Supplementary material

STARD checklists

	Model creation dataset
Title	**STARD compliant**
Abstract	STARD compliant
Introduction	STARD compliant
Hypothesis	We hypothesised that it may be possible to create model to detect advanced liver disease in primary care using only data currently available from routine tests.
Objectives	The objective was to develop the model using data from a mixed Primary / Secondary Care population with a low prevalence of cirrhosis, and validate the model as a predictive test for an admission with cirrhosis, varices or liver-related ascites in two large validation cohorts, including community subjects.
Study design	A mixed retrospective / prospective analysis of consecutive subjects undergoing upper GI endoscopy (OGD) at University Hospitals Southampton (UHS) that included subjects admitted with a diagnosis of cirrhosis or portal hypertension.
Participants	Anonymised clinical data was extracted from 40,427 unselected subjects undergoing an OGD between 1st January 2005 and 1st November 2016. From October 2010 onwards subjects were recruited prospectively. Relevant data was extracted from UHS data systems matched by UHS number: Patient Administration System (PAS), biochemistry, haematology, pathology and liver HICCS, and merged into SPSS databases. Of these subjects 20,222 were within the age range 18-70 inclusive and had at least one full set of test results.
Eligibility	Consecutive patients were included with no exclusions and matched pseudo-anonymised data extracted from the UHS clinical information systems.
Exclusions	Subjects out of the age range 18-70, or without sufficient data to calculate at least one model result within the time interval of 7-365 days before the first evidence of cirrhosis or portal hypertension were excluded. Subjects with a liver admission or other evidence of liver disease, but with undetermined cirrhosis or portal hypertension status were excluded from the regression model derivation, with sensitivity analyses performed subsequently.
Index test	The index test was derived by logistic regression analysis of full blood count, electrolyte and standard liver profiles. Variables were excluded if they were not part of the most routine Primary Care profiles, for example urea, alkaline phosphatase, aspartate transaminase, gamma glutamyl transferase. Data for the index test were restricted to 7–365 days prior to the first evidence of cirrhosis, either from OGD, biopsy, fibroscan or fibrosis markers. The study cohort was divided into two interchangeable creation / validation cohorts using SPSS uniform random number generation. The mean value for each index test variable over the time interval was entered into a logistic regression analysis against the reference standard, and the model was forward fitted in line with the procedure recommended by David Collett (Collett D. *Modelling binary data, 2nd Edition, Chapman and Hall. Page 93.* 1991).
Reference standard	Subjects were categorised as follows: **Controls**: no evidence of portal hypertension on endoscopy, no other evidence of cirrhosis. **Test subjects**: evidence or portal hypertension, or cirrhosis on liver biopsy or cirrhosis as determined by fibroscan > 15kPa or serum fibrosis markers (Hyaluronic acid and Collagen P3 Peptide) in the cirrhotic range.
Rational for reference standard	Subjects were categorised as follows; Controls: no evidence of portal hypertension on endoscopy, no other evidence of cirrhosis. Test subjects: evidence or portal hypertension, or cirrhosis on liver biopsy or cirrhosis as determined by fibroscan > 15kPa or serum fibrosis markers (Hyaluronic acid and Collagen P3 Peptide) in the cirrhotic range. Exclusions: subjects with a liver admission or other evidence of liver disease, but with undetermined cirrhosis or portal hypertension status were excluded from the regression model derivation.
Rationale for cut-offs	The prevalence of cirrhosis in Primary Care is low, so cut-offs were set at high levels of specificity. Outputs were converted to a specificity to aid clinical interpretation, and further categorised into four colours: crimson, red, amber, green corresponding to specificity cut offs of ≥ 99%, 98%, 94-97% and <94% respectively. Clinical information and reference standard results were not available to the programmers of the index test results. Reference standard data was categorised using SPSS syntax of ICD codes before linking the clinical and index test databases.
Analysis	Area under the curve (AUC) analyses were cross-tabulated using models derived from each randomised cohort. There was no difference in the performance of the two models. For a model derived in cohort 0, applied to cohort 1, the AUC was 0.90 (95% CI 0.88-0.92), and for a model derived in cohort 1, applied to cohort 0, the AUC was 0.90 (0.88-0.92). As there was no difference, the final model was derived by combining the two datasets.
Data handling	Subjects were excluded from the analysis if they were missing any of the mean index test variables, similarly subjects with evidence of liver disease but with undetermined cirrhosis or portal hypertension status were also excluded.

