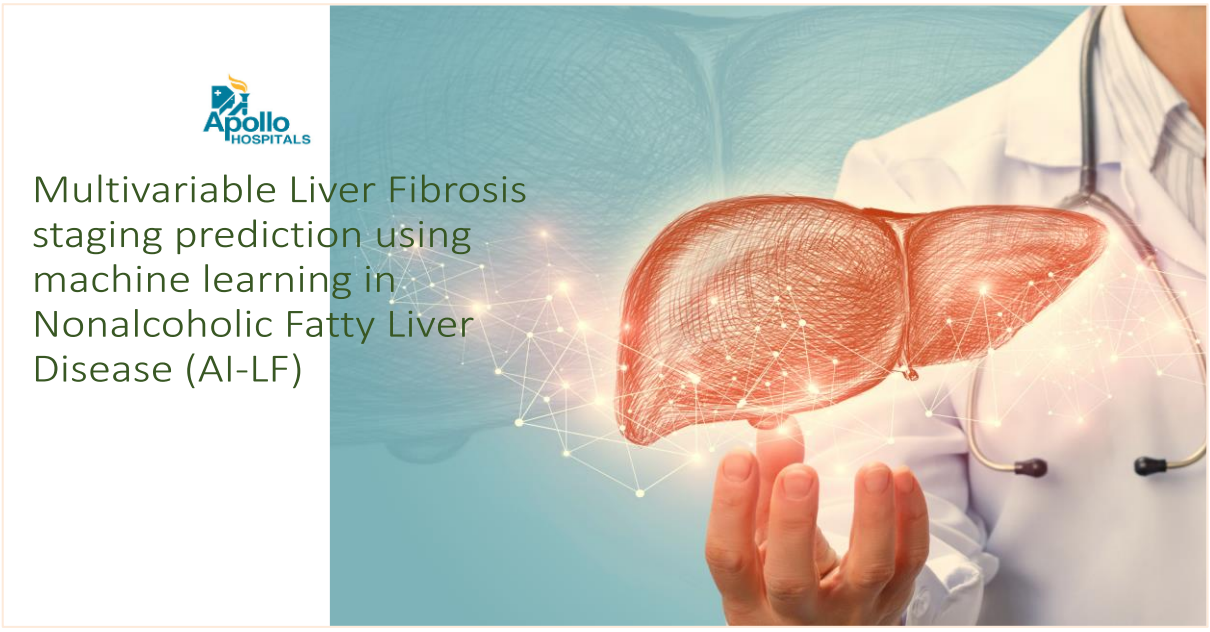

Introduction.

AI LF – Liver Fibrosis in Individuals with Non-Alcoholic Fatty Liver Disease is a novel artificial intelligence-based risk score system that classifies the individual's risk of having Higher Grades of Liver Fibrosis versus No / Low Grades of Liver Fibrosis. The risk is developed by Apollo Hospitals and undergoing prospective use and validation. The methodology helps to stratify the patient's risk and provide individualized protocol using a Clinical Decision Support System on the next best actions with an accuracy above 85%.

Why is AILF different or What is the advantage of this score?

1. Machine Learning Model developed with Clinical Features, Medication History, and Lab Reports having Higher Accuracy.
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    b. Accuracy - AUC – >0.9 (Development) and 0.85 (Validation)
2. Developed with Indian Data having Higher Accuracy than a conventional risk score.
3. Feedback Loop from the prospective use in patients
4. Comprehensive & Holistic Risk Assessment
5. Validated at different National & International Institutions
6. Integrated Clinical Decision Support Tool (What Next to Do)

What is the Interpretation & Adoption Message

1. AI Algorithm + Clinicians - This risk assessment tool has been built as an adjunct tool for physicians to identify global/holistic risks for Liver Fibrosis in NAFLD patients.
2. Risk Identification and Prevention - This Risk Assessment Tool is not to be used to diagnose Liver Fibrosis. Its limitations include already-diagnosed Liver Fibrosis and currently under treatment.

Where can the physicians use the AILF tool –

This Risk Assessment tool has been prepared for use in Preventive Gastroenterology & Liver Disease Screening programs at Outpatient Clinics, Emergency Rooms, and Health Check Clinics specifically looking at Non-Alcoholic Fatty Liver Disease.

What are the Risk Factors Included –

a. Personal parameters as Age | Gender | Height | Weight | BMI

b. Past Medical History - Liver Disease | Alcoholism | Hepatitis (Infective)| Diabetes | Dyslipidemia
c. Lab Parameters – Bilirubin | AST | ALT | Alkaline Phosphatase | Albumin | A/G Ratio | Total Cholesterol | HDL | LDL | Triglycerides | Platelet Count

What is the Output and Follow-Up For the Risk Score

a. Risk Categorization – Low – Moderate – High Risk of F2 – F4 Liver Fibrosis vs F0/F1 Fibrosis
b. AI Liver Risk Score
c. Top Modifiable Risk Attributes
d. Clinical Decision Support System (What Next to Do)
    i. Lab, Imaging and Investigations
    ii. Pulmonology Referral
    iii. Treatment Goals
    iv. Education
    v. Revisit Guidelines

