RESEARCH ARTICLE

Development and validation of diagnostic risk score for fatty liver grading among rural population visiting tertiary care hospital

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ABSTRACT

Background: Fatty liver disease caused by alcoholic or non-alcoholic etiologies is an emerging major public health issue in India as well as worldwide. Non-alcoholic fatty liver disease has a global prevalence of approximately 25%.

Aims and Objectives: We aim to develop and validate a risk-scoring system for the diagnosis of fatty liver disease among high-risk individuals (diabetes mellitus and obesity) using basic clinical history, laboratory investigations, and radiological examinations.

Materials and Methods: Study design: Cross-sectional study conducted in a tertiary care teaching hospital. A patient case form has been designed for this study which includes all the relevant information under three headings, personal history, laboratory investigation findings, and radiological examination findings. Patients who have a known medical history of diabetes mellitus and/or body mass index (BMI) more than or equal to 25.00 will be included in this study.

Results: The total number of patient data included in the study was 164. The total sample under consideration comprised 88 males (53.7%) and 76 females (46.3%). The average height was reported to be 159 ± 10.27 cm. The average weight of participants was 68.4 ± 12.6 kg. The average BMI of the study populace was 27 ± 4.46 kg/m². Fatty score grading showed a significant positive univariate correlation with the weight, BMI, and triglyceride levels of the patients. Rest all correlations were found to be insignificant. Patients additionally presented with fibrosis grading and LSM score which were found to be positively correlated significantly with fatty liver grading. Fibrosis score and low-density lipoprotein level showed a significant negative correlation. All significant univariate factors were found to produce an insignificant multivariate regression model. The receiver operating characteristic curve and cutoff scores could not be determined. Therefore, the study was not able to develop and validate a multivariable scoring system.

Conclusion: Even though the study was not able to fulfill the objectives intended, problems were identified and solutions were recommended for conducting such a study. This study can be taken as a baseline for future studies taking the recommendations into consideration at the time of execution.

KEY WORDS: Fatty Liver; Scoring; Non-Alcoholic Fatty Liver Disease; Negative Study

INTRODUCTION

Fatty liver disease caused by alcoholic or non-alcoholic etiologies is an emerging major public health issue in India as well as worldwide. Non-alcoholic fatty liver disease (NAFLD) has a global prevalence of approximately 25%.[1] According to estimates, the prevalence in the Indian general...
population stands at 9–32%.[3] Alcohol consumption is increasing in India, and associated disorders such as alcoholic liver disease have recorded increased morbidity and mortality. The alcohol-attributable years of life lost score was 4 in 2016, whereas alcohol-attributable liver cirrhosis in Indian males was 60% and 33.33% in females.[3] However, there is no national legislation on alcohol control in the country. 20–30% of patients suffering from fatty liver disease will develop liver cirrhosis, which ultimately requires liver transplantation.[4,5] This increased burden on transplant status in India calls for increased measures to curb the problem in the initial stages to provide long-term benefits to the patient and the community at large. NAFLD was incorporated into the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke in February 2021.

Liver biopsy is the gold standard for the diagnosis of NAFLD; however, due to its high cost and complications, non-invasive techniques such as ultrasonography are commonly used for screening in high-risk individuals.[6] Ultrasonography has limitations, such as being operator-dependent and having a limited ability to identify the grade of the fatty liver.[7] Therefore, a risk-scoring system for clinical correlations is required to improve outcome prediction. We observed that the operational guidelines recommend the use of fibrosis-4 (FIB-4) and NAFLD fibrosis score (NFS) to rule out advanced fibrosis in primary health-care settings.[2] However, the NFS was not modified to interpret the body mass index (BMI) of the Indian population. The FIB-4 score is associated with an indeterminate range in approximately 40% of patients, making the use of secondary diagnostic tests necessary. Both scores showed reduced specificity in older patients.[8] Alcohol consumption was absent in both models. Therefore, we aimed to develop a new risk-scoring system that overcomes the limitations of the currently used scoring systems and aids in a better clinical diagnosis.

Objectives
1. To develop and validate a risk-scoring system for the diagnosis of fatty liver disease among high-risk individuals (diabetes mellitus and obesity) using basic clinical history, laboratory investigations, and radiological examinations
2. To measure the prevalence of fatty liver disease and alcohol consumption among high-risk groups
3. To formulate the risk score in various forms of presentation (nomogram, table, and equation) for ease of use by medical professionals.

