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ORIGINAL ARTICLE

Validation of the liver traffic light test as a predictive model for survival and development of liver-related events

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Declaration of conflict of interest: Nick Sheron undertook paid consultancy work and received traveling expenses from pharmaceutical companies Norgine (2014) and Kyowa Kirin Limited (2014), as well as undertaking medicolegal work in hepatitis C- and alcohol-related liver disease. None of the remaining authors have any competing interests.

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Abstract

Background and Aim: Liver disease mortality rates continue to rise due to late diagnosis. We need noninvasive tests to be made available in the community that can identify patients at risk from a serious liver-related event (SLE). We examine the performance of a blood test, the liver traffic light test (LTLT), with regard to its ability to predict survival and SLEs.
Methods: Using routinely gathered clinical data, sequential LTLT test results from 4854 individuals with suspected liver disease were prospectively analyzed (median follow-up 41 months). An SLE was defined as the development of cirrhosis, liver failure, ascites, or varices. Patients were graded as follows: red (high risk), amber (intermediate risk), and green (low risk).
Results: Overall, 565 individuals experienced an SLE (11.6%). The area under the curve (AUC) for the continuous LTLT variable was 0.87 (95% confidence interval 0.85–0.89) for prediction of an SLE and 0.81 (0.78–0.84) for mortality. When categorized into red/amber/green grades, a red LTLT result predicted an SLE with negative and positive predictive values of 0.97 and 0.29, respectively. A red LTLT score predicted mortality with negative and positive predictive values of 0.98 and 0.18, respectively. Kaplan–Meier plots demonstrated increased mortality and SLEs in the red group *versus* the green and amber groups ($P < 0.001$) and an increase in SLEs in the amber *versus* green group ($P < 0.001$).
Conclusion: Here, the LTLT is further validated for the prediction of survival and SLE development. The LTLT could aid primary care risk management and referral pathways with the aim of detecting and treating liver disease earlier in the general population.

Introduction

Over the last few decades, mortality rates have steadily decreased for most diseases.[1] In striking contrast, mortality rates from liver disease in the United Kingdom have risen fourfold and may outstrip ischemic heart disease as the leading cause of years of working life lost over the next few years.[2,3] Liver disease develops without signs or symptoms, and we found that up to three-quarters of patients who will die from liver disease present late with advanced disease.[1,4] If disease was observed earlier in primary care, it is possible that nonelective admissions and consequent mortality could be reduced as a result of lifestyle interventions or medication.

With this in mind, we developed the liver traffic light test (LTLT), previously called the Southampton traffic light test (STL), a simple blood test that could be used in a primary or secondary care setting to identify patients at risk from a future liver event.[5] The LTLT is a simple blood test utilizing two fibrosis markers, hyaluronic acid (HA) and collagen P3N peptide (P3NP), alongside platelet count to detect liver fibrosis and cirrhosis. The test was found to be accurate for the prediction of fibrosis and cirrhosis in a developmental cohort ($n = 397$) when compared to liver biopsy data (area under the curve [AUC] 0.88 for severe fibrosis) and was predictive of survival and clinically relevant outcomes (varices and ascites) in a validation cohort ($n = 641$).[5] The test has been in use in secondary care clinics since 2003 and has been implemented in two community studies. The first examined the feasibility of detecting liver disease using the LTLT in at-risk drinkers in an attempt to impact hazardous drinking habits (Alcohol and Liver Disease Detection study (ALDDeS study)).[6] The second implemented the LTLT alongside transient elastography for the identification of patients at risk of fibrosis or cirrhosis (Local care and treatment of liver disease (LOCATE study)).[7]

In this study, we used routinely available pseudo-anonymized clinical data from the United Kingdom's National Health Service (NHS) to follow up patients who had undergone sequential LTLTs to examine how accurate the LTLT was as a predictive test for liver-related mortality or the development of a serious liver event (SLE).