Workflow of AI- Liver Fibrosis APP

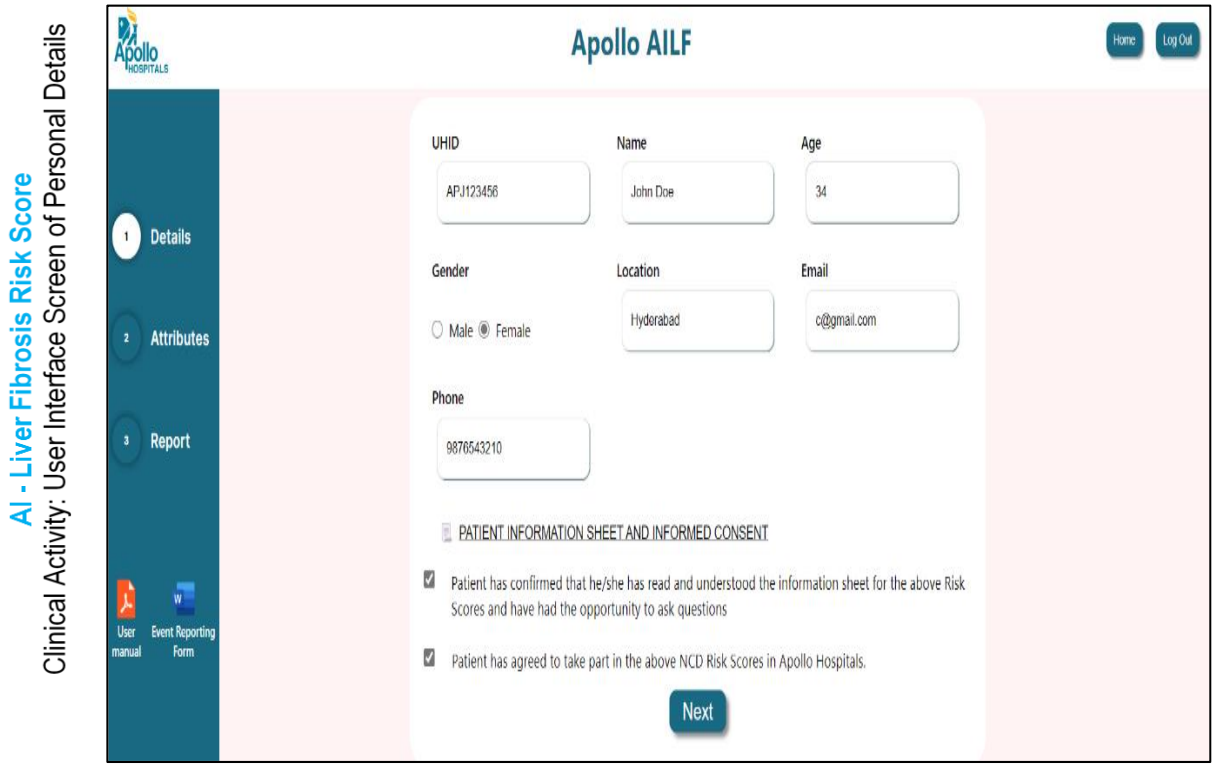


Figure 1 – Entry of Patient Personal Details

Patient details Dashboard: The first step to use the AILF App is to log into the Doctor Dashboard using your unique credentials. After login, Fill in the Patient Details and accept consent.

AI - Liver Fibrosis Risk Score
Clinical Activity: User Interface Screen of Attributes

