Original Article



# Gender Implications on Left Ventricular Diastolic Dysfunction in Non Alcoholic Fatty Liver Disease Patients

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## Abstract

**Objective:** To assess the impact of gender on the risk of Left Ventricular Diastolic Dysfunction in Non Alcoholic Fatty Liver Disease.

**Methodology:** This comparative cross sectional study was conducted at the major hospitals of Khyber Pakhtunkhwa, after proper ethical approval was taken. The sample size was 192, using the non probability purposive sampling. All patients having non alcoholic fatty liver disease on imaging studies were screened for Left Ventricular Diastolic Dysfunction (LVDD) and then were included in the study. Patients with deranged liver function tests and having liver cirrhosis were excluded. The data analysis was conducted using SPSS 23 software package.

**Results:** The mean BMI of the patients was 20. The males comprised 53%(n-102) of the total patients, while females accounted for 47% (n-90). The p value of 0.043 does show statistically significant difference in ventricular diastolic dysfunction between both the genders, especially more in female gender.

**Conclusion:** Left ventricular diastolic dysfunction is a common finding in Non Alcoholic Fatty Liver Disease patients having low BMI and female gender. Routine echocardiography should be performed to start the management on time.

**Keywords:** Cardiovascular disease, Gender, Left ventricular diastolic disfunction, Non alcoholic fatty liver disease



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# Introduction

Non Alcoholic Fatty Liver disease (NAFLD) has been the lynchpin of hepatology for number of years and has mysteriously leaded to cirrhosis in lean underweight patients.[1] With the decline of hepatitis B and C in our country, diseases such as NAFLD has gained further reputation of physicians and hepatologists across the globe. Burn out NASH is one of the leading causes of liver transplantation.[2]

The prevalence of NAFLD is continuously on the rise. It is an integral part of metabolic syndrome apart from marked insulin resistance, obesity, and systemic hepatic inflammation, and the dilemma of hepatocellular carcinoma occurrence. Many of the patients have advanced liver fibrosis.[3] Recently, new guidance has been published to screen thin, lean patients with a body mass index (BMI) less than 23 based on an increasing number of cases diagnosed as nonalcoholic fatty liver disease either on ultrasound scan or fibroscan, and in some cases, liver biopsy being the diagnostic modality.[4]

There is an increased incidence of ischemic heart disease and myocardial infarction, leading to fatal mortalities even in patients with normal body weight.[5] Cardiovascular diseases and obesity are two major culprits leading to death in patients with non alcoholic fatty liver disease.[6] The disease burden of non alcoholic steatohepatitis (NASH) especially in countries have stretched health care systems to a colossal extent.[7]

The screening of patients for left ventricular diastolic function in NAFLD has a lot of significance. In addition to the reduction of ejection fraction, left ventricular diastolic volume and E/A ratio which further enhances the importance of the NALFD as a disease to be looked for especially in women in menopausal age.[8] It is essentially to be screened even in younger aged women due to increase in testosterone level in polycystic ovarian syndrome. The reduction of testosterone levels in males having hypogonadism decreases the risk.[9] The sex hormones do play a significant role in varying adiposity levels among the men and women. The gender differences are also noticed in levels of fatty acids, triglycerides and cholesterol levels in patients with NALFD.[10] Therefore, the screening of NALFD patients by doing ultrasound and echocardiography for left ventricular diastolic dysfunction is of paramount importance. The objective of this study is to assess the impact of gender on the risk of LVD in obese and nonobese NAFLD.

