Six-Minute Walk Test: A Useful Tool for Evaluating Functional Capacity in Chronic hepatitis C

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ABSTRACT

BACKGROUND AND AIM: Chronic liver disease leads to reduction in health-related quality of life, particularly functional capacity. The data about the use of Six Minute Walk Test (6MWT) among cirrhotic patients are limited. The current study was done to evaluate the use of 6MWT in patients with HCV related chronic liver disease for assessing the functional capacity and to determine the correlation between the 6MWD and severity of chronic liver diseases.

METHODS: This analytic cross-sectional study was carried out on 20 healthy volunteers (Group I), 40 HCV patients with early liver disease (Group II), and 40 HCV patients with liver cirrhosis (Group III). Six minute walk distance (6MWD) was calculated.

RESULTS: The mean 6MWD was significantly lower in Groups II and III (325.8 ± 56.65 meter, and 131.79 ± 43.40 meter) compared to that of Group I (359.91 ± 38.63 meter) (p < 0.01; p < 0.001). The mean 6MWD was significantly lower in Group III compared to that of Group II (p < 0.001). 6MWD was positively correlated with hemoglobin, platelets, and albumin (p < 0.01). On the other hand, 6MWD was negatively correlated with bilirubin, AST, ALP, creatinine, and INR (p < 0.05). There was a significant negative correlation between 6MWD and BMI in Groups II and III (p < 0.05). There was no significant correlation between 6MWD and Child score or MELD score in Group III (p > 0.05).

CONCLUSIONS: Six-minute walk test is a reliable indicator to measure the functional capacity for patients with HCV related chronic liver diseases.

Key words: Cirrhosis; Exercise; 6MWT; Assessment
patients can quickly walking in a flat, hard surface within 6 minute. In general 6MWT used to measure functional status, and the response to medical intervention in patients with moderate to severe lung or heart diseases. Also it used as predictor of morbidity and mortality[11]. Also, 6MWT have been used to measure FC, and the 6-minute walked distance (6MWD) correlated with exercise capacity and muscle strength as measured using cardiopulmonary exercise tests[12]. Alam et al[13] demonstrated that 6MWT was a useful tool for assessing FC in patients with CLD and was a prognostic indicator. In addition, the 6MWD correlated with all physical performance tests at 3rd, 6th, and 12th month after orthotopic liver transplantations (OLT)[14].

Data about the use of 6MWT among patients with HCV-related liver cirrhosis of different severities are limited. Therefore, this study was designed to evaluate the use of 6MWT in assessing the FC in patients with hepatitis C virus (HCV-related CLD compared to healthy controls, and to correlate between the 6MWD and demographic, clinical, and biochemical markers of CLD as well as the severity of CLD as indicated by the model for end-stage liver disease (MELD) and Child-Turcotte-Pugh (CTP) scores.

PATIENTS AND METHODS

Subjects
This prospective cross-sectional study was conducted in Tropical Medicine and Gastroenterology Department’s inpatients or the Hepatitis Viruses Outpatient Clinic in a tertiary-care Hospital over a period of one year. Participants were classified into three groups:

- **Group I**: Age- and sex-matched healthy controls ($n = 20$),
- **Group II**: Patients had chronic hepatitis C (CHC) without cirrhosis ($n = 40$), and
- **Group III**: Patients had HCV-related liver cirrhosis ($n = 40$).

The diagnosis of CHC was based on HCV antibody +ve by ELISA, HCV RNA positive by polymerase chain reaction (PCR), normal blood count, liver function, prothrombin time as well as normal abdominal ultrasound (US) examination and absence of features of portal hypertension and liver cell failure.

The diagnosis of HCV-related cirrhosis was based on presence of features of cirrhosis by abdominal US examination (course liver echogenic pattern), irregular surface ± reduced size ± attenuated hepatic veins ± enlarged caudate lobe), evidence of portal hypertension (as evidenced by presence of splenomegaly, dilated portal vein, platelets’ count <100×10^3/mm^3, and/or presence esophageal varices), ascites with or without other features of liver cell failure (Albumin level less than 3 mg/dl, INR > 1.4, and Bilirubin level more than 3 mg/dl).