Methods

Over a 14-year period (July 2003 to October 2017), 4854 patients had one or more LTLT assay results stored on the University Hospitals Southampton (UHS) Foundation Trust pathology system. Tests were taken either during the course of routine care or from within two community-based research projects.[6,7] Patients were followed up over a median of 41 months (interquartile range [IQR] 17–87 months) for death or an SLE. An SLE was defined as a hospital episode with International Classification of Diseases (ICD)-10 coding for: cirrhosis, liver failure, liver-related ascites, or gastroesophageal varices. The last date of follow-up was 1 June 2018. All patients in whom an LTLT result could be calculated were included.

Clinical and pathology data. Pseudoanonymized pathology data were extracted from UHS pathology, endoscopy, and radiology datasets. Pseudoanonymized clinical data comprising ICD-10 admission codes were extracted from UHS patient administration systems (PAS) by AH, and clinical trial data for patients enrolled in ALDDeS and LOCATE were provided by NS.[6,7] The NHS PAS dataset is updated regularly with mortality data from everywhere in the United Kingdom. The reason for the blood test and/or etiology of liver disease was determined from clinical data provided on the blood test request form, supplemented by the results of liver etiology blood tests (viral serology, iron studies, autoantibodies, and immunoglobulins), data from other pathology request forms, ICD-10 coding of liver admissions, and research data.

Assay methodology. The LTLT algorithm was originally created in a secondary care cohort (mixture of inpatients and outpatients) and published in 2012.[5] P3NP (Orion Diagnostica, Espoo, Finland) (cP3NP μg/L) and HA (Corgenix Inc., Broomfield, CO, USA) (oHA μg/L) were assayed using commercial immunoassays. Our laboratory later switched to the Siemens multianalyzer system, which was also used to calculate the commercially patented algorithm, the Enhanced Liver Fibrosis (ELF) test.[8] A regression calibration factor was calculated after examining samples with both assays in order to apply the LTLT algorithm to the new Siemens results. The conversion factors for the Siemens HA (sHA) and P3NP (sP3NP) assay results are: oHA = sHA*0.733−3.328; cP3NP = sP3NP*0.297+1.396.

The LTLT algorithm is as follows: LTLT = EXP (oHA*0.015 + cP3NP*0.447 − PLT*0.005 − 0.61)/(1 + exp ((oHA*0.015 + cP3NP*0.447 − PLT*0.005 − 0.61))).[5] In addition to the continuous probability calculation output, clinicians are provided with a traffic light category calculated as follows: red >0.7532; amber 0.6163–0.7532; green <0.6163. The rationale for choosing these cut-offs is discussed in Supplementary Material.

Graphs and statistical methods. Data analysis was performed using SPSS software v.26. AUC analyses, Kaplan–Meier survival function graphs, and Cox regression analyses were used to study mortality and the development of SLEs. Kaplan–Meier curves were compared using the Mantel-Cox log rank test. The time to an event was measured from the week following the first LTLT result and was censored after a participant's death or termination of the study. Where multiple test results were available for one patient, the first test result was used, except when analyzing the changes in LTLT results over time.

Results

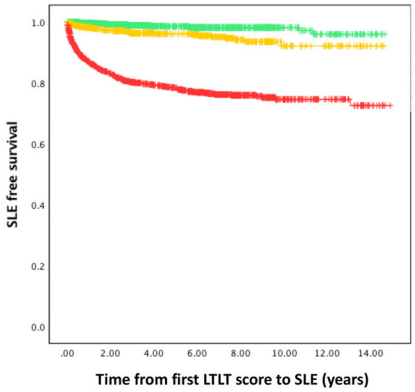
Study population. The study population consisted of 6289 consecutive LTLT results from 4854 patients in whom the LTLT was requested. Overall, 2898 (59.7%) were male. The mean age was 48 years (range 16–79 years). It was possible to ascertain a probable etiology of liver disease for 3653 subjects (75%) (Table S1). Alcohol-related liver disease and non-alcoholic fatty liver disease (NAFLD) accounted for over two-thirds of cases. The majority of patients were tested in secondary care (3562), a further 896 subjects came from community research studies of patients with known risk factors for liver disease,[6,7] and 396 patients were tested for the first time by their primary care physician.