# Methodology

This comparative cross-sectional study was conducted at major hospitals of at major hospitals of Khyber Pakhtunkhwa, i-e; Saidu Teaching Hospital Swat, Kabir Medical College and Hayatabad Medical Complex Peshawar, after obtaining ethical approval as a prerequisite for ethical considerationn. The sample size was 192, calculated on the basis of the estimated prevalence of 14.63%5 for LVDD in nonobese NALFD patients, 95% confidence level, and 5% margin of error, taking into consideration the burden of LVDD in nonobese NALFD. The sampling technique was non probability convenient. All those patients who were diagnosed on Ultra Sound abdomen with Non Alcoholic Fatty Liver disease, and then confirmed with Left Ventricular diastolic dysfunction in Cardiac Echocardiography were included in the study. Patient with deranged liver function tests due to other causes including liver cirrhosis; infective hepatitis, herbal medications, patients having systolic heart failure (having Left Ventricle Ejection Fraction <50%), patients with uncontrolled diabetes Mellitus/hypertension were excluded from the study. The non obese NALFD were screened for left ventricular diastolic dysfunction by echocardiography. Left Ventricular diastolic dysfunction was graded into 04 grades as below;4

1. Normal Diastolic function: E/A 1.0-1.5DT >160msec

2. Grade I/Impaired Relaxation: E/A < 1.0DT > 200msec

3. Grade II/Pseudonarmal: E/A 0.8-1.5 DT 160-200msec

4. Grade III/Reversible Restricted: E/A ≥ 2.0 DT < 160msec

5. Grade IV/Fixed Restricted: E/A ≥ 2.0 DT < 160msec

The Ultrasound abdomen was used for grading of fatty liver disease and echocardiography for severity of left ventricular diastolic dysfunction. Statistical analysis was conducted using SPSS 23 software package. Mean and SD were applied to quantitative data. Categorical data was summarized using frequencies and percentages. Chi Square test was used to see the association of LVDD in both the groups (males and females) of NAFLD and the odd ratio was calculated to determine the risk of LVVD. Multinomial regression analysis was utilized to see the risk of LVDD between both the groups. The data was presented as text and tables/figures.

# Results

The mean age of the patients was 45±9 years with range of 18 to 73 years. The mean BMI of the patients was 20±2.6. The males comprised 53% (n-102) of the total patients, while females accounted for 47% (n-90). Table 01 shows the count for individual categories, showing how males and females fall into each grade for normal ventricular function versus different grades of cardiac ventricular diastolic dysfunction .The p value of 0.043 does show statistically significant difference in ventricular function between both the genders and that is eminent in grade 1 and grade 2 fatty liver disease. The difference is more evident in the early stages of fatty liver disease, where the cardiac impairment is more prominent, as reflected in the results in table 01.


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According to the table above, the logistic regression model examined the association between gender, BMI, and fatty liver severity with ventricular function. The intercept represents the log odds of the reference category (GRADE 3 LVDD) when all predictors are zero.

For example, the coefficient for gender=1 (male) for the outcome "GRADE 1 LVDD" is 0.283 with a p-value of 0.613 and a 95% confidence interval of (0.001, 0.565). This means that, after adjusting for other factors, males are 1.33 times (exp (0.283)) more likely to have GRADE 1 LVDD compared to females, but this difference is not statistically significant as the p-value is greater than 0.05. The 95% confidence interval also includes 1, indicating that we cannot be 95% confident that the true odds ratio is different from 1. However patients with normal ventricular function and grade 2 LVDD, gender was the significant predictor as reflected by a p value of less than 0.05.

## Discussion

According to the study of UNOS-STAR data base that included 76149 patients (2005-2012) for hepatic transplant 7.2% were related to NASH. The analysis also showed that the disease was found more common in females with BMI variation as a cause for gender disparity. Females with Non Alcoholic Fatty Liver disease frequently require dual liver and renal transplants, which further explains the importance of gender disparity for transplant in NASH patients.[11]

Dai et al. did report a significant difference in the gender wise prevalence of NAFLD in type 2 diabetic patents. In a research conducted by Yi et al., there was an enhanced prevalence of NAFLD in males (48%) as compared to females (42.9%) with T2DM and increase in BMI. Type 2 diabetes mellitus has also been observed as a consequence of NAFLD. In a study of such patients in Japan, the incidence of T2DM was 9.95 per 1000 person annually. Female gender was identified as a statistically significant factor influencing the progression to T2DM.[12]

Perseghin et al[19] did show that non-diabetic men with a higher fat content, as measured by 1 HMRS, had significant changes in myocardial high energy phosphate metabolism as compared with those with decreased intrahepatic fat content. Despite comparable LV morphology and function observed through cardiac MRI, alterations in myocardial energy metabolism were still identified.[13]

