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Original Article

Assessment of pulmonary functions with spirometry method in hepatic impairment patients

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Abstract

Aim: In this study, it has been aimed to investigate whether there is a relationship between pulmonary functions measured by spirometry and hepatic impairment tables. This may contribute to a better understanding of the mechanisms of liver pathophysiology which hasn't been fully understood.

Materials and Methods: This study is a randomized controlled prospective trial. 39-63 years of age, 19 male and 9 female, a total of 28 patients diagnosed with liver failure, with 15 male and 17 female, a total of 32 healthy volunteers with similar social characteristics were studied. All of the participants' pulmonary parameters (FEV1, FVC, FEV1/FVC, PEF, FEF25-75%, FEF25%, FEF50%, FEF75%, PIF, VC, MVV) were performed by pulmonary function tests (PFT). Groups' data have been analyzed statistically. The significance level was considered as $p<0.05$.

Results: In hepatic impairment patients, there was no significant difference in terms of the expected percentage values of PFT parameters that indicate obstruction. Weak restriction in 8 cases, moderate restriction in 9 cases and severe restriction in 4 cases were diagnosed. PFT parameters of patients with mid-level and refractory ascites were found to be significantly lower compared with those without ascites (FEV1: $p=0.009$; FVC: $p=0.010$; VC: $p=0.008$). There was no remarkable correlation between AST, ALT, ALP, GGT levels and PFT parameters of patients as with ascites status.

Conclusion: Ascites that can frequently coexist with chronic liver disease cases, may cause restrictive type pulmonary dysfunctions in PFT by creating mechanical pressure. But also, there is no correlation between the ascites status or PFT diagnoses and liver function tests.

Keywords: Ascites; hepatic impairment; pulmonary function tests; spirometry

INTRODUCTION

Acute and chronic liver diseases are leading causes of morbidity and mortality worldwide, accounting for about 1-2 million deaths annually (1). Although it has high morbidity and mortality, its overall survival has improved through advancements in intensive care management and emergency liver transplantation (2-4). A high index of suspicion, early referral to a specialist liver transplantation center and adequate supportive management remain the cornerstone for the management of liver failure. Future better understanding and knowledge of the pathophysiology of liver injury and management of multi-organ failure will help to improve outcomes. Management of liver failure consists of supportive care, prevention and management of complications, determination of specific treatment and prognosis when the exact etiology is known, and the need for liver support, including possible liver transplantation (5).

Metastatic carcinoma, severe infection, active alcoholism, drug addiction, and concomitant medical problems are absolute or relative contraindications for liver transplantation. In addition, transplantation is not possible in case of severe restriction and obstruction of the respiratory tract. In this case, respiratory

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support treatments are at the forefront. For example, hyperventilation protocol (PCO2: 25-30 mmHg) should be applied to reduce intracranial pressure in patients requiring mechanical ventilatory therapy (1, 6). Pulmonary complications, especially in chronic liver disease, can be seen (7). The main purpose of the treatment of chronic liver disease is; to reduce the pathologies and severe complications that the disease causes, and to improve the life span and quality of life of the patient (8, 9).

While chronic liver diseases cause clinical cases such as cirrhosis, portal hypertension and ascites; may also lead to side effects related to lung (10). In this context, ascites, which restricts pulmonary functions by creating mechanical compression on the diaphragm, is a matter that requires attention.

Pulmonary function tests (PFT) are important in the evaluation of people with complaints about the respiratory system. They are used to detect the presence of the disease, to determine its severity and to monitor the treatment response. (11). In this study, it was aimed to investigate whether there is a relationship between pulmonary functions measured by spirometry and hepatic impairment tables caused by different factors. This may contribute to a better understanding of the mechanisms of hepatopulmonary pathophysiology not fully understood.

MATERIALS and METHODS

The research was carried out between December 2015 and May 2016 in Departments of Physiology and Chest Diseases. The sample group of the study was identified as a total of 60 persons with similar social characteristics consisting of 28 (19 male and 9 female, 39-63 years of age) patients who were diagnosed with liver failure among the Gastroenterology policlinic patients and 32 (15 male and 17 female, 34-65 years of age) healthy volunteers were selected randomly. This research is a prospective, randomized and controlled study.