Prognostic performance. When the follow-up cohort was grouped according to LTLT grade, the red group developed the most SLEs (467/1585, 29.5%) and had the highest mortality rate (280/1585, 17.7%) compared to the amber (SLEs 49/873, 5.6%; deaths 31/873, 3.6%) and green groups (SLEs 49/2396, 2.0%; deaths 49/2396, 2.0%), which had similarly low rates for mortality and SLE incidence. A red LTLT score predicted a subsequent SLE (cumulative incidence 11.6%) with a sensitivity of 83%, specificity of 74%, positive predictive value (PPV) of 0.29, and negative predictive value (NPV) of 0.97 (*Table* 1). The AUC for the continuous LTLT variable was 0.87 (95% confidence interval [CI] 0.85–0.89) for the development of an SLE and 0.81 (0.78–0.84) for mortality. The AUCs for the prediction of cirrhosis, varices, and ascites were 0.87 (0.85–0.89), 0.90 (0.88–0.92), and 0.91 (0.88–0.93), respectively.

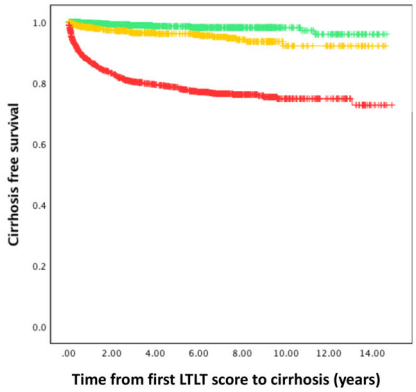
Table 1 Sensitivity, specificity, and positive predictive and negative predictive values of dichotomous liver traffic light test (LTLT) grades (red *vs* amber/green) for mortality and the development of serious liver-related events (SLE), *n* = 4854

	LTLT grade: Red *vs* amber/green						
Event	Event, *n*	Sensitivity	Specificity	PPV	NPV	PLR	Cumulative incidence
SLE	565	0.83	0.74	0.29	0.97	3.17	11.6
Cirrhosis	553	0.83	0.74	0.29	0.97	3.16	11.4
Varices	231	0.89	0.70	0.13	0.99	2.99	4.8
Ascites	170	0.91	0.69	0.10	1.00	2.97	3.5
Death	360	0.78	0.71	0.18	0.98	2.68	7.4

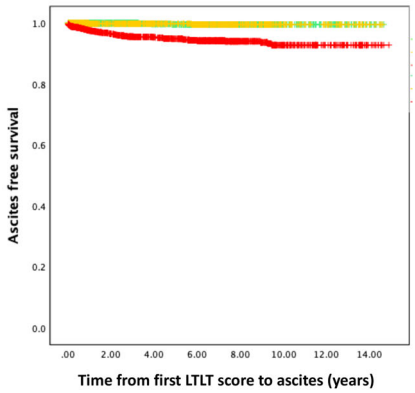
NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.



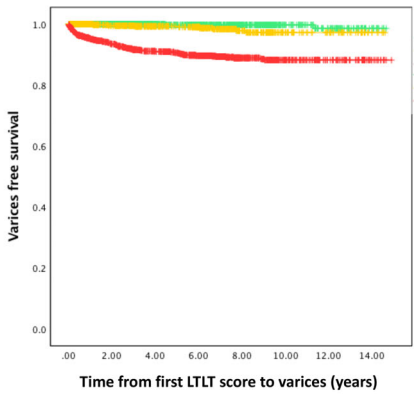
No. at risk								
Green	1972	1132	612	398	193	86	39	7
Amber	737	494	349	241	116	51	24	4
Red	1250	798	610	393	184	84	34	5