	Model validation dataset 1 (University Hospital Southampton cohort)
Title	STARD compliant
Abstract	STARD compliant
Introduction	STARD compliant
Hypothesis	We hypothesised that it may be possible to create model to detect advanced liver disease in primary care using only data currently available from routine tests.
Objectives	The objective was to develop the model using data from a mixed Primary / Secondary Care population with a low prevalence of cirrhosis, and validate the model as a predictive test for an admission with cirrhosis, varices or liver-related ascites in two large validation cohorts, including community subjects.
Study design	This was a retrospective analysis of routinely collected pseudo-anonymised data obtained from unselected patients from the University Hospital Southampton (UHS) pathology system, which comprised blood test data obtained from both Primary and Secondary Care, cross referenced with admissions data from the Patient Administration System (PAS).
Participants	The analysis dataset comprised blood test results from 503,540 Primary and Secondary Care patients aged 18-65 with UHS blood test results within the study period (5th April 2002 to 7th January 2018). Overall 109,287 of 503,540 (22%) patients were excluded because they were missing data. The final study population comprised 394,253 patients.
Eligibility	Consecutive subjects were eligible for inclusion if they had had at least one full blood count, electrolytes or liver profile blood tests within the study period.
Exclusions	Subjects outside age range 18-65, or with insufficient data to calculate at least one CIRRUS result were excluded.
Index test	Index tests results were calculated using the CIRRUS model from a combination of blood test data comprising: albumin (alb), total bilirubin(tb), creatinine(cr), mean cell volume (mcv), platelet count(plt), sodium(na) and total protein(tp) using the CIRRUS model, and converted to four coloured categories as described for the creation cohort: crimson (C), red (R), amber (A), green (G). Multiple CIRRUS results were obtained for each subject dependent upon the number of blood tests in the system. The index test date was the first date on which the most severe result was obtained within the data set. For example, if a subject progressed from green to amber to red to crimson, the first index test was crimson, and the index test date was the date of the first crimson result.
Reference standard	The aim of our study was to detect an admission with either liver disease (LD) or a serious liver event (SLE). An SLE was defined as cirrhosis, varices or liver-related ascites. The SPSS syntax ICD codes used to select these codes are given in supplementary table 4. The index test results were not available to the assessors of the reference standards.
Rational for reference standard	The objective of the study was to develop a test that could potentially identify subjects likely to be admitted with cirrhosis or the complications of cirrhosis, so the reference standard was a liver admission with relevant ICD codes for cirrhosis, portal hypertension or liver-related ascites.
Rationale for cut-offs	Cut-offs were used as described for the model creation dataset. Cut-offs divided CIRRUS results into four coloured categories (crimson, red, amber, green) corresponding to specificity cut-offs of ≥ 99%, 98%, 94-97% and <94% respectively. Clinical information and reference standard results were not available to the programmers of the index test results. Reference standard data was categorised using SPSS syntax of ICD codes before linking the clinical and index test databases.
Analysis	Time periods were calculated from the index date to the date of the reference standard outcome. CIRRUS predicted a first admission for a SLE within five years of the CIRRUS test with AUC 0.90 (95% CI 0.89-0.91) continuous or 0.88 (95% CI 0.87-0.89) when categorised into CRAG grades. Data were aggregated by day. For patients pre-selected according to known liver risk factors, CIRRUS predicted a subsequent SLE with a sensitivity of 72%, specificity 87%, PPV 26%, NPV 98% for a CRvAG result.
Data handling	Missing variables led to the exclusion of data from that time point, no imputation was used in any of the analyses. There were no indeterminate index test results, all data were included.

