

Fatty Liver Index is a valid predictor of non-alcoholic fatty liver disease (NAFLD) in pregnancy

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ABSTRACT

Background Despite the evidence for adverse pregnancy outcomes, non-alcoholic fatty liver disease (NAFLD) is not routinely addressed in early pregnancy. The Fatty Liver Index (FLI) has been proposed as a screening tool for NAFLD in the general population. We aim to develop mathematical models for predicting NAFLD in pregnancy and validate the FLI for first-trimester pregnant women.

Methods Biochemical and biophysical parameters were analysed in pregnant women with period of gestation <12 weeks was done among Rajarata Pregnancy Cohort, Sri Lanka. Fatty liver was graded as (FLG) 0, I or II by ultrasound scan. Binary logistic regression models were employed to identify the factors predicting FLG-II. Six FLIs were developed to predict FLG-II. Validity of the FLIs was compared using the receiver operating characteristic curves.

Results The study sample consisted of 632 pregnant women with a mean age of 28.8 years (SD: 5.8 years). Age (OR: 1.6, 95% CI 1.1 to 2.3), body mass index (OR: 1.7, 95% CI 1.1 to 2.5) and gamma-glutamyl transferase levels (OR: 2.1, 95% CI 1.5 to 3.0) were the independent predictors of FLG-II. While the model with liver enzymes provided the best prediction of NAFLD (both FLG I and II) (area under the curve [(AUC)]: 0.734), the highest AUC (0.84) for predicting FLG-II was observed with the full model (model with all parameters). The proposed budget model (AUC >0.81) is the best model for screening fatty liver in community health setup.

Conclusion FLIs could be used as screening tools for NAFLD based on resource availability in different settings. External validation of the FLI and further investigation of the proposed FLI as a predictor of adverse pregnancy outcomes are recommended.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an emerging global health concern worldwide because of its increasing incidence in recent decades.¹ The exact prevalence of NAFLD has not been evaluated properly due to low accuracy in assessing the fat content of the liver.^{2–4} However, in the past 12 years, the reported prevalence has increased from 8.2% to 10.9% worldwide, and highest among Asians.⁵ NAFLD is associated with several

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Screening for NAFLD is not a routine practice in pregnancy care despite its' adverse maternal outcomes, especially in low- and middle-income countries. The Fatty Liver Index (FLI) has been proposed as one of the screening tools for NAFLD in the general population, but it is not validated for pregnancy.

WHAT THIS STUDY ADDS

⇒ Six models (FLIs) were generated by using biochemical investigations and anthropometric parameters, and the validity was assessed compared with the original FLI proposed by Bedogni *et al*

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The predictive models could be used as a screening tool for NAFLD, especially in community healthcare setup. Early identification of NAFLD and prompt interventions would minimise the global burden of the disease, hence improve maternal mortality and morbidity.

metabolic diseases, and it is a major predictor of non-communicable diseases.^{6,7} NAFLD is considered the most common condition that causes derangement of biochemical parameters of the liver, and it is a well-recognised cause of liver-related deaths in early childhood.⁸ In addition, it represents a spectrum of disease extending from non-alcoholic steatohepatitis (NASH) to cirrhosis and hepatocellular malignancies. NASH is the leading cause of liver transplantation worldwide and increases the risk of liver-related, cardiovascular and overall morbidity and mortality. Nevertheless, clinical symptoms and signs of fatty liver (FL) are not present in the early stages of the disease, which limits early identification and intervention in the context of FL.⁹ Furthermore, although dietary interventions are the main preventive strategy for FL, this practice usually fails to control the disease.¹⁰ Screening for FL using simple

methods is important for the early diagnosis and prevention of liver-related morbidity and mortality.

NAFLD has been reported as one of the underlying causes of indirect maternal deaths because it is complicated with diabetes in pregnancy, hypertension, pre-eclampsia and miscarriages.^{11–18} Evidence suggests that the early identification of FL can minimise adverse maternal outcomes because it can predict many complications such as gestational diabetes mellitus.^{8, 19} NAFLD can predict metabolic syndrome, coronary artery disease, hypertension and colorectal carcinoma.^{8, 14, 15, 20–23} However, detecting FL during early pregnancy is still not a routine procedure.