Consent and approvals
This study was conducted in accordance with the regulations of Helsinki 2008 Declaration and was approved by the Faculty of Medicine Ethics and Scientific Research Committees. An Informed written consent was obtained from each participant prior to being included in the study.

Inclusion criteria
Patients with HCV Genotype-4 related chronic liver disease of any severity.

Exclusion criteria
Patients were excluded from the study if they were co-infected with either HBV or HIV, had liver disease due to other etiologies (e.g., autoimmune, biliary, steatohepatitis, alcoholic, metabolic, etc.), had hepatocellular carcinoma, have any associated cardiopulmonary or skeletal disease, or were unable to give consent.

METHODS

All participants were subjected to full medical history, clinical examination with special emphasis on age, sex, body mass index (BMI), and laboratory investigations including blood picture, liver function test, prothrombin time, and kidney function.

Liver disease severity in cirrhotic patients was assessed by the Child-Pugh grade and score[15] and the Model for End Stage Liver Disease (MELD) score[16].

Six minute walk distance (6MWD) was calculated by the distance walked in a six minute. Data which were calculated before and after the six minute walk test (6MWT) included the following: heart rate (HR), oxygen saturation, and blood pressure (systolic and diastolic blood pressure).

Percentage of change = $\frac{100 \times (\text{Value of variable after 6MWT} - \text{Value of variable before 6MWT})}{\text{Value of variable before 6MWT}}$.

RESULTS

The personal characteristics and the laboratory investigations of the study groups are shown in Table 1

The study Groups were age and sex matched ($p > 0.05$). Group III (Patients had HCV-related liver cirrhosis) had significantly higher body mass index when compared with either that of Group I (Control) or Group II (Patients with chronic hepatitis C (CHC) without cirrhosis) ($p < 0.05$; $p < 0.01$, respectively).

Group III (Patients had HCV-related liver cirrhosis) had significantly lower Hb mean level, mean platelet count, and albumin mean level when compared with either Group I (Control) or Group II (Patients with chronic hepatitis C (CHC) without cirrhosis) ($p < 0.001$ for each).

However Group III had significantly higher mean levels of bilirubin, creatinine, and INR when compared with either that of Group I or Group II ($p < 0.01$ for each). Group II and III had significantly higher mean levels of ALT, AST and ALP when compared with those of Group I ($p < 0.01$ for each). Moreover, AST mean level in group III was significantly higher than that of group II ($p < 0.05$).
Table 1 Personal characteristics and laboratory investigations of the study Groups.

|                          | Group I (n = 20) | Group II (n = 40) | Group III (n = 40) | P-value
|--------------------------|-----------------|-------------------|-------------------|---------
| Age (year)               | 47.7 ± 8.2      | 45.4 ± 12.7       | 49.2 ± 10.3       | 0.325   | 0.219 | 0.166 |
| Sex No. (%) Male         | 16 (80.0%)      | 34 (85.0%)        | 31 (77.5%)        | 0.903   | 0.825 | 0.39  |
| BMI (Kg/m²)              | 26.8 ± 4.0      | 27.1 ± 3.7        | 32.8 ± 9.1        | 0.95    | 0.012*| 0.001*|
| Hb (gm/dl)               | 13.3 ± 0.8      | 13.4 ± 1.7        | 10.4 ± 2.2        | 0.735   | 0.000*| 0.000*|
| WBCs (× 10³/mm³)         | 6.1 ± 0.8       | 5.8 ± 1.8         | 7.1 ± 4.5         | 0.323   | 0.875 | 0.416 |
| Platelets (× 10³/mm³)    | 268.7 ± 61.5    | 229.9 ± 77.0      | 134.5 ± 95.6      | 0.038*  | 0.000*| 0.000*|
| Albumin (gm/L)           | 41.9 ± 3.4      | 41.9 ± 4.8        | 24.3 ± 6.6        | 0.948   | 0.000*| 0.000*|
| ALT (U/L)                | 17.5 ± 5.3      | 52.1 ± 37.0       | 38.9 ± 26.5       | 0.000*  | 0.000*| 0.084 |
| AST (U/L)                | 14.6 ± 5.3      | 50.8 ± 33.8       | 61.4 ± 30.2       | 0.000*  | 0.020*| 0.000*|
| ALP (U/L)                | 39.2 ± 18.3     | 101.7 ± 52.5      | 103.6 ± 47.6      | 0.000*  | 0.000*| 0.061 |
| Bilirubin (umol/L)       | 10.6 ± 2.1      | 50.8 ± 33.8       | 61.4 ± 30.2       | 0.000*  | 0.020*| 0.000*|
| Creatinine (mg/dL)       | 0.7 ± 0.1       | 0.8 ± 0.2         | 1.1 ± 0.4         | 0.134   | 0.000*| 0.000*|
| INR                      | 1.0 ± 0.0       | 1.0 ± 0.1         | 1.4 ± 0.3         | 0.475   | 0.000*| 0.000*|