Respiratory parameters of all of the participants [volume of forced expiration in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC, peak expiratory flow (PEF), forced expiratory flow during 25-75% of expiration (FEF25-75%), forced expiratory flow during 25% of expiration (FEF25%), forced expiratory flow during 50% of expiration (FEF50%), forced expiratory flow during 75% of expiration (FEF75%), forced inspiratory flow (PIF), vital capacity (VC) and maximal voluntary ventilation (MVV)] were performed in Spirometry unit. PFT were performed with a portable spirometer (Spirolab, SDI Diagnostics, USA) taking into account the American Thoracic Society/ European Respiratory Society (ATS/ERS) acceptability criteria (12). Expected percentage values were taken into consideration for all PFT parameters. Between 80% and 120% was accepted as the normal value range. Patient surveys and laboratory results were obtained by providing access to patient files. None of the participants in the study had a disease diagnosis and alcohol/drug addiction that could affect their respiratory functions.

Participants were sampled taking into consideration the inclusion and exclusion criteria. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Bursa Uludag University, Faculty of Medicine, Ethics Board (2015-22/11 on December 22, 2015), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

SPSS 20.0 program (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Compliance of data with the normal distribution was determined by Shapiro Wilk test. Results were given as 'Mean±Standard Deviation' for parametric data. The differences between the averages were estimated by T-test. Mann-Whitney U and Kruskal-Wallis tests were used and results were given as 'Median (Minimum-Maximum)', for nonparametric data. Relations between values were estimated by Tukey test. The significance level was considered as $p<0.05$.

RESULTS

The etiological distribution of patients identified through patient files is shown in Table 1. All patients were divided into four groups according to their etiological distribution. The groups were compared according to the expected percentage values of PFT parameters. There was no statistically significant difference between groups in terms of FEV1 (p=0.801), FVC (p=0.785), FEV1/FVC (p=0.526), PEF (p=0.958), FEF25-75% (p=0.977), FEF25% (p=0.944), FEF50% (p=0.621), FEF75% (p=0.845), PIF (p=0.830), VC (p=0.975) and MVV (p=0.892) parameters.

Table 1. Etiological factors of patients

Diagnosis	n (%)
Hepatitis B	10 (35.7%)
Hepatitis C	4 (14.3%)
Hepatocellular carcinoma (HCC)	6 (21.4%)
Alcohol	4 (14.3%)
Autoimmune hepatitis	1 (3.6%)
Cryptogenic	1 (3.6%)
Other	2 (7.1%)
Total	28 (100.0%)

n: Number of patients

A comparison of the expected percentage values obtained from PFT of the groups, were formed according to the etiologic distribution, is shown in Table 2.

Patients with ascites, patients with no ascites and all patients were compared according to laboratory values of liver enzymes. There was no statistically significant difference between the groups in terms of aspartate aminotransferase (AST) (p=0.945), alanine aminotransferase (ALT) (p=1.000), alkaline phosphatase (ALP) (p=0.100) and gamma glutamyl transpeptidase (GGT) (p=0.507) enzymes.

Table 2. Comparison of PFT expected percentage values according to the etiologic distribution of patients

PFT parameter	Viral hepatitis (n=14)	HCC (n=6)	Alcohol (n=4)	Other* (n=4)	p
FEV_1	75 (46-96)	79.50 (64-102)	79.50 (60-104)	78 (48-95)	0.801
FVC	72 (37-86)	76.50 (57-94)	72 (56-88)	72.50 (43-85)	0.785
FEV_1/FVC	113.50 (88-129)	108 (101-115)	114.50 (107-122)	119 (102-121)	0.526
PEF	49 (27-100)	60.50 (34-82)	59 (45-77)	56.50 (18-114)	0.958
$FEF_{25-75\%}$	66 (55-134)	63.50 (60-105)	74.50 (58-138)	78 (37-126)	0.977
$FEF_{25\%}$	52 (16-111)	51.50 (37-92)	56.50 (50-80)	61.50 (19-126)	0.944
$FEF_{50\%}$	55.50 (43-125)	48.50 (45-94)	65 (50-122)	68 (34-110)	0.621
$FEF_{75\%}$	87.50 (49-136)	74 (57-96)	89.50 (54-182)	95 (47-104)	0.845
PIF	33 (20-74)	46 (28-59)	36.50 (20-82)	45.50 (21-76)	0.830
VC	76 (46-99)	74.50 (54-90)	76 (63-96)	75 (43-90)	0.975
MVV	47.50 (30-82)	51.50 (44-73)	47.50 (41-69)	60 (34-84)	0.892