Though liver biopsy is the gold standard, it cannot be used because of the invasiveness of the test.^{24–26} Therefore, imaging modalities, such as MRI and ultrasound scanning (USS), are often used to diagnose FL. At the same time, these imaging modalities are costly and require technical experts to perform and interpret the findings; moreover, they are not feasible in field set-ups, where most screening procedures for pregnant women are performed.^{27–30} The concept of the Fatty Liver Index (FLI) was first proposed by Bedogni *et al* in 2006 to predict FL for the general population.⁹ The FLI is a simple and easy tool that includes waist circumference (WC), body mass index (BMI), serum triglyceride level and serum gamma-glutamyl transferase (GGT) to predict FL. It has been validated in several countries, such as Iran, Japan and China, and the results have confirmed that FLI has the ability to separate the NAFLD group from the non-NAFLD group, with an area under the curve (AUC) of >0.8.^{20, 31, 32} However, the applicability of FLIs in pregnancy has not been reported in the literature. The purpose of this study was to generate new FLIs to predict FL grade II (FLG-II) in early pregnancy.

METHODOLOGY

Study setting

This study was carried out as part of a large population-based prospective cohort study, namely, the Rajarata Pregnancy Cohort (RaPCo). The full RaPCo study design has been published elsewhere.³³

Recruitment of participants and data collection procedure

Study participants were pregnant women at less than 12-week gestation, who were registered in the field antenatal clinics of Anuradhapura district under Sri Lanka's routine antenatal care programme at the time of recruitment. Participants were recruited from 1 July 2019 to 30 September 2019 during special clinics conducted in all Medical Officers of Health areas. The RaPCo study had a recruiting percentage of more than 90% of newly registered pregnant women in the Anuradhapura district. A subsample from the original RaPCo group was obtained using two-stage cluster sampling. Mothers were excluded from the study if their gestational age was uncertain; they had a history of diabetes or diagnosed liver diseases; they

were suffering from any type of chronic illness, such as chronic hypertension, epilepsy, metabolic disorder or thyroid disorder; their ultrasounds showed evidence of chronic liver diseases or any pathological liver conditions except FL; or their daily alcohol consumption was more than 20 g/day.

All pregnant women who attended the clinic were given an information leaflet. Informed written consent was obtained following a detailed explanation. The initial baseline assessment included an interviewer-administered questionnaire, anthropometric measurements and blood sample collection for biochemical tests.

Clinical evaluation and anthropometric measurements

An interviewer-administered questionnaire was used to take clinical history. Blood pressure and anthropometric measurements, including height, weight, waist and hip circumference (HC), were taken by using quality equipment and measured and recorded in standard units according to the standard WHO protocol. For the calculation of BMI and waist to hip ratio (W/H ratio) in pregnant women, we used standard calculation methods and ranges for the normal Asian adult population.³⁴ Some data were obtained from maternal pregnancy records.

Biochemical analysis

Venepuncture was performed by a well-qualified nursing officer, who adhered strictly to universal precautions. Ten-millilitre blood samples were taken using several tubes. Every pregnant woman underwent a one-step method of screening for hyperglycaemia. Venous blood was collected in potassium fluoride/Na₂ EDTA tubes for fasting plasma glucose testing. All pregnant women, except those with prediagnosed diabetes mellitus, underwent re-venepuncture to collect plasma in potassium fluoride/Na₂ EDTA tubes for the 2-hour oral glucose tolerance test (OGTT). Other blood samples were collected for lipid profile and aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT and serum creatinine tests. Every blood sample was transported to the public health research laboratory with optimum temperature and time of sample collection for analysis. All blood investigations were analysed using a Mindray BS-240 Clinical Chemistry Analyser.

Evaluation of NAFLD

Abdominal ultrasound was performed in the first trimester under the supervision of a consultant radiologist with a Toshiba Xario 100 machine with colour Doppler, grayscale, power Doppler and spectral Doppler capabilities and curvilinear array transducer in the range of 2–5 MHz. Occasionally, a high-resolution linear array transducer in the range of 4–8 MHz was used to assess the liver surface. More than 5 images were taken from participants after 6 hours of fasting. The images were re-examined by consultant radiologists on the same monitor under the same lighting conditions. At the time of scanning, the radiologist (the fourth author) and main

author were blinded to the patients' clinical and laboratory data and unaware of previous reports. Diagnosis of FL was made using the ultrasound criteria for FL based on the findings of both radiologist and the main author.²⁹ When there was a disagreement between the two authors regarding the grade of FL, the final grade was decided based on the consensus.