Table 2 Clinical data and severity of liver disease in Group III (Patients with HCV-related liver cirrhosis).

|                          | No. (n = 40) | %
|--------------------------|--------------|---------
| Ascites                  | 9            | 22.50%  |
| Hepatic encephalopathy   |              |         |
| Yes                      | 8            | 20.00%  |
| No                       | 32           | 80.00%  |
| Child Pugh grading       |              |         |
| B                        | 23           | 57.50%  |
| C                        | 17           | 42.50%  |
| MELD score               | 6.79 ± 4.24  | (range: 0.438 - 25.50 ) |

Table 3 Heart rate, oxygen saturation, and systolic blood pressure, diastolic blood pressure before and after the 6MWT among the study Groups.

| Variable                  | Group I (n = 20) | Group II (n = 40) | Group III (n = 40) | P-value
|---------------------------|-----------------|-------------------|-------------------|---------
| Heart rate                |                 |                   |                   |         |
| Before                    | 73.8 ± 10.7     | 79.5 ± 13.6       | 89.8 ± 15.6       | 0.098   | p < 0.001*| 0.001*|
| After                     | 95.8 ± 12.6     | 103.6 ± 19.4      | 101.8 ± 19.4      | 0.461   | 0.215   | 0.017*|
| P-value2                  | p < 0.001*     | p < 0.001*        | p < 0.001*        |         |
| Percentage change in heart rate | 30.7 ± 14.7 | 17.6 ± 9.9       | 13.4 ± 10         | 0.001   | < 0.001 | 0.034 |

| Oxygen saturation         |                 |                   |                   |         |
| Before                    | 97.8 ± 1.1      | 96.2 ± 2.2        | 94.2 ± 2.8        | 0.001*  | p < 0.001*| 0.001*|
| After                     | 96.9 ± 0.9      | 95.4 ± 2.3        | 93.4 ± 3.0        | 0.001*  | p < 0.001*| 0.001*|
| P-value2                  | p < 0.001*     | p < 0.001*        | p < 0.001*        |         |
| Percentage change in Oxygen saturation | -0.7 ± 0.8 | -0.8 ± 1.9       | -0.8 ± 1.9        | 0.018   | 0.001  | 0.055 |

| Systolic BP               |                 |                   |                   |         |
| Before                    | 108.5 ± 6.7     | 108.0 ± 10.2      | 107.1 ± 11.4      | 0.98    | 0.658   | 0.657 |
| After                     | 117.5 ± 7.9     | 116.5 ± 11.2      | 117.0 ± 13.2      | 0.928   | 0.787   | 0.921 |
| P-value2                  | p < 0.001*     | p < 0.001*        | p < 0.001*        |         |
| Percentage change in Systolic BP | 8.3±4.1 | 7.9 ± 5.5       | 9.4 ± 7.1         | 0.674   | 0.612   | 0.363 |

| Diastolic BP              |                 |                   |                   |         |
| Before                    | 69.0 ± 7.9      | 70.5 ± 9.3        | 66.9 ± 10.9       | 0.626   | 0.445   | 0.182 |
| After                     | 77.0 ± 8.7      | 78.3 ± 9.6        | 74.8 ± 9.9        | 0.592   | 0.397   | 0.111 |
| P-value2                  | p < 0.001*     | p < 0.001*        | p < 0.001*        |         |
| Percentage change in Diastolic BP | 11.8±6.3 | 11.5 ± 8.9       | 13 ± 13.1         | 0.949   | 0.729   | 0.685 |