HCC: Hepatocellular carcinoma
*: Autoimmune hepatitis, non-cirrhotic portal hypertension, non-alcoholic steatohepatitis, cryptogenic

A comparison of patients with ascites, patients with no ascites and all patients according to AST, ALT, ALP and GGT values is shown in Table 3.

The patients were divided into four groups as normal, weak restrictive, moderate restrictive and severe restrictive pulmonary dysfunction according to PFT diagnoses, and compared according to laboratory values of liver enzymes. There was no statistically significant difference between the groups in terms of AST (p=0.880), ALT (p=0.981) and GGT (p=0.370) enzymes. However, there was a statistically significant difference between the groups according to ALP values (p=0.039). ALP values of patients with weak restrictive respiratory dysfunction were distinctly lower than those with severe restrictive respiratory dysfunction (p=0.066).

A comparison of AST, ALT, ALP and GGT values of patients with no restriction (normal), weak restriction, moderate restriction and severe restriction according to PFT diagnoses is shown in Table 4.

FEV1 (p<0.001), FVC (p<0.001) and MVV (p<0.001) were determined to be statistically significantly lower in the patient group compared to the control group. There was no significant difference between the groups in terms of FEV1/FVC (p=0.943) (Table 5). However, all of the expected percentage values of PFT had non-normal distribution were statistically significantly lower in the patient group compared to the control group (Table 6).

The patients were divided into two groups according to gender and compared in terms of PFT parameters. The expected percentage values of all PFT parameters except MVV in female and male patients were similar. A statistically significant difference was found only in terms of MVV values between the patient groups formed by gender (p=0.007), (Table 7).

Table 3. Comparison of liver enzyme values of patients with ascites, patients with no ascites, and all patients

Laboratory value (normal values)	With ascites (n=16)	With no ascites (n=12)	All patients (n=28)	p
AST (11-25 U/L)	45.50 (20-110)	48 (16-198)	46 (16-198)	0.945
ALT (7-28 U/L)	27.50 (14-79)	31 (6-139)	28 (6-139)	1.000
ALP (40-150 U/L)	157.50 (67-224)	99.50 (42-215)	108.50 (42-224)	0.100
GGT (9-36 U/L)	74 (13-104)	50 (8-129)	63 (8-129)	0.507

AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma glutamyl transpeptidase

Table 4. Comparison of liver enzyme values of patients according to PFT diagnoses

Laboratory value (normal values)	Normal (n=7)	Weak restriction (n=8)	Moderate restriction (n=9)	Severe restriction (n=4)	p
AST (11-25 U/L)	45 (24-120)	46 (21-198)	51 (25-110)	61 (16-107)	0.880
ALT (7-28 U/L)	28 (21-92)	30.50 (6-139)	27 (8-76)	46 (12-79)	0.981
ALP (40-150 U/L)	125 (96-166)	73.50 (42-155)	110 (83-221)	217.50 (67-224)	0.039*
GGT (9-36 U/L)	71 (13-129)	63.50 (13-97)	43 (8-103)	92.50 (43-104)	0.370

*: As a result of multiple comparison test of Tukey test, the most significant difference for ALP values was found between the weak restriction group and the severe restriction group. (p=0.066)

Table 5. Comparison of parametric PFT expected percentage values of control and patient groups

PFT parameter	Control group (n=32)	Patient group (n=28)	p
FEV_1 ± SD	103.62 ± 14.83	75.53 ± 17.37	0.000*
FVC ± SD	96.65 ± 13.56	71.07 ± 16.31	0.000*
FEV_1/FVC ± SD	111.75 ± 4.39	111.89 ± 10.22	0.943
MVV ± SD	76.53 ± 14.68	54.07 ± 15.12	0.000*

SD: Standard Deviation
*: As a result of T-test, a significant difference was found between the control group and the patient group [FEV_1 (p<0.001), FVC (p<0.001) and MVV (p<0.001)].