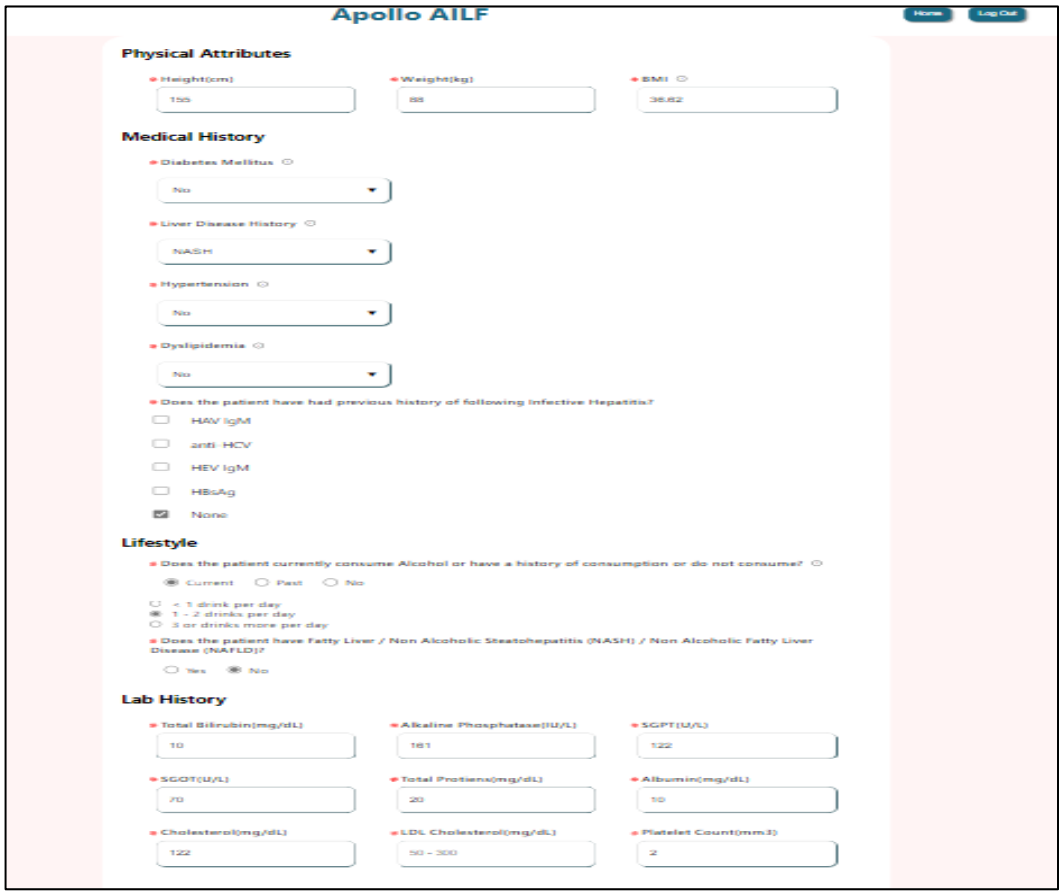


Figure 2 – Entry of Patient Attributes

Patient Attributes: The following categories are used to collect the patient attributes data:

- Physical Attributes
- Medical History
- Lifestyle Attributes
- Laboratory History

These Parameters are considered as data inputs to the model.

AI - Liver Fibrosis Risk Score
Clinical Activity: User Interface Screen of Report