	Model validation dataset 2 (Care and Health Information Exchange cohort)
Title	**STARD compliant**
Abstract	STARD compliant
Introduction	STARD compliant
Hypothesis	We hypothesised that it may be possible to create model to detect advanced liver disease in primary care using only data currently available from routine tests.
Objectives	The objective was to develop the model using data from a mixed Primary / Secondary Care population with a low prevalence of cirrhosis, and validate the model as a predictive test for an admission with cirrhosis, varices or liver-related ascites in two large validation cohorts, including community subjects.
Study design	This was a mixed retrospective / prospective analysis of subjects identified via the Care and Health Information Exchange (CHIE) (previously known as Hampshire Health Records Analytics (HHRA)), a fully anonymised database containing Primary Care data from subjects in participating general practices from across Hampshire.
Participants	Data was extracted from 379,279 patients from an estimated total population of 1,094,456 alive and active on the CHIE database between 1st January 2013 and 1st July 2015, who had either a liver blood test result or evidence of liver disease on Read coding. Retrospective blood test data from this cohort was available from 1st July 2007 onwards, and a further tranche of updated outcome data on the cohort was collected in September 2016. The initial dataset comprised 275,929 patients. Overall 92,884 of 275,929 (34%) were excluded because they were missing data. The final study population comprised 183,045 patients.
Eligibility	Consecutive subjects were eligible for inclusion if they had had at least one full blood count, electrolytes or liver profile blood tests within the study period. Data were obtained via an SQL query on the fully anonymised CHIE database with data requests approved by the Central South and Southwest Commissioning Group HHRA Governance Committee.
Exclusions	Subjects outside age range 18-65, or with insufficient data to calculate at least one CIRRUS result were excluded.
Index test	Index tests results were calculated using the CIRRUS model from a combination of blood test data comprising: albumin (alb), total bilirubin(tb), creatinine(cr), mean cell volume (mcv), platelet count(plt), sodium(na) and total protein(tp) using the CIRRUS model, and converted to four coloured categories as described for the creation cohort: crimson (C), red (R), amber (A), green (G). Multiple CIRRUS results were obtained for each subject dependent upon the number of blood tests in the system. The index test date was the first date on which the most severe result was obtained within the data set. For example, if a subject progressed from green to amber to red to crimson, the first index test was crimson, and the index test date was the date of the first crimson result.
Reference standard	The aim of our study was to detect an admission with either liver disease (LD) or a serious liver event (SLE). An SLE was defined as cirrhosis, varices or liver-related ascites. The SPSS syntax ICD codes used to select these codes are given in supplementary table 4. The index test results were not available to the assessors of the reference standards.
Rational for reference standard	The objective of the study was to develop a test that could potentially identify subjects likely to be admitted with cirrhosis or the complications of cirrhosis, so the reference standard was a liver admission with relevant ICD codes for cirrhosis, portal hypertension or liver-related ascites.
Rationale for cut-offs	Cut-offs were used as described for the model creation dataset. Cut-offs divided CIRRUS results into four coloured categories (crimson, red, amber, green (CRAG)) corresponding to specificity cut-offs of ≥ 99%, 98%, 94-97% and <94% respectively. Clinical information and reference standard results were not available to the programmers of the index test results. Reference standard data was categorised using SPSS syntax of ICD codes before linking the clinical and index test databases.
Analysis	Time periods were calculated from the index date to the date of the reference standard outcome. For a first admission with a SLE within five years of the index test, AUCs were 0.84 (95% CI 0.82-0.86) continuous or 0.83 (95% CI 0.81-0.85) when categorised into CRAG grades. In patients with a specified risk factor for liver disease CIRRUS predicted a subsequent SLE with a sensitivity of 59%, specificity 93%, PPV 18%, NPV 99% for a CRvAG result.
Data handling	Missing variables led to the exclusion of data from that time point, no imputation was used in any of the analyses. There were no indeterminate index test results, all data were included. The sample size was determined by the availability of the data in the CHIE cohort, which was in turn limited by data governance issues from the CSSWCGG. We would have liked to have analysed data from all CHIE subjects but this degree of access was not permitted for the initial data extraction. Having obtained promising results from our analysis we did seek permission to extend the cohort, but data governance again precluded this.

RESULTS

Sensitivity analyses

CIRRUS performance in the model creation dataset according to different outcome measures (supplementary table 2)

We performed a sensitivity analysis to ensure that the performance of the CIRRUS algorithm was robust to the time window and definition of the outcome measure in the model creation dataset. This demonstrated that CIRRUS performed well for all outcome measure definitions tested, with an AUC of at least 0.88 in all models.

