)* that dyspnea is a frequent complaint in cirrhotic patients.

On examination, none of the included patients had encephalopathy, 84% of them did not have ascites, 9% of them had mild ascites and 7% of them had moderate ascites. The present study revealed that by the end of the study, 100% of the patients had survived.

The high incidence of pneumonia in cirrhotic patients comes in line with what was reported by *Jalan et al. (2014)* that pneumonia is a common infectious disease in cirrhotic patients and was reported as the third common infection complication in cirrhosis. This can be explained by the profound immunodeficiency and systematic inflammation in cirrhotic patients which make them more liable to get infected (*Albillos et al., 2014*). Other factors leading to the increased risk for infections in these patients include: the alterations in the gut microbiome, the small intestinal bacterial overgrowth, the increased bacterial translocation and the increased rate of resistant organism colonization (*Qin et al., 2014* and *Nadim et al., 2016*).

As regards the incidence of pleural effusion, the finding in this study comes in line with what was published by *Cardenas*

et al. (2018) as they mentioned that hepatic hydrothorax occurs in approximately 5 to 10 percent of patients with cirrhosis. However, a higher incidence of pleural effusion was reported by *Badillo and Rockey (2014)* who performed their retrospective study on hospitalized cirrhotic patients and found that pleural effusion was diagnosed in 16% of patients and was most often right-sided (73%).

In order to achieve the study objectives, patients included in the present study were classified based upon their Child-Pugh score and it was found that 100% of the included patients were HCV positive and this finding comes in line with what was mentioned by *Lee et al. (2012)* that chronic infection with the hepatitis C virus is one of the most common causes of liver cirrhosis and its sequelae as well as what was mentioned by *Pradat et al. (2018)* that chronic HCV infection can promote liver damage, cirrhosis and hepatocellular carcinoma in affected individuals.

The present study revealed no statistically significant differences found among the three classes as regards gender distribution. This balance in the baseline characteristics provides the basis for comparison between the study groups as it helps to minimize bias (*Sedgwick, 2014*). The present study revealed statistically significant differences existed among the three classes as regards the associated comorbidities.

As regards symptoms at presentation, the present study revealed no statistically significant differences among the three classes as regards symptoms at presentation including abdominal pain,

loss of appetite, fatigue or itching. However, statistically significant difference was found among the three groups as regards presence of jaundice at presentation. The increasing incidence of jaundice with higher Pugh score is logic since bilirubin level is one of the measures used to determine the Pugh score (*Frothingham, 2018*). Furthermore, jaundice is an indicator of significant underlying disease (*Fargo et al., 2017*).

Meanwhile, the present study revealed that no statistically significant differences were found among patients in the three classes as regards presenting symptoms of pulmonary complications. Also none of the patients in the three classes had encephalopathy. On the other hand, a statistically significant difference was found among the three classes as regards the degree of ascites. The increasing degree of ascites with higher Pugh score is logic since the degree of ascites is one of the measures used to determine the Pugh score (*Frothingham, 2018*). Furthermore, ascites is an indicator of progression of liver cirrhosis (*Mortimore, 2018*).

The present study revealed statistically significant differences among the three classes as regards results of investigations. Patients had the highest levels of mean serum bilirubin, mean INR and mean PUGH score whereas class A patients had the highest mean albumin level which are logic since serum bilirubin level and INR are among the measures used to determine the Pugh score (*Frothingham, 2018*).

The present study revealed statistically significant difference existed among patients in the three classes as regards the incidence of pulmonary complications. Pulmonary abnormalities and symptoms

are common in patients with chronic liver disease (Goldberg and Fallon, 2015). Possible causes included intrinsic cardiopulmonary disorders not specifically related to liver disease as well as unique problems associated with the presence of liver disease and/or portal hypertension (Galal et al., 2017). The finding related to worsening of the condition with progression of the liver disease comes in line with that reported by Helmy and Awadallah (2014) who found that the presence of hypoxemia was higher in patients with advanced liver disease and the severity of hypoxemia was positively correlated with the severity of liver disease assessed by the Child Pugh score.

Study limitations: The relatively small sample size did not provide much statistical power for the results and our study excluded number of cirrhosis patients who did not meet the criteria that may result in statistic bias and inexact conclusion as some of these factors might affect the outcome.

CONCLUSION

Liver cirrhosis was associated with unique pulmonary complications, which differed in incidence with progression of the disease.

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دراسة المضاعفات الصدرية في المرضى الذين يعانون من تليف الكبد

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خلفية البحث: تليف الكبد ومضاعفاته هي السبب الرئيسي للوفاة بين البالغين. يلعب الكبد دوراً مركزياً في الصحة وداء الدم وبالتالي فإن الكبد المريض يؤدي إلى العديد من التأثيرات الضارة على أنظمة الأعضاء المتعددة، بما في ذلك الجهاز الرئوي.

الهدف من البحث: تحديد أنواع وتواتر المضاعفات الرئوية في المرضى الذين يعانون من تليف الكبد وتقييم العلاقة بين حدوث المضاعفات الرئوية وشدة تليف الكبد.

المرضى وطرق البحث: هذه الدراسة أجريت على 100 من المرضى المشمولين في هذه الدراسة. وقد تمت الدراسة في الفترة ما بين يناير 2018 وحتى فبراير 2019 وتم تقسيم الحالات طبقاً لمقياس تشايلد بو لثلاث مجموعات (ايه) 71 مريض والمجموعة (بي) 15 مريض والمجموعة (سي) 14 مريض وقد تمت في مستشفى دكرنس العام ومستشفى صدر دكرنس/ محافظة الدقهلية.

نتائج البحث: 58% من المرضى المشمولين كانوا من الإناث و42% منهم ذكور. وتراوحت أعمارهم بين 38 و77 سنة مع متوسط عمر 56.24 ± 9.39 سنة. وكانت النتائج الرئيسية لهذه الدراسة أن 65% من مرضى تليف الكبد قد ارتبطوا بالمرضاة المشتركة. وقدمت مضاعفات رئوية في هؤلاء المرضى والسعال، ضيق التنفس، حمى وضيق التنفس

مع الصفير; وكان هناك حاجة إلى الاستشفاء في 12% منهم لإدارة
الالتهاب الرئوي والتهاب الشعب الهوائية والربو القصبي والانصباب
الجنبى; 100% من المرضى كانوا إيجابيين بفيروس التهاب الكبد C
وبحلول نهاية الدراسة نجا 100% من المرضى. عندما تم تصنيف
المرضى على أساس درجة بوغ، وأظهرت هذه المجموعات اختلافات
ذات دلالة إحصائية فيما يتعلق بالمرضاة المشتركة المرتبطة بها،
ووقوع اليرقان عند العرض، ودرجة الاستسقاء، ونتائج التحقيقات،
فضلا عن حدوث أنواع مختلفه من المضاعفات الرئوية.

الإستنتاج: يرتبط تليف الكبد بمضاعفات رئوية فريدة من نوعها، والتي
تختلف في الإصابة مع تطور المرض.