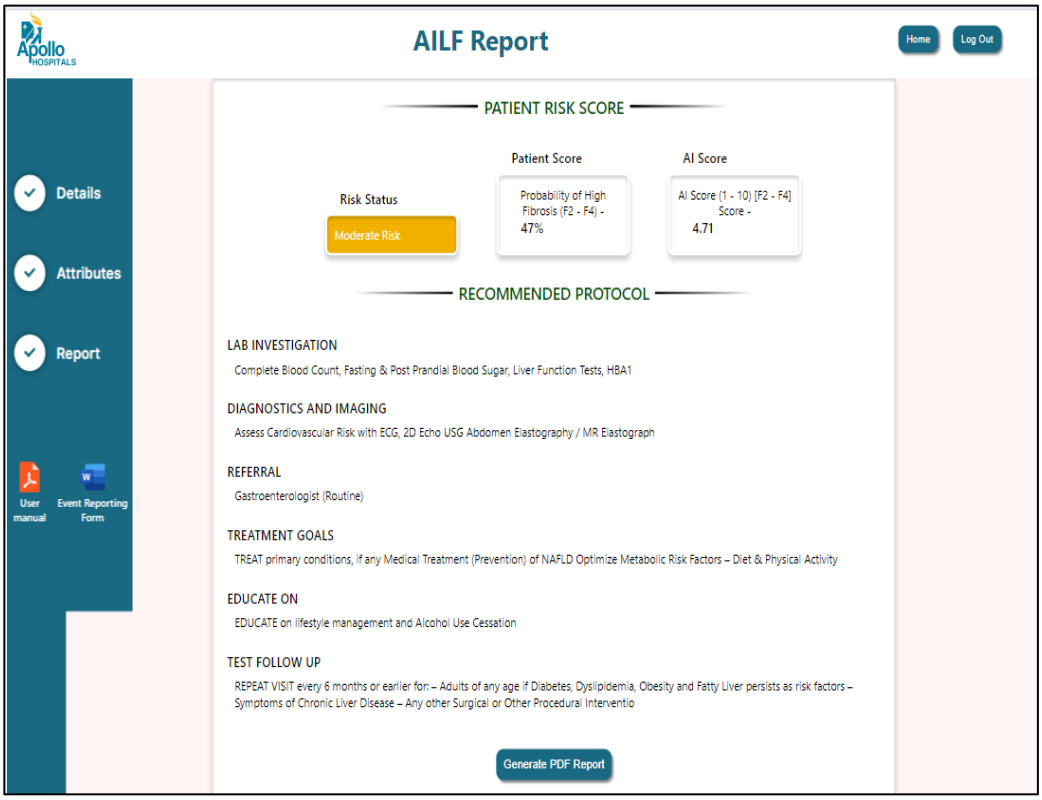


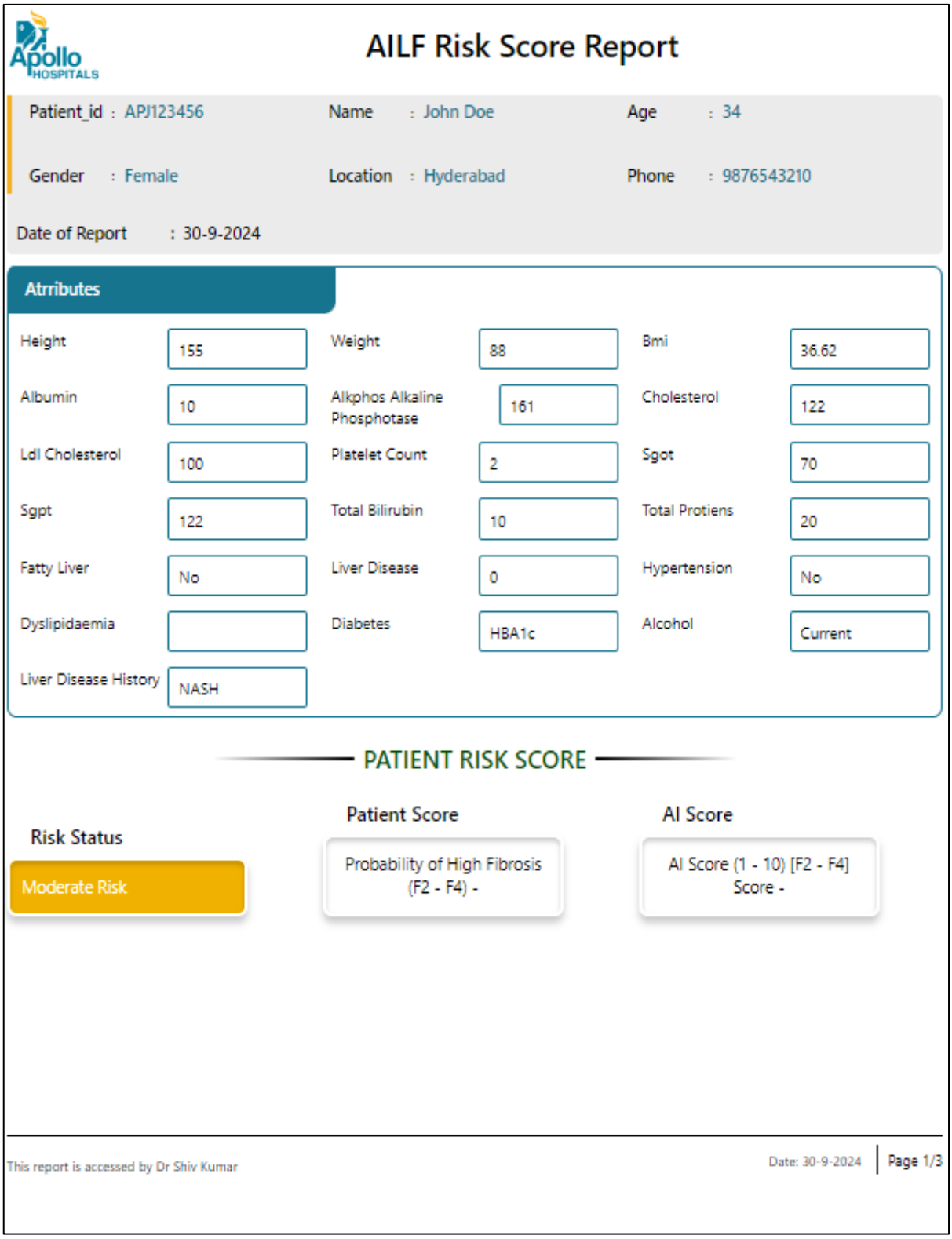
Figure 3: Risk Score Report Generation

Output:

Considering the input parameters given, the model gives an output of

a. Risk Categorization – Low – Moderate – High Risk of F2 – F4 Liver Fibrosis vs F0/F1 Fibrosis
b. AI Liver Risk Score
c. Top Modifiable Risk Attributes
d. Clinical Decision Support System (What Next to Do)
    I. Lab, Imaging, and Investigations
    II. Gastroenterology Referral
    III. Treatment Goals
    IV. Education
    V. Revisit Guidelines

Printed Report



AILF Risk Score Report

Patient_id : APJ123456 | Name : John Doe | Age : 34
Gender : Female | Location : Hyderabad | Phone : 9876543210
Date of Report : 30-9-2024

Atrributes

Height	155	Weight	88	Bmi	36.62
Albumin	10	Alkphos Alkaline Phosphotase	161	Cholesterol	122
Ldl Cholesterol	100	Platelet Count	2	Sgot	70
Sgpt	122	Total Bilirubin	10	Total Protiens	20
Fatty Liver	No	Liver Disease	0	Hypertension	No
Dyslipidaemia		Diabetes	HBA1c	Alcohol	Current
Liver Disease History	NASH				

PATIENT RISK SCORE

Risk Status: Moderate Risk

Patient Score: Probability of High Fibrosis (F2 - F4) -

AI Score: AI Score (1 - 10) [F2 - F4] Score -

This report is accessed by Dr Shiv Kumar

Date: 30-9-2024 | Page 1/3

Patient_id	: APJ123456	Name	: John Doe	Age	: 34
Gender	: Female	Location	: Hyderabad	Phone	: 9876543210

Date of Report : 30-9-2024

RECOMMENDED PROTOCOL

LAB INVESTIGATION

Complete Blood Count, Fasting & Post Prandial Blood Sugar, Liver Function Tests, HBA1

DIAGNOSTICS AND IMAGING

Assess Cardiovascular Risk with ECG, 2D Echo USG Abdomen Elastography / MR Elastograph