MATERIALS AND METHODS

Study Design
Cross-sectional study.

Duration of Study
2 months.

Setting
The study was conducted in a tertiary care teaching hospital. It will be coordinated by the Department of Community Medicine and will involve the Department of Medicine, Surgery, Biochemistry, and Radiology for data collection and laboratory and radiological investigations.

Ethical Approval
Approval from the Institutional Ethics Committee was obtained before the commencement of the study. (GMCJ/IEC Approval/063/2022).

Sample Size
The study was designed according to the guidelines of the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement.[9] As we have considered 25 variables for the development of the model, we take at least 10 events per variable by the general rule. Therefore, the sample size for the developmental model was 250. The model will be validated using temporal validation, that is, the entire dataset collected over a period of 2 months will be split based on duration. Data collected during the past 15 days of the study were considered for validation.

Data Collection
A patient case form was designed for this study, which includes all relevant information under three headings: Personal history, laboratory investigation findings, and radiological examination findings. Patients will be selected from the outpatient and inpatient wards of the Department of Medicine and Surgery. Patients who have a known medical history of diabetes mellitus and/or BMI more than or equal to 25 were included in this study. The eligible patients will be explained the benefits of the study, investigations to be conducted, and any associated risks, and written informed consent will be obtained from them. Patient confidentiality was maintained. Personal history from the patients will be collected by interview. Quantitative data such as age (in years), height (in m), weight (in kg), BMI (in kg/m²), personal history of diabetes mellitus (in years), and alcohol consumption in standard units will be recorded. Qualitative data such as gender, physical activity of more than 30 min per day (yes/no), diet history (veg./non-veg.), and family history of diabetes mellitus (yes/no) will be collected. Blood samples will be collected for laboratory investigations using standard techniques. Investigations such as random blood sugar, HbA1c, low-density lipoprotein (LDL), high-density lipoprotein, triglycerides, total cholesterol, serum glutamic-oxaloacetic transaminase, serum glutamic pyruvic
transaminase, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, and total protein will be recorded as quantitative data in standard units. Ultrasonography of the liver will be performed and the grading of the fatty liver will be noted (grade 0/1/2/3).

Model Development and Validation

Using the appropriate statistical software, the univariate correlation will be found between the collected variables and the presence or absence of fatty liver disease diagnosed on ultrasonography. All the significant variables obtained will then be included in the development of a multivariate regression model. Individual scores of significant variables will be formed. Cutoff scores for all respective grades of the fatty liver will be determined. Receiver operating characteristic (ROC) will be plotted to estimate the discriminative power of the developed prediction model. The model will be validated using the validation dataset. The diagnostic performance will be determined using sensitivity, specificity, positive predictive value, negative predictive value, etc., and will be performed at the time of development as well as validation.

Statistical Analysis

Descriptive statistics will be calculated for all significant variables. The model obtained will be represented in the form of a table with individual scores, an equation for calculation, and a nomogram for easy interpretation.

Operational Definitions

High-risk individuals

Patients suffering from diabetes mellitus and obesity are at an increased for fatty liver disease. Therefore, this group of patients will be included in the study.

Diabetes mellitus

Patients have a known medically diagnosed history of diabetes mellitus and have been advised medications by a registered medical practitioner for management.

Obesity

As per Indian standards, patients having a BMI of more than or equal to 25.00 kg/m$^2$ will be included in the study.

RESULTS

The total number of patient data included in the study was 164. Loss of follow-up with radiology report on fatty liver grading was noted as the major cause. Other causes include failure to report laboratory values and loss of samples collected for testing.

The mean age of participants was 52.7 ± 11.9 years. Age distribution curve is shown in Figure 1.

The total sample under consideration comprised 88 males (53.7%) and 76 females (46.3%). The pie chart in Figure 2 depicts the sex-wise distribution.

The average height was reported to be 159 ± 10.27 cm. The average weight of participants was 68.4 ± 12.6 kg. The average BMI of the study populace was 27 ± 4.46 kg/m$^2$. The histogram in Figure 3 depicts the distribution of BMI in the study sample.