Statistical analysis

All statistical analyses were conducted using a beta version of SPSS software. The total sample was separated into two groups. Group 1 included participants with FLG-II, and group 2 included both FLG-I and FLG-0. Initially, categorical variables of the two groups were compared using the χ^2 test, and continuous variables were compared using a two-sample t-test. Although some variables did not follow the normal distribution, we still used a two-sample t-test, assuming the normality of the sampling distribution according to the central limit theorem. All significant variables ($p < 0.05$) from the χ^2 test and two-sample t-test were included in the multivariate analysis. Binary logistic regression with backward selection method was performed as a multivariate analysis to identify the independent predictors of FLG-II. Hosmer and Lemeshow test was used as the goodness of fit test and non-significant p value indicates that the model-estimated probabilities agree with the observed outcomes. The χ^2 test was used to test whether the model was significantly improved with the added parameters, and significant p value indicates that the model is significantly better than the constant only model.

Six models (six FLIs) were created for the use of different practical requirements (table 1).

The final probability (FLI score) of FLG-II of each patient was calculated for all six FLIs. The receiver operating characteristic (ROC) curves were plotted for the FLI scores of all six models by considering the two original FL groups as the binary variable (FLG-II vs others). Then, the FLI score for each patient in our database was calculated using the model proposed by Bedogni *et al*, and the AUC was calculated using ROC curves, as mentioned above. The AUC of all six FLIs was compared with the AUC in Bedogni *et al*'s model. Finally, the sensitivity, specificity and likelihood ratios of the full model at each cut-off level of the FLI were calculated. The models are summarised in table 1.

RESULTS

Socio-demographic data of the study participants

In total, 632 pregnant women at a gestation of ≤ 12 weeks were recruited. The mean age of the sample was 28.95 years (SD: 5.8 years), and most (55.2%) were in the age category of 21–30 years. Most (31.5%) of the mothers had completed postprimary education. These data have already been published elsewhere.¹⁹

Of the pregnant women recruited, 324 (51.2%) had either FLG-I (n=234, 37%, 95% CI 33% to 41%) or FLG-II (n=90, 14%, 95% CI 12% to 17%). None of the participants had FLG-III.

Online supplemental table 1 summarises the categorical variables (factors) associated with FLG-II in bivariate analysis. Multiparity was the only significant factor associated with FLG-II.

Table 2 summarises the continuous variables associated with FLG-II and the results of the two-sample t-test.

Table 1 Description of the six models and underlying rationale for the model

Model number	Model name	Supplementary table	Description
1	Full model	Online supplemental table 2	All the parameters studied are included (socio-demographic, biophysical and biochemical values)
2	Non-invasive model	Online supplemental table 3	All the non-invasive parameters are included. This model can be used in any community health set-up with minimal equipment
3	Budget model	Online supplemental table 4	In addition to the non-invasive model, this model includes low-cost biochemical parameters.
4	Model without liver enzymes	Online supplemental table 5	The highest number of missing values in this study is from AST, ALT and GGT. This model was created to avoid the effects of the above missing values. This model includes all parameters in the full model except AST, ALT and GGT
5	Model with non-invasive parameters and liver enzymes	Online supplemental table 6	This model was created to determine the effect of liver enzymes together with non-invasive parameters
6	Model with anthropometric parameters and lipid profile	Online supplemental table 7	This model was created to determine the effect of lipid profile together with non-invasive parameters

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Table 2 Covariates associated with FLG-II (bivariate analysis)