Most of the studies have reported NALFD to be associated with low cardiac index and myocardial dysfunction leading to congestive cardiac failure. These findings have been reported found in non-obese NAFLD. However, there are even greater chances of developing heart failure in obese NAFLD. These results are similar to those reported by Saluja M et al., who found that such patients had suboptimal findings recorded

**Table 1. Factors associated with ventricular diastolic dysfunction**

| Gender | | | Left Ventricular Function | | | | Total |
|---|---|---|---|---|---|---|---|
| | | | GRADE 1 LVDD | NORMAL VENTRICULAR FUNCTION | GRADE 2 LVDD | GRADE 3 LVDD | |
| MALE | Fatty liver | GRADE1 | 12 | 5 | 8 | 3 | 28 |
| | | GRADE2 | 16 | 7 | 2 | 7 | 32 |
| | | GRADE3 | 13 | 13 | 10 | 5 | 41 |
| | Total | | 41 | 25 | 20 | 15 | 101 |
| FEMALE | Fatty liver | GRADE1 | 5 | 12 | 3 | 1 | 21 |
| | | GRADE2 | 13 | 20 | 9 | 1 | 43 |
| | | GRADE3 | 6 | 6 | 11 | 4 | 27 |
| | Total | | 24 | 38 | 23 | 6 | 91 |
| Total | Fatty liver | GRADE1 | 17 | 17 | 11 | 4 | 49 |
| | | GRADE2 | 29 | 27 | 11 | 8 | 75 |
| | | GRADE3 | 19 | 19 | 21 | 9 | 68 |
| | Total | | 65 | 63 | 43 | 21 | 192 |

LVDD: Left Ventricular Diastolic dysfunction

P Value : 0.043 (FEMALE GENDER)

**Table 2. Prediction of Left Ventricular Diastolic Dysfunction in presence of Independent factors (Multivariate)**

| Left Ventricular Functiona | | B | Std. Error | Wald | df | Sig. | Exp(B) | 95% Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Lower Bound | Upper Bound |
| GRADE 1 LVDD | Intercept | -4.001 | 3.733 | 1.149 | 1 | .284 | | | |
| | Gender | .283 | .560 | .256 | 1 | .613 | 1.327 | .443 | 3.977 |
| | BMI | .214 | .180 | 1.408 | 1 | .235 | 1.239 | .870 | 1.765 |
| | [fatty liver=1.00] | .687 | .690 | .991 | 1 | .319 | 1.988 | .514 | 7.684 |
| | [fatty liver=2.00] | .533 | .582 | .840 | 1 | .359 | 1.704 | .545 | 5.328 |
| | [fatty liver=3.00] | 0b | . | . | 0 | . | . | . | . |
| NORMAL VENTRICULAR FUNCTION | Intercept | -3.048 | 3.744 | .663 | 1 | .416 | | | |
| | Gender | 1.312 | .558 | 5.527 | 1 | .019 | 3.713 | 1.244 | 11.082 |
| | BMI | .099 | .181 | .298 | 1 | .585 | 1.104 | .774 | 1.574 |
| | [fatty liver=1.00] | .655 | .698 | .881 | 1 | .348 | 1.925 | .490 | 7.554 |
| | [fatty liver=2.00] | .232 | .591 | .154 | 1 | .695 | 1.261 | .396 | 4.018 |
| | [fatty liver=3.00] | 0b | . | . | 0 | . | . | . | . |
| GRADE 2 LVDD | Intercept | 2.452 | 3.819 | .412 | 1 | .521 | | | |
| | Gender | 1.179 | .585 | 4.061 | 1 | .044 | 3.250 | 1.033 | 10.229 |
| | BMI | -.158 | .186 | .723 | 1 | .395 | .854 | .593 | 1.229 |
| | [fatty liver=1.00] | .124 | .717 | .030 | 1 | .863 | 1.131 | .277 | 4.614 |
| | [fatty liver=2.00] | -.748 | .631 | 1.405 | 1 | .236 | .473 | .138 | 1.630 |
| | [fatty liver=3.00] | 0b | . | . | 0 | . | . | . | . |

LVDD: Left Ventricular Dysfunction

a. The reference category is: GRADE 3 LVDD.

b. This parameter is set to zero because it is redundant.