CIRRUS performance in different age groups (supplementary table 4)

Our analysis was restricted to patients aged 18-65 because the performance of the CIRRUS test in terms of PPV falls off above the age of 65 as the prevalence of SLEs falls and the incidence of co-morbidities that can cause a false positive result increases (supplementary table 3).

CIRRUS calculated using mean blood test data aggregated over 4 week period (supplementary table 7)

We examined the impact of using blood test data aggregated over a longer period to see if this reduced false positive tests triggered by unrelated short-term metabolic disturbances. CIRRUS results calculated in this way had a higher PPVs, using a crimson / red cut point in UHS patients with any risk PPV increased from 0.26 to 0.34, sensitivity dropped from 72% to 67% (supplementary table 7). We plan to use data aggregated by month in our POLeMMIC study (Prevention of Liver Mortality and Morbidity In the Community) in view of the higher PPV as this will reduce the number of subjects needed to answer the research question.

CIRRUS in a subset of UHS patients with an index test at least 100 days before the first SLE (supplementary table 9)

The median time period between the index and first SLE was relatively short in patients with a red or crimson CIRRUS result in the model validation dataset 1 (UHS), so we performed a sensitivity analysis excluding any subject with an index test within 100 days of a first SLE (supplementary table 9). In this subgroup the AUC for a first SLE within 5 years was as good as the whole study group: SLE subjects n=1,163, no LD control subjects n=380,287, AUC 0.91 (0.90-0.92). In this subset the median time (years) from index test to SLE for each of the CIRRUS categories was as follows: green 6.7 years, amber 4.8 years, red 2.9 years, crimson 2.4 years, suggesting that the CIRRUS test performs reasonably well over the longer time span of 2-3 years before the first SLE.

Supplementary Table 1 Model creation dataset: Population characteristics and liver disease aetiology

Creation dataset	Cohort 0	Cohort 1	Total
Mean age	51.7	51.9	51.8
Males	3,681	3,742	7,423
No evidence liver disease	7,973	8,063	16,036
Viral hepatitis	58	46	104
Autoimmune liver disease	18	16	34
Alcohol-related liver disease	193	230	423
Non-alcoholic fatty liver disease	67	61	128
Miscellaneous	8	6	14
Metabolic liver disease	5	2	7
Unknown cause of liver disease	108	113	221
Total	8,430	8,537	16,967

Supplementary Table 2 A sensitivity analysis was performed in the model creation dataset to determine if the performance of CIRRUS was robust to the time window and definition of the outcome measure

Outcome measure definition	Time interval	Cirrhosis / portal hypertension (n)	No liver disease controls (n)	AUC	95% CI
OGD	7-365 days prior to first diagnosis	811	16,036	0.91	0.90-0.92
OGD, biopsy		872	16,036	0.91	0.90-0.92
OGD, biopsy, fibroscan, fibrosis markers		931	16,036	0.91	0.89-0.92
OGD, biopsy, fibroscan, fibrosis markers, liver admissions with unknown cirrhosis		931	17,595	0.90	0.89-0.91
OGD	6-18 months prior to first diagnosis	547	9,820	0.89	0.87-0.91
OGD, biopsy		585	9,820	0.88	0.87-0.90
OGD, biopsy, fibroscan, fibrosis markers		629	9,820	0.88	0.86-0.90

A sensitivity analyses was performed on subjects with OGD data, liver biopsy, fibroscan, fibrosis markers +/- a liver admission with unknown cirrhosis status, which did not improve the accuracy of the test. Subjects with liver disease, but undetermined cirrhosis or PH status were therefore not included.