Table 6. Comparison of nonparametric PFT expected percentage values of control and patient groups

PFT parameter	Control group (n=32)	Patient group (n=28)	p
PEF	89 (67-129)	49.50 (18-114)	0.000*
$FEF_{25-75\%}$	103.50 (75-156)	65 (37-138)	0.000*
$FEF_{25\%}$	94 (73-140)	52 (16-126)	0.000*
$FEF_{50\%}$	95.50 (70-137)	52.50 (34-125)	0.000*
$FEF_{75\%}$	102 (68-195)	87.50 (47-182)	0.000*
PIF	57 (32-103)	35 (20-82)	0.006*
VC	92 (52-120)	75 (43-99)	0.000*

*: As a result of Mann-Whitney U test, a significant difference was found between the control group and the patient group [PEF (p<0.001), FEF25-75% (p<0.001), FEF25% (p<0.001), FEF50% (p<0.001), FEF75% (p<0.001), PIF (p=0.006; p<0.05) and VC (p<0.001)].

Table 7. Comparison of PFT expected percentage values of female and male patient groups

PFT parameter	Female patients (n=9)	Male patients (n=19)	p
FEV1	69 (48-95)	76 (46-104)	0.362
FVC	67 (40-86)	78 (37-94)	0.445
FEV1/FVC	113 (99-127)	113 (88-129)	0.787
PEF	48 (39-68)	69 (18-114)	0.431
$FEF_{25-75\%}$	67 (50-106)	63 (37-138)	0.825
$FEF_{25\%}$	51 (44-73)	53 (16-126)	0.640
$FEF_{50\%}$	52 (43-93)	53 (34-125)	0.491
$FEF_{75\%}$	88 (47-104)	79 (54-182)	0.446
PIF	31 (27-61)	40 (20-82)	0.730
VC	72 (48-90)	80 (43-99)	0.313
MVV	44 (34-61)	59 (30-84)	0.007*

*: As a result of Mann-Whitney U test, a significant difference was found between the control group and the patient group [PEF (p<0.001), FEF25-75% (p<0.001), FEF25% (p<0.001), FEF50% (p<0.001), FEF75% (p<0.001), PIF (p=0.006; p<0.05) and VC (p<0.001)].

The expected percentage values of PFT parameters of patients with no ascites, with moderate ascites, and with refractory ascites were compared. A significant difference was not found in terms of FEV1/FVC (p=0.315), PEF (p=0.184), FEF25-75% (p=0.246), FEF25% (p=0.145), FEF50% (p=0.630), FEF75% (p=0.758) and PIF (p=0.124) parameters between the groups, whereas FEV1 (p=0.009), FVC (p=0.010), VC (p=0.008) and MVV (p=0.015) values were significantly different. However, when cross-tables by pairwise comparisons were examined between the groups according to PFT parameters determined to be statistically significant, a significant difference was found between patients with no ascites and patients with refractory ascites in terms of FEV1 (p=0.007), FVC (p=0.009), VC (p=0.006) and MVV (p=0.017) values.

A comparison of the expected percentage values obtained from PFT of the groups, were formed according to the presence and level of ascites, is shown in Table 8.

Table 8. Comparison of PFT expected percentage values of patients according to their ascites status

PFT parameter	No ascites (n=12)	Moderate (n=8)	Refractory (n=8)	p
FEV_1	87.50 (48-104)	75 (61-98)	61.50 (46-76)	0.009*
FVC	82 (43-94)	81 (57-86)	61.50 (37-68)	0.010*
FEV_1/FVC	112 (102-123)	110 (88-120)	116 (99-129)	0.315
PEF	71.50 (18-100)	45.50 (33-114)	47 (27-63)	0.184
$FEF_{25-75\%}$	74.50 (37-138)	60.50 (59-126)	62.50 (55-86)	0.246
$FEF_{25\%}$	72 (19-111)	47.50 (37-126)	50.50 (16-70)	0.145
$FEF_{50\%}$	68 (34-125)	51 (45-110)	55.50 (43-78)	0.630
$FEF_{75\%}$	91.50 (47-182)	74.50 (55-124)	87.50 (49-132)	0.758
PIF	53.50 (21-82)	33.50 (25-76)	31 (20-48)	0.124
VC	83 (43-99)	77 (54-96)	68 (46-74)	0.008*
MVV	59.50 (34-82)	54 (43-84)	39 (30-67)	0.015*