Fatty score grading showed a significant positive univariate correlation with the weight, BMI, and triglyceride levels of the patients. Rest all correlations were found to be insignificant. Insignificant correlations were excluded from the multivariate regression modeling. Patients additionally presented with fibrosis grading and LSM score which were found to be positively correlated significantly with fatty liver grading.

Fatty liver score and weight showed a significant positive correlation with a factor of 0.395 (P < 0.001). The correlation is depicted in the scatter plot below in Figure 4.

Fatty liver score and BMI showed a significant positive correlation with a factor of 0.437 (P < 0.001). The correlation is depicted in the scatter plot below in Figure 5.

Fatty liver score and triglyceride level showed a significant positive correlation with a factor of 0.247 (P < 0.005). The correlation is depicted in the scatter plot below in Figure 6.

Fibrosis score and LDL level showed a significant negative correlation with a factor of 0.23 (P < 0.005). The correlation is depicted in the scatter plot below in Figure 7.

All significant univariate factors were found to produce an insignificant multivariate regression model. ROC curve and cutoff scores could not be determined. Therefore, the study was not able to develop and validate a multivariable scoring system.

DISCUSSION

The increase in fatty liver grading on ultrasonography directly proportional to weight, BMI, and triglyceride levels is consistent with findings in Li et al. The negative correlation between liver fibrosis and LDL levels is consistent with the findings of Valkov et al. Visceral adipose tissue, particularly, releases free fatty acids into the bloodstream, overwhelming the liver’s processing capacity. This surplus leads to hepatic lipid deposition, insulin resistance, and inflammation, creating a cyclical pattern of fat accumulation.
Adipose tissue also secretes adipokines and pro-inflammatory cytokines, contributing to the inflammatory environment associated with non-alcoholic steatohepatitis. Genetic factors, lifestyle choices, and dietary patterns further modulate the risk of NAFLD in the obese population.\textsuperscript{[13]} Lower LDL cholesterol levels were associated with greater severity of liver fibrosis in individuals with NAFLD. The proposed mechanism suggests that LDL may exert protective effects on the liver by suppressing inflammatory responses and reducing oxidative stress, both contributing factors to fibrogenesis.\textsuperscript{[14]}

Since the objectives of this study could not be fulfilled due to a lack of sufficient correlations being found between the variables in the study, it is imperative to enlist the improvements necessary to produce successful results in subsequent studies.
The problems identified and improvements suggested are categorized according to the stages of the study conducted.

1. Patient selection: It was intended to select the patients from outpatient and inpatient departments of the hospital. However, it was observed that the individuals visiting the outpatient department showed a lack of interest in participating throughout the entire process of the study. Lack of time and increased footfall during rush hours made it difficult for a single investigator to trace the selected patients between laboratory and radiology. Various individuals after submitting blood samples in the laboratory did not visit the radiology department for ultrasonography thereby causing incomplete data which needed to be excluded from the study.

Improvements:
- Increase the number of on-field investigators and ensure coordination between them to trace patients at different locations.
- Generating interest among eligible patients for completing the entire process, especially during the early hours of the outpatient department.

2. History taking: Patients were encouraged to share relevant points in history such as duration since they were diagnosed with diabetes mellitus and alcohol consumption. However, the majority of the patients visiting the government setup were unaware of the time when they were diagnosed or started on treatment for diabetes mellitus. Conflicting answers were observed on the topic of alcohol consumption between patients and relatives. Patients also did not reveal a history of drugs being consumed over-the-counter which may have hepatic or lipid interactions causing distortion of results.

Improvements:
- Since it is necessary to get an alcohol consumption history and treatment history for diabetes mellitus, patients will have to be persuaded more to obtain the correct responses as much as possible.
- The sample size may need to be increased to rectify discrepancies in the data obtained.
- The history of drugs being used having hepatic or lipid interactions needs to be included and highlighted at the time of analysis.

3. Investigative data: Missing values in laboratory investigations were created due to a lack of resources at multiple points in the study. This led to the exclusion of data at the time of analysis. Discrepancies were noted in the grading of fatty liver at the time of ultrasonography.

Improvements:
- Subjective grading of fatty liver can be improved by introducing input from two radiologists.
- Laboratory investigations need to be streamlined depending on the investigations available at the source.

CONCLUSION

Even though the study was not able to fulfill the objectives intended, problems were identified and solutions were recommended for conducting such a study. This study can be taken as a baseline for future studies taking the recommendations into consideration at the time of execution.

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