Data were expressed as mean ± SD. 1: Mann-Whitney Test, 2: Wilcoxon Signed Ranks Test,* Statistical significant difference (p < 0.05).
Clinical data and severity of liver disease in Group III (Patients with HCV-related liver cirrhosis) (Table 2)
Among Group III (Patients with HCV-related liver cirrhosis), tense ascites was found in 22.5 % of the cases, moderate ascites in 55%, mild ascites in 22.5%, and hepatic encephalopathy was recorded in 20% of the cases. As regard Child Pugh grading, 23 (57.5%) were Class B, and 17 (42.5%) were Class C. MELD score was 9.8 ± 4.2.

Figure 1 shows the Six Minute Walk Distance (6MWD) among the study Groups
The mean 6MWD was significantly lower in Group III and Group II compared to that of Group I (p < 0.001; p < 0.01 respectively). Also, the mean 6MWD was significantly lower in Group III in comparison with that of Group II (p < 0.001).
As regard the severity of CLD in Group III as assessed by Child Pugh Grading, the mean 6MWD was lower in Child Pugh Class C (122.3 ± 51.7) than Child Pugh Class B (138.8 ± 35.7), but the difference did not reach the statistical significance (p value = 0.129).

Table 3 shows heart rate, oxygen saturation, systolic blood pressure, and diastolic blood pressure before and after the 6MWT among the study Groups
The heart rate was significantly higher in Group III compared to that of Group I before the test (p < 0.001). Moreover, the heart rate was significantly higher in Group III compared to that of Group II before and after the 6MWT (p < 0.01, p < 0.05 respectively). Also, heart rate significantly increased after the 6MWT in the 3 Groups (p < 0.001 for each).
Oxygen saturation (PaO$_2$) was significantly lower in Group II and Group III compared to that of Group I before and after the test (p < 0.01, p < 0.001 respectively). Also, there was a significant decrease in PaO$_2$ in Group III compared to that of Group II before and after the test (p < 0.01 for each). Moreover, PaO$_2$ significantly decreased after the 6MWT in the 3 Groups (p < 0.001 for each).
There was no significant difference between the three groups before and after the test (p > 0.05) as regard systolic blood pressure (SBP) and diastolic blood pressure. However, systolic and diastolic BP significantly increased after the 6MWT in the three groups (p < 0.001 for each) as shown in table 3.
As regard the percentages of change in heart rate, there was an increase in heart rate after 6 MWT among the study groups. The percentage of increase in heart rate was significantly lower in Group II compared to that of Group I before and after the test (p < 0.01). As regard the severity of CLD in Group III as assessed by Child Pugh Grading, the mean 6MWD was lower in Child Pugh Class C (122.3 ± 51.7) than Child Pugh Class B (138.8 ± 35.7), but the difference did not reach the statistical significance (p value = 0.129).

Correlations between 6MWD and laboratory investigations among study Groups
6MWD was positively correlated with hemoglobin (r = 0.652, p < 0.01), platelets (r = 0.486, p < 0.01), and albumin (r = 0.799, p < 0.01). On the other hand, 6MWD was negatively correlated with bilirubin (r = -0.499, p < 0.01) (Figure 2), AST (r = -0.253, p < 0.05), ALP (r = -0.226, p < 0.05), creatinine (r = -0.420, p < 0.01) and INR (r = -0.505, p < 0.01). There was no correlation between 6MWD and age in all study groups (p value > 0.05 for each).
There was a significant negative correlation between 6MWD and BMI in Group II and Group III (r = -0.348, p = 0.023 for each) as shown in (Figure 3: A & B).
There was no significant correlation between 6MWD and oxygen saturation, Child score or MELD score among Group III (Patients with HCV-related liver cirrhosis) (r = -0.194, p = 0.230; r = -0.225, p = 0.163; r = 0.050, p = 0.075) respectively.