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on echocardiography, including the ejection fraction and left ventricular diastolic volume. They concluded that diabetic patients had low cardiac function indexes with NALFD even with normal morphology and cardiac structure, and so the dysfunction of the left ventricle isn't a rare finding during screening of such patients.[14]

Farouk did perform a cross sectional study on 35 patients with non-alcoholic fatty liver disease and assessed the risk of LVDD by doing an echocardiography. There was a significant association between the disease and left ventricular diastolic dysfunction as depicted by p value of less than 0.05. The major limitation of this study was a small sample size, limiting the generalizability of results.[15]

According to findings by Wang as compared with men, females had greater cholesterol as well as LDL levels but decreased diastolic pressure), BMI, visceral adipose fat deposition, blood glucose levels and triglycerides Females had increased ejection fraction as compared to opposite sex (68.17 ± 6.055 vs 67.5 ± 6.096, P < 0.05). More female patients as compared to men in the middle aged group patients old had left ventricular diastolic dysfunction (women vs men 54.5% vs 46.9%, P < 0.05).[16]

Another systematic review as well as meta-analyses done by Rocha et al., the prevalence of NAFLD was found to be very high in females with polycystic ovarian syndrome having soaring serum androgen concentrations compared to women low serum androgens. The sex hormones do play a significant role in varying adiposity levels among the men and women.[16]

STRENGTHS OF THE STUDY:

1- Our study is first kind to assess the impact of NAFLD on LVDD especially lean patients having a low BMI who are generally ignored in clinical setups with early discharge from the clinics with no recommendations for treatment except for low fat diet

2- The research is extremely useful for clinicians as they will screen especially the post menopausal women even with thin lean patients who are otherwise non hypertensive and does have NALFD on Ultrasound

3- The research will coincide the hepatologists to look for alternate causes of deranged liver function tests for other chronic hepatitis B and C, which were leading causes of liver transplantation until now when updated treatments like oral anti viral drugs have emerged

The thesis has a well-defined objective, which is to assess the impact of gender on the risk of LVD in obese and non-obese NAFLD

## Limitations Of The Study:

1-This study has several limitations. Primarily, as a cross-sectional study, it posed challenges in determining the causal relationship between NAFLD and left ventricular dysfunction.

2- Investigations such as fibro scan and liver biopsy should be used in great clinical settings having a higher sensitivity for NALFD patients

## Conclusion

This study found strong association of NAFLD with left ventricular diastolic dysfunction in non obese NAFLD and female gender have more propensity to have LVDD when they have NAFLD.

## Recommendations

1- All clinicians and general practitioner should screen the patients for left ventricular diastolic dysfunction by advising echocardiography in patients with NAFLD.

2- More research is needed to establish the risk of LVDD in non-obese NAFLD. Further studies should be done in multicenters across the country to persuade cardiologists and physicians to screen such patients on time to reduce cardiovascular mortality and morbidity.

3- The significance of early detection of LVDD by performing echocardiography and timely treatment by cardiologist is the need of the day.

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**Authors' Contribution Statement**

AH contributed to the conception, design, acquisition, analysis, interpretation of data, drafting of the manuscript, and final approval of the version to be published. JUAK contributed to the design, acquisition, analysis, and interpretation of data. SHB contributed to the acquisition, analysis, interpretation of data, and drafting of the manuscript. DKK contributed to the acquisition, analysis, interpretation of data, and drafting of the manuscript. IA contributed to the acquisition, analysis, interpretation of data, and drafting of the manuscript. BA contributed to the analysis, interpretation of data, and drafting of the manuscript. All authors are accountable for their work and ensure the accuracy and integrity of the study.

**Confilct of Interest**

Authors declared no conflict on interest

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None

**Data Sharing Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.