Variable	FLG-II (total N=90)		FLG-1 and FLG-0 (total N=542)		T value	P value
	N	Mean (SD)	N	Mean (SD)		
Age	87	31.2 (5.4)	515	28.4 (5.6)	4.3	<0.0001
AST	65	20.3 (9.3)	385	17.1 (4.9)	4.1	<0.0001
ALT	66	22.8 (14.5)	379	16.1 (8.1)	5.3	<0.0001
GGT	66	22.5 (14.0)	382	14.2 (7.6)	7.0	<0.0001
Systolic BP	90	107.3 (11.5)	529	101.7 (11.0)	4.4	<0.0001
Diastolic BP	90	68.0 (9.2)	529	64.8 (8.0)	3.3	0.001
BMI	85	27.2 (3.9)	507	22.7 (4.4)	8.7	<0.0001
W/H ratio	86	0.88 (0.06)	503	0.82 (0.07)	6.3	<0.0001
FPG	89	83.2 (16.8)	535	78.5 (12.3)	3.1	0.001
2nd hour PG value of OGTT	87	123.4 (34.0)	526	108.9 (26.2)	4.5	<0.0001
Total cholesterol	86	174.4 (34.5)	511	163.3 (33.7)	2.7	0.005
Triglycerides	87	102.3 (44.0)	514	77.5 (34.4)	5.9	<0.0001
LDL	85	129.5 (30.3)	501	114.0 (30.2)	4.3	<0.0001
HDL	88	44.4 (11.5)	514	49.2 (11.7)	-3.5	<0.0001
Serum creatinine	88	51.6 (7.2)	521	49.4 (8.5)	2.3	0.022
Blood urea	89	2.1 (0.5)	517	2.3 (0.6)	-1.8	0.064
Haemoglobin	89	12.0 (0.9)	524	11.7 (1.0)	2.6	0.009

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; FLG, fatty liver grade; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; PG, plasma glucose; W/H, waist to hip.

All the demographic, biophysical and biochemical variables except blood urea were significantly associated with FLG-II at a p value <0.05. Only high-density lipoprotein (HDL) levels showed a significant negative effect toward FLG-II.

Online supplemental table 2 shows the prediction model (model 1: full model) results for FLG-II using all the significant factors in table 2 and online supplemental table 1. Among 331 participants included in the full model, 54 (16.3%) had FLG II. There were 303 cases that were not included in the analysis because of having at least one missing value. The χ^2 statistic was significant (p<0.0001) and Hosmer and Lemeshow statistic was not significant (p=0.75). Increased levels of GGT, W/H ratio, BMI, minimum systolic blood pressure (SBP) and age were the independent predictive factors of FLG-II.

Based on model 1, the generated FLI is as follows:

$$FLI = e^{(-2.1 + (0.48 * ZAge) + (0.74 * ZGGT) + (0.3 * ZSBP) + (0.55 * ZBMI) + (0.35 * ZW/H))} / (1 + e^{(-2.1 + (0.48 * ZAge) + (0.74 * ZGGT) + (0.3 * ZSBP) + (0.55 * ZBMI) + (0.35 * ZW/H))})$$

Online supplemental table 3 shows the prediction model results for FLG-II using non-invasive significant factors identified via bivariate analysis (non-invasive model). Among 537 participants included in the non-invasive model, 81 (15.08%) had FLG-II. Only 97 cases were excluded from the analysis; this was because missing values were minimal in the non-invasive parameters. This model had the lowest number of missing values and this is the parsimonious model with minimal number of

missing values. The χ^2 statistic was significant (p<0.0001). However, Hosmer and Lemeshow statistic was also significant (p=0.08). Increased W/H ratio, BMI, minimum SBP and age were the independent predictive factors of FLG-II.

According to the model described in online supplemental table 3, the FLI is as follows:

$$FLI = e^{(-2.19 + (0.31 * ZAge) + (0.29 * ZSBP) + (0.71 * ZBMI) + (0.46 * ZW/H))} / (1 + e^{(-2.1 + (0.31 * ZAge) + (0.29 * ZSBP) + (0.71 * ZBMI) + (0.46 * ZW/H))})$$

Online supplemental table 4 indicates the prediction model results for FLG-II using low-cost parameters (budget model). Among 422 participants included in the budget model, 77 (18.2%) had FLG II. Although fewer parameters are included, the χ^2 statistic was significant (p<0.0001) and Hosmer and Lemeshow statistic was not significant (p=0.31). Other than the significant factors observed in the full model, the increased creatinine level and second-hour plasma glucose value of OGTT independently predict FLG-II. In this model, age is still not an independent predictor.