REFERRAL

Gastroenterologist (Routine)

TREATMENT GOALS

TREAT primary conditions, if any Medical Treatment (Prevention) of NAFLD Optimize Metabolic Risk Factors – Diet & Physical Activity

EDUCATE ON

EDUCATE on lifestyle management and Alcohol Use Cessation

TEST FOLLOW UP

REPEAT VISIT every 6 months or earlier for: – Adults of any age if Diabetes, Dyslipidemia, Obesity and Fatty Liver persists as risk factors – Symptoms of Chronic Liver Disease – Any other Surgical or Other Procedural Interventio

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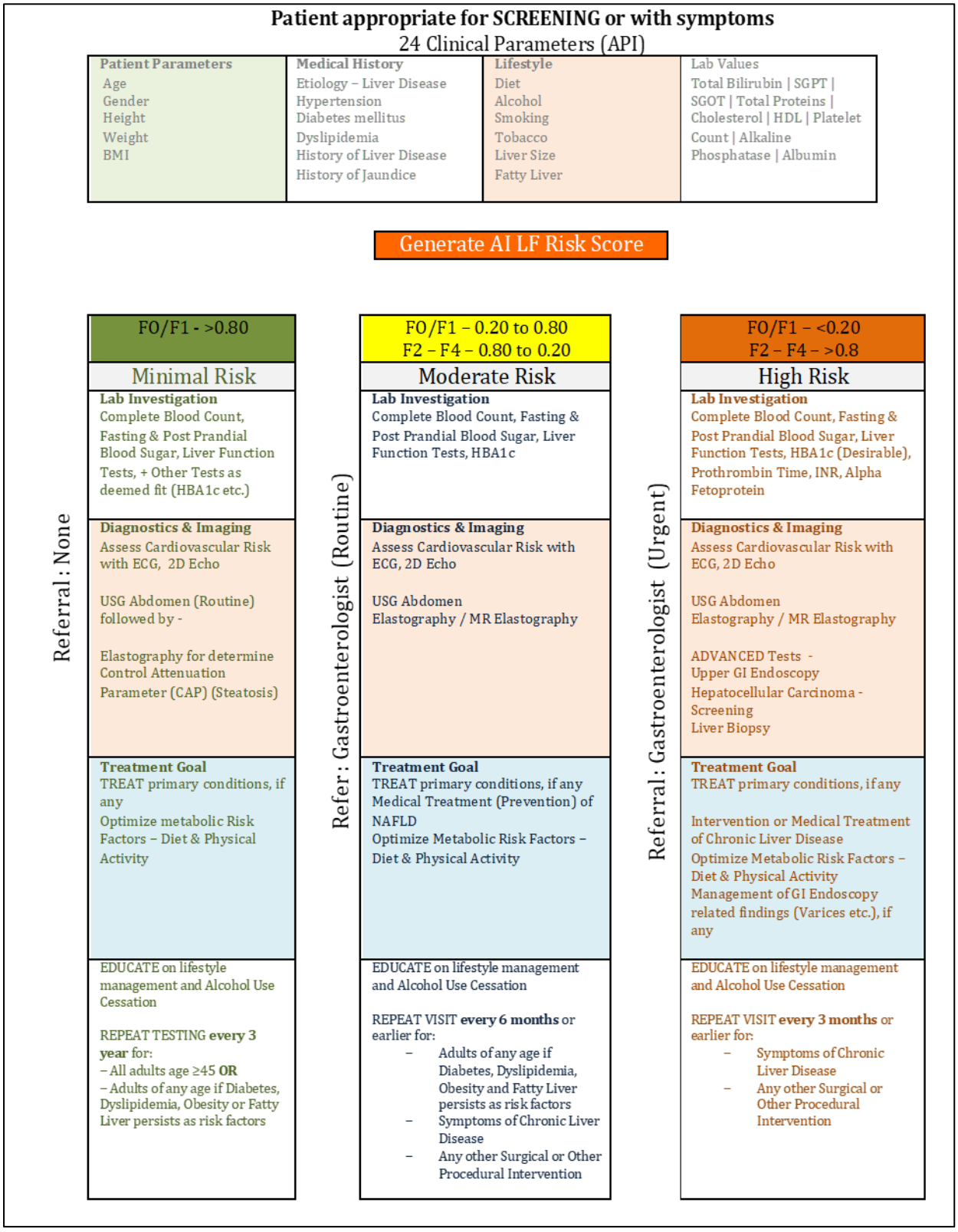
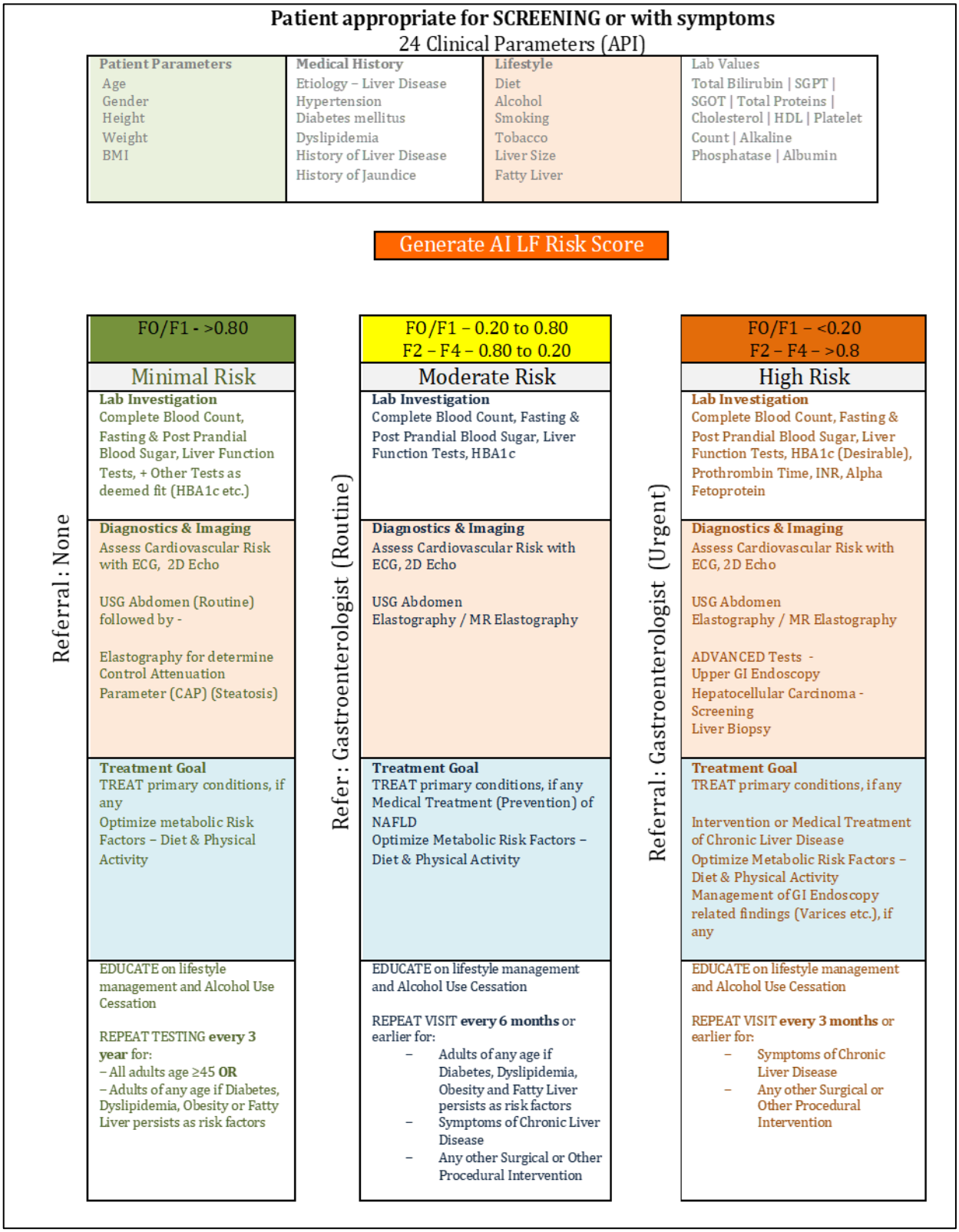
Date: 30-9-2024 | Page 3/3