Supplementary Table 3 The International Classification of Disease (ICD)-10 codes used to define liver risk factors and serious liver events in the two validation datasets

ICD-10 letter	3 figure code	Brief description	Viral hepatitis	Alcohol	T2 DM	Liver Disease	Serious Liver Event
B	15.0-19.9	Viral hepatitis	x				
F	10.0-10.9	Alcohol abuse, dependence disorder, alcohol use		x			
E	11.0-11.9	T2 diabetes mellitus			x		
I	81.0	Portal vein thrombosis					x
I	85.0-85.9	Oesophageal varices					x
R	18.0	Ascites					If liver disease
T	51.0	Alcohol toxicity		x			
Z	94.4	Liver transplant					x
K	70.0-77.8	Alcoholic liver disease, toxic liver disease, hepatic failure, chronic hepatitis, fibrosis & cirrhosis of the liver, other inflammatory liver disease, other diseases of the liver, liver disorders in diseases classified elsewhere				x	
K	70.3-70.4	Alcoholic cirrhosis, alcohol hepatic failure					x
K	71.7	Toxic liver disease with fibrosis & cirrhosis					x
K	72.1-72.9	Chronic hepatic failure, hepatic failure unspecified					x
K	74.4-74.6	Secondary biliary cirrhosis, biliary cirrhosis, other & unspecified cirrhosis					x
K	76.6-76.7	Portal hypertension, hepatorenal syndrome					x

SLE definition: A hospital admission with varices, liver-related ascites or cirrhosis.

Supplementary Table 4 A sensitivity analysis was performed including patients of all ages for validation dataset 1 (UHS cohort)

Age band	SLE (n)	No LD (n)	Liver risk	Prevalence (%)	Grade	Sensitivity	Specificity	PPV	NPV
<35	97	4,360	Any	2.2	CRvAG	0.73	0.92	0.18	0.99
35-45	287	3,402	Any	8.4	CRvAG	0.80	0.95	0.34	0.98
45-55	550	5,871	Any	9.4	CRvAG	0.78	0.86	0.34	0.98
55-65	594	8,518	Any	7.0	CRvAG	0.76	0.84	0.25	0.98
65-75	241	6,658	Any	3.6	CRvAG	0.67	0.82	0.12	0.99
>75	17	1,004	Any	1.7	CRvAG	0.65	0.79	0.05	0.99
<35	170	128,260	No risk	0.1	CRvAG	0.46	0.96	0.01	1
35-45	199	64,927	No risk	0.3	CRvAG	0.60	0.95	0.03	1
45-55	346	71,086	No risk	0.5	CRvAG	0.64	0.94	0.05	1
55-65	458	56,821	No risk	0.8	CRvAG	0.65	0.92	0.05	1
65-75	181	30,090	No risk	0.6	CRvAG	0.65	0.9	0.04	1
>75	13	2,697	No risk	0.5	CRvAG	0.46	0.87	0.02	1

Data was split into age bands according to the age at the most recent blood test.
PPV: positive predictive value, NPV: negative predictive value

Supplementary Table 5 Categorisation of the model creation dataset into crimson, red, amber, green CIRRUS results with time between the index test and the determination of the reference standard.

	Model creation dataset			**Index test to reference standard (median no. days)**	
	No LD controls	Cirrhosis / portal hypertension.	Total	No LD controls	Cirrhosis / portal hypertension
Green	15,076	217	15,293	201	281
Amber	609	120	729	221	248
Red	146	82	228	219	244
Crimson	205	512	717	236	266
Total	16,036	931	16,967	877	1,039

Supplementary Table 6 Demographics of the validation datasets

Validation dataset 1 (UHS cohort)									
	Female	Mean age at tests	No liver risk factors	Specified liver risk factor	Alcohol risk	Type 2 diabetes	Viral hepatitis	Dead	Total
No LD	205,003	44	356,823	27,472	8,619	18,750	672	21,123	38,4295
LD no SLE	3,060	50	4,180	2,734	970	1,100	930	1,223	6,914
SLE	1,094	52	1,311	1,733	1,053	649	288	1,423	3,044
Overall	209,157		362,314	31,939	10,642	20,499	1,890	23,769	394,253
Validation dataset 2 (CHIE cohort)									
	Female	Mean age at tests	No liver risk factors	Specified liver risk factor	Alcohol risk	Type 2 diabetes	Viral hepatitis	Dead	Total
No LD	103,038	49	145,228	33,573	13,328	22,576	N/A	3,474	178,801
LD no SLE	1,606	52	1,691	1,383	702	879	N/A	247	3,074
SLE	504	54	294	876	636	441	N/A	379	1,170
Overall	105,148		147,213	35,832	14,666	23,896	N/A	4,100	183,045

LD: Liver Disease, SLE: Serious Liver Event

Validation dataset 1 (UHS cohort) liver risk factors: alcohol (previous admission with an alcohol ICD code), diabetes (elevated HbA1C or a previous admission with type 2 diabetes), viral hepatitis (HBsAg, HBV DNA or HCV RNA).