According to the model described in online supplemental table 4, the FLI is as follows:

$$FLI = e^{(-2.19 + (0.25 * ZCreatinine) + (0.3 * ZSBP) + (0.72 * ZBMI) + (0.41 * ZW/H) + (0.36 * ZOGTT))} / (1 + e^{(-2.1 + (0.25 * ZCreatinine) + (0.3 * ZSBP) + (0.72 * ZBMI) + (0.41 * ZW/H) + (0.36 * ZOGTT))})$$

In addition to these three models outlined above, three other models were created to incorporate different practical requirements. Online supplemental table 5

comprises the prediction model results for FLG-II using all the significant parameters identified by the bivariate analysis except AST, ALT and GGT. Of all the predictive factors included in the full model, the highest number of missing values was observed for AST, ALT and GGT. Therefore, this model was created to overcome the effect of these missing values of the liver enzymes. Among the 464 participant included in this model, 72 (15.5%) had FLG II. Only 170 cases were excluded in the analysis of this model, whereas 303 cases were excluded in the full model. The χ^2 statistic was significant ($p < 0.0001$) and Hosmer and Lemeshow statistic was not significant ($p = 0.44$). Other than the significant factors observed in the full model, an increased creatinine level, the second-hour PG value of OGTT, total cholesterol and lowering of HDL independently predicted FLG-II. Age was not an independent predictor in this model.

Online supplemental table 6 shows a model created using non-invasive variables and liver enzymes. This model is also significant and can be applied to people with information on the included variables. Among the 386 participant included in this model, 62 (16.06%) had FLG II. The χ^2 statistic was significant ($p < 0.0001$) and Hosmer and Lemeshow statistic was not significant ($p = 0.94$). Online supplemental table 7 includes the prediction model results for FLG-II using anthropometric and lipid profile parameters. Among the 491 participant included in the full model, 74 (15.07%) had FLG II. The χ^2 statistic was significant ($p < 0.0001$) and Hosmer and Lemeshow statistic was not significant ($p = 0.75$). Other than the significant factors observed in the full model, increased total cholesterol and decreased HDL levels independently predicted FLG-II. In this model, age is also not an independent predictor.

According to the model described in online supplemental table 5, the FLI is as follows:

$$FLI = e^{\frac{(-2.24 + (0.32 * ZCreatinine) + (0.3 * ZSBP) + (0.58 * ZBMI) + (0.4 * ZW/H) + (0.35 * ZOGTT) + (0.36 * \text{cholesterol}) + (-0.54 * HDL))}{(-2.1 + 0.32 * ZCreatinine) + (0.3 * ZSBP) + (0.58 * ZBMI) + (0.4 * ZW/H) + (0.35 * ZOGTT) + (0.36 * \text{cholesterol}) + (-0.54 * HDL)}} / \left(1 + e^{\frac{(-2.1 + 0.32 * ZCreatinine) + (0.3 * ZSBP) + (0.58 * ZBMI) + (0.4 * ZW/H) + (0.35 * ZOGTT) + (0.36 * \text{cholesterol}) + (-0.54 * HDL)}{(-2.1 + 0.32 * ZCreatinine) + (0.3 * ZSBP) + (0.58 * ZBMI) + (0.4 * ZW/H) + (0.35 * ZOGTT) + (0.36 * \text{cholesterol}) + (-0.54 * HDL)}} \right)$$

According to the model given in online supplemental table 6, the FLI is as follows:

$$FLI = e^{(-2.2 + (0.5 * Zage) + (0.36 * ZSBP) + (0.58 * ZBMI) + (0.34 * ZW/H) + (0.36 * ZOGTT))} / \left(1 + e^{(-2.1 + (0.5 * Zage) + (0.36 * ZSBP) + (0.58 * ZBMI) + (0.34 * ZW/H) + (0.36 * ZOGTT))} \right)$$

According to the model given in online supplemental table 7, the FLI is as follows:

$$FLI = e^{\frac{(-2.18 + (0.5 * ZHDL) + (0.29 * ZSBP) + (0.59 * ZBMI) + (0.48 * ZW/H) + (0.36 * Ztotal\ cholesterol))}{(-2.1 + (0.5 * ZHDL) + (0.29 * ZSBP) + (0.59 * ZBMI) + (0.48 * ZW/H) + (0.36 * Ztotal\ cholesterol))}} / \left(1 + e^{\frac{(-2.1 + (0.5 * ZHDL) + (0.29 * ZSBP) + (0.59 * ZBMI) + (0.48 * ZW/H) + (0.36 * Ztotal\ cholesterol))}{(-2.1 + (0.5 * ZHDL) + (0.29 * ZSBP) + (0.59 * ZBMI) + (0.48 * ZW/H) + (0.36 * Ztotal\ cholesterol))}} \right)$$

Table 3 compares the AUC values of the model published by Bedogni *et al* and the six models introduced in this paper. The AUC values of the full model, non-invasive model, low-cost model and liver enzyme models were higher than the AUC of Bedogni *et al*'s model for separating FL from non-FL groups. In addition, AUC values of the full model and liver enzyme models were higher than in Bedogni *et al*'s model for separating the FLG-II group from the FLG-I/0 group.