Clinical Algorithm





The Research

Multivariable Liver Fibrosis staging prediction using machine learning in Nonalcoholic Fatty Liver Disease (AI-LF)

Introduction

Nonalcoholic fatty liver disease (NAFLD) has emerged to be a global epidemic and is the most common liver disease worldwide, ranging from isolated steatosis to steatosis plus inflammation with or without fibrosis. The objective of this study is to develop and validate a Machine Learning Model to identify and distinguish advanced fibrosis using Elastography and Liver Biopsy.

Methodology

Data of 5150 NAFLD patients (Advanced Fibrosis F2-4 – 30.34%) was collected from Apollo Hospitals, Kolkata period 2011 to 2017 using a standardized template and electronic medical records (ICD 10 codes). 25 Clinical and Laboratory parameters were studied along with patients' Elastography reports and ARFI values. The Machine Learning (ML) modeling was performed using the eXtreme Gradient Boosting (XGB) algorithm. The prospective validation cohort was selected of 1261 patients (F2-4 – 31.24%) from 2018 to 2020 and compared with the Fib4 Score. This was further validated with 98 Liver Biopsies from the validation cohort.

Results

Out of the 25 clinical and laboratory parameters, 11 variables including Age [Multivariate Odds Ratio (OR)– 3.39; 95%CI 2.99 – 3.84], History of Diabetes Mellitus [OR – 6.80, 95%CI 5.92 – 7.81], Albumin [OR– 3.70, 95%CI 3.25 – 4.20], Aspartate aminotransferase (AST) [OR- 3.65, 95%CI – 3.21 – 4.16}, Total Bilirubin [OR– 3.13, 95%CI 2.76 – 3.56] and Platelet Count [OR–2.74, 95%CI 2.40 – 3.13] were found to be significant. The performance parameters of the development model are an AUC ROC Score of 0.94 and the validation cohort had the AUC and accuracy of 0.88. The AUC for the 98-liver biopsy validation cohort was 0.83. The model performed better than the Fib4 Score with Net Reclassification Improvement (NRI) at 0.499.