Validation dataset 2 (CHIE cohort) liver risk factors: alcohol (previous admission with an alcohol ICD code, or harmful dependent drinking or an alcohol co-morbidity in the Primary Care record) or diabetes (type 2 diabetes in Primary or Secondary Care records).

The mortality data for validation dataset 2 (CHIE cohort) is derived from data collected after 2013 following a second extraction of data.

Supplementary Table 7 A sensitivity analysis of CIRRUS calculated using mean blood test data aggregated over a 4 week period for validation dataset 1 (UHS cohort)

		Event / total	Prevalence	Sensitivity	Specificity	PPV	NPV	PLR
CvRAG	Any liver risks	1,699/31,905	5.82	0.58	0.95	0.43	0.97	12.27
CRvAG				0.67	0.92	0.34	0.98	8.20
CvRAG	No risks	1,295/362,298	0.36	0.42	0.98	0.08	1.00	23.35
CRvAG				0.50	0.97	0.05	1.00	14.44
CvRAG	Alcohol	1,031/10,620	10.68	0.70	0.92	0.51	0.96	8.59
CRvAG				0.77	0.87	0.42	0.97	6.02
CvRAG	Type 2 diabetes	640/20,490	3.30	0.42	0.97	0.31	0.98	13.16
CRvAG				0.53	0.94	0.23	0.98	8.65
CvRAG	Viral hepatitis	272/1,874	28.81	0.53	0.90	0.69	0.83	5.60
CRvAG				0.66	0.86	0.65	0.86	4.61

Blood tests data for the CIRRUS algorithm were aggregated (mean) by month prior to calculation of the CIRRUS result. This evened out day-to-day fluctuations reducing the sensitivities slightly, but increased the PPVs.

PPV: positive predictive value, NPV: negative predictive value, PLR: positive likelihood ratio

Supplementary Table 8 Median values for laboratory results used to calculate the index CIRRUS test in the two validation cohorts, categorised by green, amber, red and crimson grades

Validation datset 1 (UHS cohort)								
	Green		**Amber**		**Red**		**Crimson**	
	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
Albumin	43.1	43.1-44.0	37.0	37.0-37.9	33.6	33.6-34.7	31.0	30.5-31.5
Creatinine	81.4	81.4-82.0	76.9	76.0-78.0	73.6	73.0-75.0	73.6	72.5-75.0
MCV	87.7	87.7-87.8	90.3	90.2-90.5	90.8	90.5-91.1	92.3	92.0-92.7
Sodium	139.0	139-140	137.0	137-138	136.0	136-137	135.0	135-136
Platelets	252.0	252-253	182.0	181-184	164.0	162-167	133.0	130-136
Bilirubin	11.0	11-12	11.0	11.0-12.0	11.0	11.0-12.0	15.0	15.0-16.0
Total protein	71.0	71.0-72.0	71.0	71.0-72.0	69.0	69.0-70.0	69.0	69.0-70.0
Validation dataset 2 (CHIE cohort)								
	Green		**Amber**		**Red**		**Crimson**	
	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
Albumin	40.0	40.0-41.0	38.0	38.0-39.0	37.0	37.0-38.0	36.0	36.0-37.0
Creatinine	72.0	72.0-73.0	69.0	69.0-70.0	67.0	67.0-68.0	65.0	65.0-66.0
MCV	89.8	89.8-89.9	93.0	92.9-93	94.0	94.1-94.6	96.0	95.8-96.4
Sodium	139.0	139-140	138.0	138-139	138.0	138-139	137.0	137-138
Platelets	257.0	257-258	191.0	191-192	175.0	174-177	157.0	156-159
Bilirubin	12.0	12.0-13.0	11.0	11.0-12/0	10.0	10.0-11.0	12.0	12.0-13.0
Total Protein	70.0	70.0-71.0	72.0	72.0-73.0	73.0	73.0-74.0	73.0	73.0-74.0

Index values of the individual components of the CIRRUS algorithm are all taken on the CIRRUS index date. In the CHIE dataset the median and 95% CI lie within the normal laboratory range, whereas in the UHS dataset some parameters lay outside the normal laboratory range (albumin 35g/L, platelet count 150 x10^9/L). This indicates that the CIRRUS algorithm can identify patterns in patients with manifestly normal blood tests, indicating that they may be at increased risk of a future serious liver event.