Table 4 includes the sensitivity, specificity, positive and negative predictive values and likelihood ratios of the full model in diagnosing FLG-II at each cut-off level of FLI. Considerably higher sensitivity and specificity values were achieved with minimum and maximum cut-off levels of 10–20. Values of 12.3 and 19.1 are included based on the fact that either one of the two values (sensitivity or specificity) should be more than 80% and the other should not be less than 70%. The positive predictive value is lower with the above sensitivity and specificity values, whereas the negative predictive value is higher. Yield is almost compatible with the proportion of FLG-II in the sample, which is 11%–13%.

Table 5 shows the best cut-off values of the six models to achieve the best specificity by keeping >80% sensitivity. According to this, the full model (model 1) performed better than all the others, whereas the non-invasive model's performance was inferior to that of the full model but was superior to all other models.

DISCUSSION AND INTERPRETATION

NAFLD is a known metabolic disease that increases foeto-maternal morbidity and mortality.³⁵ Several

Table 3 Model comparison using ROC curves

Model	FL vs non-FL			FLG-II vs FLG-I and FLG-0		
	AUC	95% CI	P value	AUC	95% CI	P value
Bedogni <i>et al</i> ⁹	0.718	0.67 to 0.77	<0.0001	0.821	0.77 to 0.87	<0.0001
Full model	0.731	0.68 to 0.78	<0.0001	0.843	0.79 to 0.89	<0.0001
Non-invasive	0.731	0.68 to 0.78	<0.0001	0.815	0.76 to 0.87	<0.0001
Without liver enzymes	0.703	0.65 to 0.76	<0.0001	0.809	0.75 to 0.87	<0.0001
Low cost	0.720	0.67 to 0.77	<0.0001	0.817	0.76 to 0.87	<0.0001
With liver enzymes	0.735	0.68 to 0.79	<0.0001	0.842	0.79 to 0.89	<0.0001
With lipid profile	0.702	0.65 to 0.76	<0.0001	0.808	0.75 to 0.86	<0.0001

AUC, area under the curve; FL, fatty liver; FLG, fatty liver grade; ROC, receiver operating characteristic.

**Table 4** Sensitivity, specificity, predictive values and likelihood ratios of the full model at each of the FLI cut-off level

FLI cut-off point	Number of patients more than cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Yield (%)	Positive likelihood ratio	Negative likelihood ratio
≥5	61	98.4	36.3	22	99	16	1.54	0.04
≥10	56	90.3	57.4	28	97	14	2.12	0.17
≥12.3	51	81.7	70.1	34	95	13	2.73	0.26
≥19.1	44	71.7	80.1	40	94	11	3.59	0.35
≥20	43	69.4	80.7	40	93	11	3.60	0.38
≥30	35	56.5	89.4	50	92	9	5.33	0.49
≥40	27	43.5	94.0	58	90	7	7.25	0.60
≥50	18	29.0	96.4	60	88	5	8.06	0.74
≥60	11	18.0	98.5	69	87	3	12.00	0.83
≥70	9	14.5	98.8	69	86	2	12.08	0.87
≥80	6	9.7	99.1	67	85	2	10.78	0.91
≥90	4	7.0	99.7	81	85	1	23.33	0.93

Bold values signify sensitivity and specificity. There is no significance testing. FLI, Fatty Liver Index; NPV, negative predictive value; PPV, positive predictive value.

authors have developed mathematical models to predict NAFLD in the general population.^{20 31 32} After validation, some countries started to use the FLI as a screening tool.^{36 37} FLI predicts metabolic syndrome, coronary artery diseases, hypertension, gestational diabetes mellitus and colorectal carcinoma, making it a useful tool in non-communicable disease prevention.^{19 38–41} However, investigations into FLIs and the utility of FLIs in pregnancy are scarcely discussed in the literature. In general, the validity of the FLI has not been adequately studied in South Asian countries. As NAFLD is a known risk factor for adverse pregnancy outcomes, these models will considerably affect maternal well-being by predicting the disease.