Correlation between percentage of change in various parameters of 6MWT and 6MWD among the study Groups
There was a significantly positive correlation between percentage of change in heart rate and diastolic blood pressure during 6MWT and the 6MWD (r = 0.354, p < 0.001; r = 0.241, p = 0.016 respectively). However, there was no significant correlation between percentage of change in oxygen saturation or systolic blood pressure during 6MWT and the 6MWD (r = -0.059, p = 0.583; r = -0.112, p = 0.267 respectively).

DISCUSSION
This study was designed to use the (6MWT) to measure the functional capacity of patients with HCV related CLD of different severities. The present study demonstrated that the mean 6MWD was significantly lower in Group II (Patients had chronic hepatitis C (CHC) without cirrhosis) (325.84 meters) and Group III (Patients had HCV-related liver cirrhosis) (131.79 meter) compared to that of Group I (359.91). Also, the mean 6MWD was significantly lower in Group III in comparison with that of Group II. Moreover, the distance walked by Group II was lower than Group I. This indicates that the lowest performance in the 6MWT was noticed in cirrhotic patients which reflecting worse FC.

The current study was in agreement with Alamire et al[5] and Galant et al[6] regarding the mean of 6MWD in chronic liver disease patients. In the study of Alamire et al[5], the subjects were categorized into four groups: Group A (number = 45) healthy subject (control), Group B (number = 49) (chronic hepatitis B patients), Group C (number = 54) (chronic hepatitis C patients), and Group D (number = 98) (liver cirrhosis patients). The four groups differed in terms of 6MWD (p < 0.001). The longest distance walked was 421 ± 47 meters by Group A then Group B (390 ± 53 meters) then Group C (357 ± 72 meters) and Group D (306 ± 111 meters). Also, they found a significant negative correlation between 6MWD and age. On the other hand we found no significant correlation between 6MWD and age.

Also, in the cross sectional study of Galant et al[6], the 86 patients divided into three Groups: Group I (HCV Group) 40 patients, Group II (HBV) 14 patients, and Group III (alcoholic cirrhosis patients). Group III (alcoholic cirrhosis) showed the lowest performance in the (6MWT) compared to HBV and HCV Groups (373.50 ± 50.48, 464.16 ± 32 and 475.94 ± 27.84, respectively).

The current study reported a significant negative correlation between 6MWD and BMI in Group II and Group III. However, in Carey et al study[7] on listed patients for liver transplantation reported that the 6MWD was not correlated with BMI.

The 6MWD in liver cirrhosis in our study was lower than that of Alamire et al[5], Galant et al[6], and Carey et al[7] and this could explained by the presence of ascites in Group III (9 mild, 22 moderate and 9 tense ascites), presence of old aged females in high number in our study (9 cases), low culture in our society during the test to obey the orders and the presence of anemia in most of our case which may affect the 6MWD.

Other studies demonstrated that there are many potential factors that may contribute to the physical function limitations in cirrhotic patients, such as fatigue, muscle strength, and neuropsychiatric factors, as well as the presence of hepatopulmonary syndrome and cirrhotic cardiomyopathy[8,13].
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Figure 2 Correlations between 6MWD and A. Hb; B. Platelet count; C. Albumin; D. Bilirubin.