Conclusion:

The model comparing Advanced Liver Fibrosis (F2-4) from No or Low Fibrosis (F0/F1) provides insights into the Clinical and Laboratory Parameters and accurately predicts the onset of liver fibrosis in NAFLD patients which could be useful as clinical decision support in low-cost settings.

Table – Comparison between the AILF model vs FIB4

	AILF		FIB 4	
Source of Algorithm / API	Internal		https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis	
Confusion Matrix	F2-F4	F0/FI	Fibrosis	No Fibrosis
Positive Cases (Advanced Fibrosis F2-F4): 394	291	103	191	203
Negative Case (No / Low Fibrosis F0/F1): 867	86	781	74	793
Calculation Details Performed At: https://www.medcalc.org/calc/diagnostic_test.php				
Sensitivity	77.19% (72.62% to 81.33%)		72.08% (66.26% to 77.39%)	
Specificity	88.35% (86.05% to 90.39%)		79.62% (76.98% to 82.08%)	
Positive Likelihood Ratio (PLR)	6.62 (5.48 to 8.01)		3.54 (3.06 to 4.08)	

Negative Likelihood Ratio (NLR)	0.26 (0.21 to 0.31)	0.35 (0.29 to 0.43)
Positive Predictive Value	73.86% (70.03% to 77.35%)	48.48% (44.90% to 52.07%)
Negative Predictive Value	90.08% (88.28% to 91.63%)	91.46% (89.81% to 92.88%)
Accuracy	85.01% (82.92% to 86.94%)	78.03% (75.64% to 80.29%)
NRI (AILF on FIB4) NRI+ (F2-F4) NRI- (F0/F1)	0.499 0.196 0.302	

Authors: Mahesh Goenka, Gajanan Rodge, Enam Murshid Khan, Usha Goenka, Bharath Potla and Sujoy Kar

Ethical Perspectives

Title	Multivariable Liver Fibrosis staging prediction using machine learning in Nonalcoholic Fatty Liver Disease (AI-LF)	Centers	India – Apollo Hospitals - Kolkata
Principal Investigators	Mahesh Goenka | Gajanan Rodge | Sujoy Kar	Institutional Ethics Committee Approval	November 2020
Data	Retrospective – Prospective Jan 2011 to June 2020 September 2021 Onwards	Safety	Model advocates risk scores that are interpreted by clinicians through safe Machine (API) – Human (Clinician) Interaction
Sample Size + Missing Data	6509 [13455 – dropped 6946 Patients - data due to missing data] No imputations	Inclusiveness & Fairness	At admission data includes clinical comorbidities & conditions | No socioeconomic discrimination
Personal Health information	De-identified all PHI during analysis, model building, API hosting and Prospective Use	Privacy & Confidentiality	Data secured at Apollo Azure Tenant with all relevant compliance + conforming to laws
Addressing Bias (Geographical / Ethnic / Temporal / Gender etc.)	Multiethnic – All Adult Population Group – Male to Female – 55 : 45 – Time Period – Jan 2011 to June 2020 Automation Bias addressed at API Clinical Use	Accuracy + Efficacy	Classification Metrics - sensitivity: 0.77 | specificity: 0.88 | Accuracy Score : 0.85
Risk Groups	Low – Moderate – High Risk of Liver Fibrosis in NAFLD Patients	Informed Consent	Yes – Template & Protocol (Prototype Attached)
Model Specification	XGB Classification + XGB Regression Hazard Ratio + KM Plots	API – Ease of Use + Interpretation	Flows to Clinical Algorithm Standard Clinical Definitions + Lab Units Used
Clinical Algorithm Update (Version)	Version 2 – August 2021	Validation + Peer Review	Accepted by American College of Gastroenterology – ACG 2021 (October) Invite to Publish in Lancet G&H
Intellectual Property Rights (IPR)	Patent No|202441065931	Certifications & Compliance	ISO 13485:2016 Certification | MD 763515 CDSCO Application No | Apollo-Hyder-TE/M/MD/007509

Frequently Asked Questions

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Is this a diagnostic tool?

This is not a diagnostic tool and it does not guarantee the accuracy of the result and cannot be independently acted upon.

Does this contradict the Physician's view?

This Risk score and Clinical Algorithm is a general guideline for Physicians. Any additional laboratory investigations, Diagnostic Imaging, Treatment, or Patient Education related to lifestyle management is under the Physician's or Gastroenterologist's discretion.

How does one ensure the accuracy of the AI-LF tool?

To ensure the information in the report is up to date, accurate, and correct, the Doctor shall be consulted for interpretation of the report. Additionally, the input data should be accurate and as per the conventional metrics used.

Is this a substitute for any diagnostic test or clinician's advice

Absolutely Not. This is an adjunct tool made with Clinical Features and History of the Patient. It doesn't substitute for any tests or advice.

What are the disclaimers for the use of this tool?

a. Apollo Hospitals and its Staff do not offer any assurance on the information made available or be liable for any loss or damage as the said report is based on the AI Liver fibrosis Risk Score without any intervention from their side.
b. By usage of the AI Liver Fibrosis Risk Score, it is deemed that the beneficiary of this service has agreed to get the same done at his own risk and further agrees with this disclaimer without any limitation or any clauses or sub-clauses.