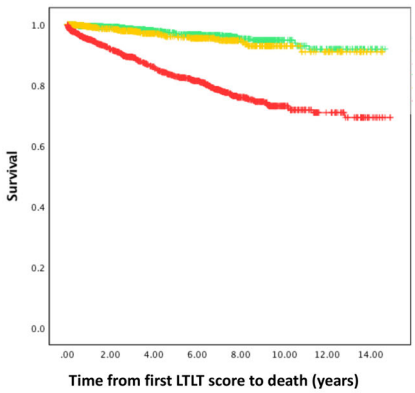
No. at risk								
Green	1974	1134	614	399	193	86	39	7
Amber	738	495	350	241	116	51	24	4
Red	1259	806	617	398	186	84	34	5



No. at risk								
Green	2389	1583	715	532	280	115	65	14
Amber	869	620	408	326	171	65	40	7
Red	1504	1113	899	715	345	153	71	13



No. at risk								
Green	1986	1152	627	408	200	92	40	7
Amber	746	514	367	251	119	53	24	4
Red	1346	993	788	512	238	108	41	7



No. at risk								
Green	1992	1148	617	398	193	90	38	7
Amber	749	511	360	244	118	50	21	3
Red	1402	1021	779	496	221	96	37	7

Figure 1 Kaplan–Meier graphs for the development of serious liver-related events and mortality using grades from the first liver traffic light test (LTLT) score. A red LTLT grade was associated with worse survival and the development of serious liver-related events (SLEs) compared to green and amber scores (Mantel-Cox, $P < 0.001$). Significant differences were observed between green and amber groups for the development of all SLEs considered together, cirrhosis, and varices (Mantel-Cox, $P < 0.001$). LTLT grade: (), Green; (), amber; (), red; (), green-censored; (), amber-censored; (), red-censored.

Kaplan–Meier graphs of the first LTLT were created for SLE development and survival (*Fig*. 1). The median time from the first LTLT to the first SLE was 2.8 years (IQR 0.9–6.4 years). Significantly more patients in the red group developed SLEs compared to the amber (Mantel-Cox, $P < 0.001$) and green groups (Mantel-Cox, $P < 0.001$), and significantly fewer patients with green grades developed SLEs compared to the amber group (Mantel-Cox, $P < 0.001$). This pattern was also observed for the development of cirrhosis and varices between all three grades. While individuals in the red group were more likely to develop ascites than those in the amber (Mantel-Cox, $P < 0.001$) and green groups (Mantel-Cox, $P < 0.001$), no significant difference was observed between the latter two groups. Similarly, for mortality rates, the only significant difference lay between the red and amber and red and green groups (Mantel-Cox, $P < 0.001$ for both).

Cox regression analysis was performed to estimate the hazard ratios (HRs) for outcomes after adjustment for confounding variables. LTLT grade (red *vs* green HR 17.27 [11.39–26.19]; amber *vs* green HR 3.26 [1.94–5.50]), age (HR 1.03 [1.02–1.04]), and disease etiology were all significantly associated with the development of an SLE.

LTLT change over time. In 880 patients, more than one LTLT result was available for analysis. Of these subjects, the LTLT improved in 200 (23%) individuals and deteriorated in 138 (16%) (Table S2). In a Kaplan–Meier analysis, significantly more patients with an initial green grade developed SLEs if their grade worsened to either amber or red (Mantel-Cox, $P = 0.006$ and $P = 0.013$); no significant differences were observed for progression from amber to red. No significant changes in survival were observed when grades worsened over time (*Fig*. 2).

Patients whose initial grade improved from red to amber (Mantel-Cox, $P < 0.001$) or green (Mantel-Cox, $P = 0.001$) had significantly higher survival than patients who remained in the red group. Fewer patients developed SLEs if they improved from red to amber (Mantel-Cox, $P = 0.004$) compared to those remaining in the red group, but no difference was observed when improving from amber to green (*Fig*. 3).