Figure 3 Correlation between 6MWD and BMI in Group II and Group III.
The present study demonstrated that, Hb level, albumen level and platelets count were significantly lower in Group III (Patients had HCV-related liver cirrhosis) compared to that of Group I (Healthy control) or Group II (Patients had chronic hepatitis C (CHC) without cirrhosis). However, serum ALT, AST, ALP, bilirubin, creatinine and INR were significantly higher in Group III compared to those of Group I or Group II. Also, serum ALT, AST and ALP were significantly higher in Group II compared to those of Group I. The current study was in agreement with Alameri et al regarding laboratory investigation which included Hb, albumin, ALT, AST, ALP, bilirubin, creatinine. They reported that, Group D (with liver cirrhosis) showed the lowest level of Hb (94.9 ± 45.6 g/l), and albumin (28.3 ± 6.8 g/l). Moreover, they demonstrated that, Group D (with liver cirrhosis) showed the highest level of ALT, AST, ALP, bilirubin, creatinine compared to other Groups. The lowest level of Hb, and albumin in liver cirrhosis could be explain by: In liver cirrhosis, patients are liable for hematemesis, bilateral epistaxis, and iron deficiency which make microcytic hypochromic anemia. Liver is a storage and manufacture for albumin so in liver cirrhosis hypoalbuminemia is common. Anemia of chronic disease is common among cirrhotics.

In the current study, there was a significant positive correlation between the 6MWD and Hb, albumin; platelets count. On the other hand our study found a significant negative correlation between 6MWD and liver function test including, AST, ALP, bilirubin and INR and creatinine. This could be explained by increasing in liver enzymes and bilirubin which occur in cirrhotic patients who had the lowest 6MWD. Similarly, Alameri et al reported that, the 6MWD was positively correlated with hemoglobin and albumin levels. In contrast, they reported that there was no significant correlation between 6MWD and liver enzymes.

These findings were consistent with previous reports showing that for severe heart failure patients, anemia was associated with poor physical function, while increasing hemoglobin levels were correlated with improved exercise capacity as measured in cardiopulmonary exercise tests[16,17]. Previous studies also found that the severity of physical limitation in relation to liver biochemical testing was more evident in liver cirrhosis patients compared to those with other chronic liver diseases[18,19].

Our study was in agreement with Alameri et al regarding oxygen saturation and heart rates before and after the 6MWT. In Alameri et al study the oxygen saturation was the lowest before the test in Group D (cirrhotic patients) and decrease after the (6MWT) which can be explained by hypoxemia in cirrhotic patients which occurred due to anemia and hepatopulmonary syndrome in some cirrhotic patients which had a severe effect in the 6MWD. In addition, respiratory acidosis in cirrhotic patients which decrease oxygen saturation and also, the heart rate increased in our study after the (6MWT) in all study groups which can be explained by physiological exercise which had effect in increasing heart rate and this was in consistent with Alameri et al. However, the percentage of increase in heart rate in the current study was significantly lower in Group II and III compared to that of control. Also, it was significantly lower in Group III compared to that of Group II.

In the present study, there was no significant correlation between 6MWD and MELD score, Child score or oxygen saturation in Group III (Patients had HCV-related liver cirrhosis). In contrast, Alameri et al found a significant negative correlation between the 6MWD and both MELD score and Child score and a significant positive correlation between oxygen saturation and the 6MWD.

The present study had a few potential limitation. One limitation is the possibility that the distance walked wasn’t assed accurately because the 6MWT was performed just once. However, the study of Mercer et al on ten patients with chronic renal insufficiency, demonstrated that, the improvement in the distance walked was 3.7% when the test was repeated after 48 hours, suggesting that the 6MWT may be more reproducible in non-cardiopulmonary disease patients. Another limitation is that the follow-up was not done, so future studies with follow-up may help in understanding of the role of 6-minute walk testing in patients with liver diseases. Finally, 6MWD data were not compared with data obtained from other physical functional assessment such as cardiopulmonary exercise test to obtain more accurate results.

CONCLUSION

Six minute walk test (6MWT) is a reliable indicator to measure the functional capacity for patients with CLD. The lowest performance in the 6MWT was noticed in HCV related cirrhosis that reflecting worse FC.

RECOMMENDATIONS

The six minute walk test can be used as a tool to evaluate functional capacity of patients with CLD. The six minute walk test can be used as a tool to follow up patients after paracentesis and TIPS (Trans jugular intra hepatic porto systemic shunt). Many factors can increase or decrease the (6MWT) which must be taken in consideration. 6MWT may be done more than once for all cases to obtain more accurate results. Another study is needed to compare 6MWT to other data obtained from physical function such as (pulmonary exercises test), indices of sarcopenia, and hand grip strength.

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