Can the report be shared with other clinicians?

Yes, each patient shall get a printed report or PDF copy which can be kept by the patient maintaining privacy and confidentiality.

Is this tool validated for research ethics committees?

Yes. Institutional Ethics Committee Approval for All Centers has been Obtained and annually followed.

How is Safety addressed?

The model advocates risk scores clinicians interpret through a safe machine (API) – human (clinician) interaction. Informed consent from each individual is obtained before the Risk Score generation.

Definition of Clinical Terms

BMI

A. Underweight, <18.5 kg/m2
B. Normal, 18.5 ≤ BMI < 25 kg/m2
C. Overweight, 25 ≤ BMI < 30 kg/m2
D. Obesity
    a. Obesity I, 30 ≤ BMI < 35
    b. Obesity II, 35 ≤ BMI < 40 kg/m2
    c. Obesity III, ≥ 40 kg/m2

Source: Centers for Disease Control and Prevention: Overweight and obesity. Available at: http://www.cdc.gov/nccdphp/dnpa/obesity/.

Hypertension/High Blood Pressure

A. Two hypertension diagnoses (≥14 days apart)

B. A hypertension diagnosis and a hypertension medication prescription
    a. angiotensin-converting enzyme inhibitors (ACE),
    b. angiotensin II receptor blockers (ARB),
    c. beta blockers,
    d. calcium channel blocks, and/or
    e. diuretics
C. A hypertension diagnosis and
    a. systolic blood pressure average ≥ 140 (if at least two results ≥ 14 days apart), or
    b. diastolic blood pressure average ≥ 90 (if at least two results ≥ 14 days apart)

Source: Tania B. Babar M.D.: Ferri's Clinical Advisor 2019, 729-735.e5

Elevated Lipids / Dyslipidaemia

1. An elevated lipids diagnosis
2. A prescription for elevated lipids medication
    a) statins or statin combinations
    b) fibrates
    c) niacin
    d) bile acid sequestrates, and/or
    e) other lipid-modifying agents
3. Lab results
    a) triglyceride level ≥250 mg/dL
    b) HDL <40 mg/dL for males and <50 mg/dL for females.
    c) non-HDL value ≥ 160 mg/dL

Source: National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels Preventive Cardiology: Companion to Braunwald's Heart Disease

Family History of Diabetes

1. A diagnosis of a family history of diabetes, or
2. A record in the Medical Record denoting family history of diabetes

Diabetes Mellitus - The American Diabetes Association (ADA) defines Diabetes Mellitus as follows:

1. A fasting plasma glucose (FPG) ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 hr.
2. Symptoms of hyperglycemia and a casual (random) plasma glucose ≥200 mg/dl. Classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss. (At the time of diagnosis as a diabetic, B cell function is at 25% to 30%.)
3. An oral glucose tolerance test (OGTT) with a plasma glucose ≥200 mg/dl 2 hr after a 75 g (100 g for pregnant women) glucose load.
4. A haemoglobin A1c (HbA1c) value ≥6.5%.

Source - David Domenichini M.D. : Ferri's Clinical Advisor 2019, 424-433.e2

Diet:

1. Vegetarian – Diet which is plant-based with adequate servings of fruits and vegetables
2. Non-Vegetarian – Diet which includes predominantly Meat, Poultry, Fish, and Eggs for more than 4 servings per week.
3. Mixed - Diet which includes Meat, Poultry, Fish, and Eggs for 4 or fewer servings per week and includes fruits and vegetables.

Source – Adapted from Cleveland Clinic

Alcohol - If a person is currently drinking Alcohol or in the past or does not drink
Smoking – If a person is Currently smoking or Past (6 or more months back) or does not smoke
Tobacco – If a person is currently using/chewing tobacco or in the Past (6 or more months back) or does not use tobacco

Liver Disease
Individuals with signs and symptoms of Liver Disease like, Skin and eyes that appear yellowish (jaundice), Abdominal pain and swelling, Swelling in the legs and ankles, Itchy skin, Dark urine color, Chronic fatigue, Nausea or vomiting, Loss of appetite and Tendency to bruise easily. It also includes derangement of Liver Function Tests (described below) and/or findings of Fatty Liver or Fibrosis in Ultrasound or other imaging techniques of the Upper abdomen or Liver.

Ref: Mayo Clinic

Liver Details (From Previous Ultrasound Reports) –

1. Liver Size - Normal or Enlarged
2. Fatty Liver – Yes / No

Liver Disease History - Any previous diagnosis of

i. Alcoholic Hepatitis
ii. Infectious Hepatitis
iii. NASH
iv. Other Liver Diseases

Laboratory Parameters (Recent in past 1 month)

1) Total Bilirubin in mg/dl
2) Alkaline Phosphatase in IU/dl
3) SGPT in IU/dl
4) SGOT in IU/dl
5) Total Proteins in gm/dl
6) Albumin in gm/dl
7) Cholesterol in mg/dl
8) HDL Cholesterol in mg/dl
9) Platelet Count