*: As a result of multiple comparison test of Tukey test, a significant difference was found between the patient group with no ascites and the patient group with ascites at refractory level [FEV1 (p=0.007; p<0.05), FVC (p=0.009; p<0.05), VC (p=0.006; p<0.05) and MVV (p=0.017; p<0.05)].

DISCUSSION

The connections of the lungs with the liver are heterogeneous and complex, with several unknowns from a mechanistic viewpoint. The evidence of gastrointestinal and liver multimorbidities that can coexist in patients with chronic respiratory diseases, in particular chronic airway diseases, is relatively limited and remains insufficiently investigated (13).

In 1884, Flückiger first described the clinical relationship of lung-liver disease in a patient with cyanosis, clubbing and cirrhosis. In 1935, Snell demonstrated the clinical association between hepatic disease and hemoglobin desaturation in three cases. In 1956, Rydell and Hoffbauer first presented intrapulmonary arteriovenous anastomoses in a 17-year-old juvenile cirrhosis patient (14-16). In 1977, Kennedy and Knudson put forward the term 'hepatopulmonary syndrome' in a patient with alcoholic cirrhosis, severe hypoxemia and exercise dyspnea (17).

Chronic liver diseases can lead to clinical conditions such as cirrhosis, portal hypertension and ascites, as well as side effects related to the lung, hematologic and neurological system (10). Cirrhotic patients may develop conditions that can affect pulmonary volumes and gas exchange (18). Ascites develops as a complication of advanced liver disease and may cause low lung volumes. Because of the accumulation of fluid, increased intra-abdominal pressure resulted in elevation and relative fixation of the diaphragm. These abnormalities, transmitted to the chest wall, cause decreased thoracic elasticity and increased intrapleural pressure. Thus, ascites may cause restrictive and/or obstructive respiratory disorders (10).

Pulmonary function tests have made it possible to determine the functional disorders of the airways whether they are due to obstructive and/or restrictive type lung disease. As a result of spirometric measurements, obstructive type pulmonary dysfunction was not found in our cases.

Yao et al. measured respiratory functions of 21 cirrhosis cases with ascites and compared them with control group (19). In their study, it was found that VC, FEV1, MVV and TLC values of pulmonary functions in patients with cirrhosis were significantly lower than the control group. In the current study, although there was no significant difference in FEV1/FVC parameter between the patient and 'healthy control' groups (Table 5); FEV1, FVC, PEF, FEF25-75%, FEF25%, FEF50%, FEF75%, PIF, VC and MVV values were significantly lower in the patient group compared to the control group (Table 6). Pulmonary function parameters had normal values in 25.0% (n=7) of all cases. At the same time, it was found that PIF (n=27), MVV (n=26) and FEF50% (n=24) were the most frequently deteriorated pulmonary function parameters of patients respectively. Flow rates in the mid-end segments (FEF25-75% and FEF75%), are indicators of the first functional disorder of the airways and not affected by effort, were distinctly lower, especially in patients with hepatocellular carcinoma (HCC) (Table 2). In addition, FEV1/FVC values that indicate upper airway obstruction were similar in female and male hepatic insufficiency patients (Table 7). This value was found within normal limits in 78.5% (n=22) of all cases.

In order to determine whether there is any correlation between the ascites status and liver function tests, patients with ascites, patients with no ascites and all patients were compared according to their laboratory values of liver enzymes. A significant difference was not found between the groups (Table 3).