We have created six mathematical models that consider practical applications (table 1). In many low-income and middle-income settings, ultrasound is still not a routine practice in the community set-up, and clinics have to wait for several weeks to conduct an ultrasound because of a lack of availability of resources. Anyway, FL scanning is not in routine practice, and the cost of USS prohibits early identification of FL in routine practice. Nevertheless, all pregnant

women undergo several biochemical investigations during prepregnancy and pregnancy in government hospitals. The proposed models used different parameters that could be applied in almost all settings based on resource availability.

Except for multiparity, none of the socio-demographic factors considered were associated with FLG in the bivariate analysis. Multiparity was previously reported as a predictor of NAFLD.⁴² To the best of our knowledge, this is the only study conducted to see the association between parity and NAFLD. Although there are limited data on the association between parity and NAFLD, this may be due to the confounding effect of ageing when parity increases. The same authors conducted another study and showed that the prevalence of NAFLD is significantly higher with increasing age.⁴³

NAFLD is one of the most common causes of unexplained mild elevation of serum transaminases.⁴⁴ The model using liver enzymes had the highest AUC among the models compared. Several studies have shown that increasing ALT and AST are markers of liver injury and can be described as useful measures of NAFLD. When the degree of FL increases, the degree of liver injury also increases, making it a good predictor of FL.⁴⁴ Banderas *et al*'s study has shown that GGT levels increase when the severity of the disease is increased.⁴⁵ In our study, GGT was also a significant predictor of FLG-II in models 1 and 5.

Several studies conducted worldwide have shown that a high blood glucose level is strongly associated with NAFLD.^{19 46 47} This may be due to alterations in lipid metabolism and inflammation within the adipose tissue and fat deposition in the liver, leading to insulin resistance.⁴⁶ This insulin resistance reduces

Table 5 Cut-off values of the six models to achieve the best specificity by maintaining >80% sensitivity

Model	Cut-off	Sensitivity	Specificity
1	>17.4	80.6	76.4
2	>15.5	80.2	75.0
3	>14.5	80.0	70.9
4	>13.1	81.0	67.9
5	>13.5	80.6	72.8
6	>13.6	80.8	70.0

lipolysis and increases free fatty acid transfer to the liver, causing deposition of extra fatty acids in the liver.⁴⁶ In our study, the second-hour plasma glucose value after the OGTT test was significant in models 3 and 4.

An abnormal lipid profile is a well-recognised factor associated with NAFLD. Our fourth and sixth models showed that increased total cholesterol levels are positively correlated with FL. In contrast, serum HDL levels are negatively correlated with FL disease. The Jinchang cohort study has shown a similar association, and the authors described lipid profile parameters as significant predictors of FL.⁴⁸ The pathogenesis behind this is based on the two-hit hypothesis of the pathophysiology of NAFLD.³⁹ The first hit involves accumulation of triglyceride in hepatocytes, leading to simple FL; in the second hit, oxidative stress occurs because of increased lipid pre-oxidation and high levels of reactive oxygen species, mitochondrial dysfunction and inflammation.⁴⁹ In addition, low HDL levels further increase insulin resistance and lead to hepatic steatosis.⁴⁰

The second model (non-invasive) had the lowest number of missing values and is the parsimonious model. However, goodness of fit test results indicated that the model does not explain the fitted data. According to our second model, a high BMI level and increased W/H ratio are significant predictors for FLG-II. Increased BMI and W/H ratio are good indicators for assessing obesity because of increased free fatty acid uptake from the plasma and de novo synthesis of fatty acids.⁵⁰ FL is an emerging driver of hypertension, cardiovascular disease and other metabolic diseases. Recent cross-sectional studies have shown that the presence and severity of NAFLD are associated with hypertension. Epidemiological evidence has shown that 49.5% of patients with a history of hypertension have NAFLD; hypertension is also significantly higher among people with NAFLD compared with the general population.⁵¹ A cohort study conducted in 2015 showed that even in the absence of other metabolic risk factors, hypertension has a higher risk of developing NAFLD, and it is a good predictor for developing severe FL.³⁹ The pathophysiology behind this is not fully studied, but it is thought to be due to increased insulin resistance, contributing to this association.^{15 39}

Models 3 and 4 found that elevated serum creatinine levels are also predictive of FLG-II. Although there are very limited studies related to this association, one paper has shown that it may be a part of metabolic syndrome.³⁸ In addition, from our model, we have found that a low haemoglobin level is a predictive factor for FLG-II. Growing epidemics have shown that low haemoglobin levels are associated with obesity and NAFLD in women. Hcpidin levels are reduced in patients with iron deficiency anaemia. This will contribute to the development of NAFLD.⁵² Therefore, we can predict FL if a patient has anaemia.