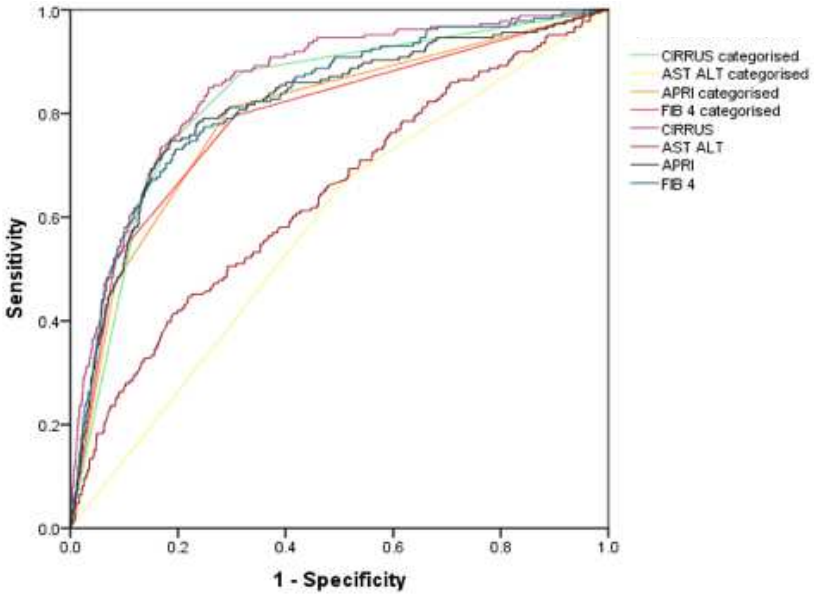
Supplementary Table 9a A sensitivity analysis of the subset of patients in whom the time period from index CIRRUS test to first SLE was ≥ 100 days within validation dataset 1 (UHS cohort)

> 100 days from index test to SLE	SLE within 5yrs	No liver disease	AUC	95% CI
CIRRUS uncategorised	1,163	380,287	0.91	0.90-0.92
CIRRUS CRAG	1,163	380,958	0.88	0.86-0.89

Supplementary Table 9b Median time period (95% CI) between index CIRRUS test and first SLE, in the subset of patients in whom the time period from index CIRRUS test to first SLE was ≥ 100 days within validation dataset 1 (UHS cohort)

	No liver disease		Liver disease no SLE		SLE	
	Index test to SLE (years)		Index test to SLE (years)		Index test to SLE (years)	
	Median	95% CI	Median	95% CI	Median	95% CI
Green	8.5	8.4-8.5	10.6	10.3-10.8	6.7	6.2-7.2
Amber	8.7	8.6-8.8	7.6	7.0-8.4	4.8	3.8-5.5
Red	7.9	7.6-8.2	6.9	6.2-7.8	2.9	2.3-3.9
Crimson	6.2	5.9-6.4	5.6	5.1-6.2	2.4	2.1-2.7

Supplementary Figure 1 Receiver Operator Curve comparisons in the subset of 6,105 validation dataset 1 (UHS cohort) patients in whom it was possible to calculate CIRRUS, APRI, FIB4 and AST/ALT ratio for prediction of an SLE within 5 years of the index test



		SLE	No SLE	AUC	95% CI
CIRRUS	Not categorised	186	5,919	0.86	0.83-0.88
FIB4	Not categorised	186	5,919	0.83	0.80-0.86
AST/ALT ratio	Not categorised	186	5,919	0.64	0.60-0.68
APRI	Not categorised	186	5,919	0.81	0.78-0.85
CIRRUS CRAG	Categorised	186	5,919	0.83	0.80-0.86
AST/ALT code	Categorised	186	5,919	0.58	0.54-0.62
APRI code	Categorised	186	5,919	0.79	0.76-0.83
FIB4 code	Categorised	186	5,919	0.79	0.75-0.83