Jameel et al. reported that most patients with advanced liver disease had one or more types of abnormality in

lung function, and the most commonly affected test of lung function was the single-breath diffusing capacity for carbon monoxide (DLCO). In their study of 116 patients with chronic liver disease, obstructive type respiratory dysfunction was noted in only 3% (20). In this study, it was determined that 28.6% (n=8) of the patients had weak restrictive respiratory dysfunction, 32.1% (n=9) had moderate restrictive respiratory dysfunction and 14.3% (n=4)) had severe restrictive respiratory dysfunction (Table 4). In order to determine whether there is any correlation between the PFT diagnoses and liver function tests, patients grouped based on PFT diagnoses were compared according to their laboratory values of liver enzymes. There was no significant difference between the groups (Table 4). Behara et al. showed that the most impaired pulmonary function parameters were FEV1, PEF and FEF, which are the indicators of airway obstruction, in patients with portal hypertension with or without chronic liver disease (21). Melot et al. found that 80% of cirrhosis patients had normal pulmonary functions in their study (22).

In this study, FEV1/FVC and VC parameters, which are the indicators of restrictive type pulmonary dysfunction, were analyzed. There was no significant difference in FEV1/FVC values between the patient and control groups. Although FEV1/FVC values were found to be high in 21.5% (n=6) of all hepatic insufficiency cases, those were within normal limits in 78.5% (n=22). VC values were found to be lower than normal values in 60.7% (n=17) of all cases. Therefore, lower values of VC and normal and/or higher values of FEV1/FVC have been evaluated as significant in terms of showing the restrictive type of pulmonary dysfunction in the current study.

Although no marked changes were observed in parameters that indicate obstruction or restriction in PFT of patients with no ascites (Table 8), restrictive type pulmonary dysfunction was found in 100% (n=8) of patients with refractory ascites and 62.5% (n=5) of patients with moderate ascites. Thus, restrictive type pulmonary disorder was detected in 81.3% (n=13) of patients with ascites. Therefore, it has been thought that this disorder may be most likely secondary to ascites. Additionally, it has been evaluated that airway restriction may be due to restraint of diaphragm functions, pleural fluid and interstitial lung pathologies.

CONCLUSION

Hepatic insufficiency patients, especially those with hepatic cirrhosis, have a high mortality risk. These patients have a critical process due to the complications of liver disease rather than the disease itself. This critical process requires a multidisciplinary monitoring and treatment. Gastroenterology, hepatology, nephrology, anesthesia, transplantation, infection and chest diseases team form this multidisciplinary approach together. In this context, one of the priorities is the protection of the airways. In accordance with this purpose, severe ascites that may accompany the clinical picture should be treated (23). In view of the foregoing, some original results that may contribute to the literature were obtained in this study.

The predominant point in determining the indications for liver transplantation is surgical risks. Another important point is the risk of recurrence of the primary cause. However, the survival of patients that underwent surgery is the most important gain despite the high surgical risks. Even though it is necessary to consider different technical difficulties in terms of surgery in hepatic impairment patients, intensive care and rehabilitation are also considerable in the postoperative period. Accordingly, it may be useful to perform the pulmonary functions of patients in both preoperative and postoperative period by spirometric method. It has been thought that these measurements may also provide a remarkable contribution to improvement of the 'Acute Physiologic Assessment and Chronic Health Evaluation' (APACHE), which is used as an important criterion that predicts life expectancy after transplantation in the intensive care (23).

Also, cost is an important factor in the delivery of effective health care services especially in the developing nations. The practice of 'routine' investigation has been questioned by several studies (24-26). Prevalence of abnormal results in routine preoperative tests is around 5-60% although it may vary with the American Society of Anesthesiologists Physical status of patients (26-31).

In conclusion, respiratory dysfunctions due to various factors may be seen especially in patients with chronic liver disease. Ascites that can frequently coexist with these cases may cause restrictive type pulmonary dysfunction by creating mechanical pressure. Respiratory risks that may be experienced both in preoperative and postoperative periods can be minimized by controlling the functional disorders to be determined by spirometric method in preoperative evaluation of patients to be treated. This may contribute to targeted early extubation with intense interest in recent times and to shortening the length of stay in the intensive care unit as well as hospital stay in the postoperative period. In addition, it has been evaluated that respiratory disorders that may develop as a complication of hepatic impairment, may be more closely related to diagnostic and treatment options if the success rate in orthotropic liver transplantation can be increased.

It is worth mentioning that because the study was prospective randomized and the prevalence rate of liver failure was relatively low, the sample size could not be as expected.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Clinical Research Ethics Committee's decision no. 2015-22/11.

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