The initial FLI study by Bedogni *et al* identified triglyceride level, BMI, WC and GGT level as the main

predictors of FL disease.⁹ Our findings are consistent with the initial FLI, with slight deviations. We included the W/H ratio instead of the WC or HC.³⁴ In the full model (online supplemental table 2), SBP and age became significant predictors, whereas triglycerides were not identified as significant predictors in Bedogni *et al*'s model. The non-invasive model is a novel concept that we introduced because it does not contain any biochemical investigations. Although the non-invasive model is the parsimonious and lowest cost model, we do not recommend it due to its goodness of fit results. We suggest the low-cost model (model 3) as more suitable to include in the field care set-up considering the statistical significance and relatively lower cost. Also, model 5 (model with liver enzymes) is the best model as the ROC is almost similar to the full model.

As shown in table 4, both sensitivity and specificity of more than 70% could be achieved at an FLI cut-off between 10% and 20%. This indicates higher validity of the full model for community screening. The lower values of the positive predictive value can easily be explained by the lower proportion of FLG-II in the studied sample. It is well known that positive predictive value is less common in settings with a lower prevalence of diseases. At the 10%–20% cut-off level in the FLI score, the yield varied between 11% and 13%. The yield of the acceptable cut-off level of FLI was slightly less than that of the original proportion of FLG-II in the study sample (15.7% in the full model). This indicates that most cases of FLG-II can be identified using this model. Since the negative predictive value is higher in the model, model test-negative patients can be excluded easily.

The population we studied was primarily rural. In settings where the prevalence of FLs is high, the predictive values of FLI could be higher. Therefore, testing the proposed FLIs in different communities is required to investigate the utility of the proposed FLI among pregnant women. More importantly, a prospective analysis of pregnancy outcomes is required to see the utility of FLI as an early predictor of poor pregnancy outcomes.

Limitations

Although 632 participants were initially recruited, a considerable number were excluded from the models because data for at least one parameter were missing. This may have influenced the selection process of the best parameters to predict FL. In addition, some of the models (models 1 and 5) have not included nearly 50% of the participants due to missing values. Therefore, there is a potential risk of introducing bias to the identified significant variables. However, most of the identified significant factors were the same in all models. As a result, we believe that the bias introduced by the missing values was minimal. In addition, we performed RUN test to identify whether the presence of missing participants (due to a missing value) is random in the order of participant recruitment. We found that participants are missing

randomly ($p > 0.05$) in the order of recruitment as the original sample is random, we assume that the subsample is also random and the bias introduced by the missing value is minimal. We excluded mothers with hepatitis based on their clinical history and not on serological tests, which may not be the best exclusion approach. Although a comparison was conducted with the previous models, none of those models were developed for pregnant women. The effect of pregnancy on all the parameters and probably FL changes may make it difficult to compare the models among pregnant and general populations. Thus, the generalisation of these findings should be limited to early pregnancy. In addition, an ultrasound scan, which we used as the standard test for comparison, is not the gold standard test to diagnose FL.

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Contributors Conceptualisation, methodology, formal analysis and investigation were done by ISK, JNW and SBA. ISK, KGD, JNW and AR did the software, validation and data curation while SBA made funding acquisitions. Experiment procedures were done by ISK, KGD and AR. All authors were involved in original draft preparation, while JNW, SBA and KGD were involved in review and editing. ISK is responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The ethical clearance was obtained from the ethics review committee of the Faculty of Medicine and Allied Sciences, the Rajarata University of Sri Lanka under ERC/2019/22 and approved on 15 August 2019. Written informed consent was taken from all pregnant mothers to participate in this study and to use routinely collected data for this research purpose. The participants were informed that this research is conducted in parallel with the routine maternal and child health service and any 'abnormality' will be reported to the health provider with the participant's consent. In addition, consent had been sought to use a serum sample to screen diabetes mellitus, liver biochemistry and serum cholesterol level, and any other future studies that may require baseline assessment of serum. Participants gave informed consent to participate in the study before taking part.

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