Although only 396 subjects were tested by their primary care physician outside of the context of a research study, it is notable that practically all of these tests occurred in the final 2 years of the study, demonstrating a change in practice (*Figure* S1, Supporting information).

Comparison between LTLT and the ELF test. In a subgroup of 1225 patients, of whom 68 had an SLE (cumulative incidence 5.6%), serum Tissue Inhibitor of Metalloproteinase 1 results were available, enabling the calculation of both the LTLT and the ELF test, a noninvasive serum fibrosis marker commonly used in Europe (Table S3). The LTLT performed as well as the ELF score for the prediction of an SLE (LTLT AUC 0.84 [0.80–0.89]), ELF (0.82 [0.77–0.87]), or death (LTLT 0.77 [0.63–0.91], ELF 0.84 [0.74–0.95]) (*Table* 2). The Spearman rank correlation coefficient between LTLT and ELF was 0.81, $P < 0.001$. With regard to predicting a subsequent SLE, an ELF score > 10.5 demonstrated a sensitivity of 62%, specificity of

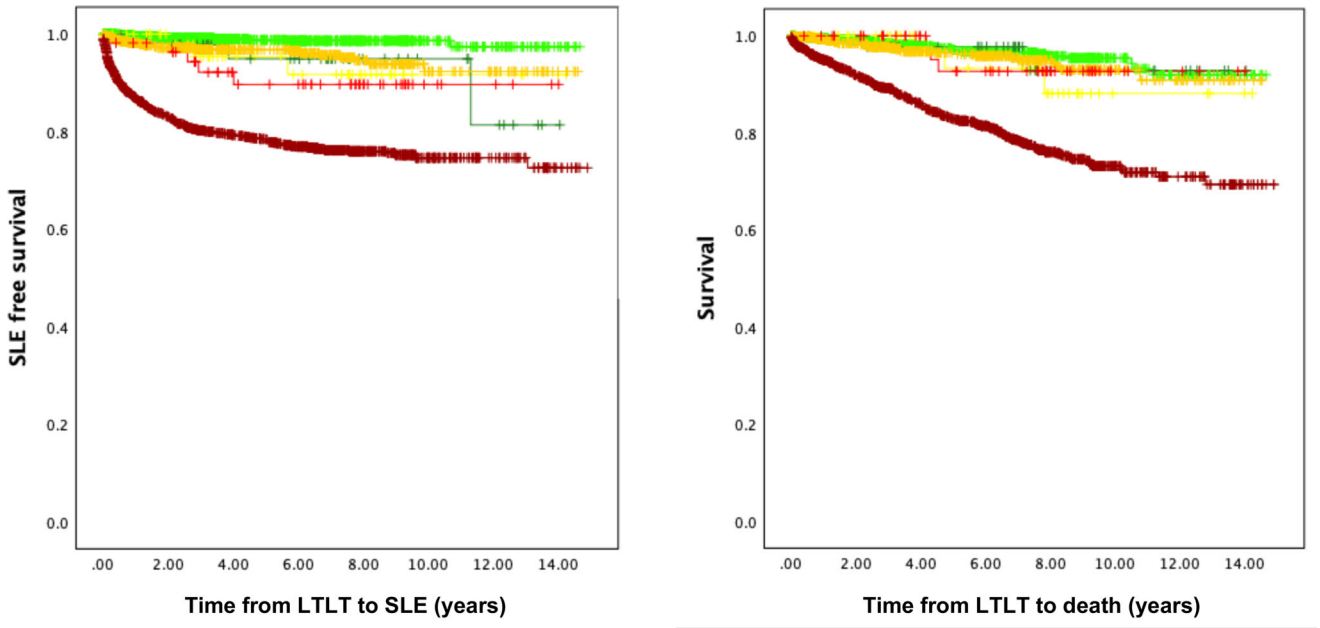


Figure 2 Kaplan–Meier graphs for development of serious liver-related events and mortality in groups whose liver traffic light test (LTLT) grades deteriorated over the follow-up period. Significantly more patients developed serious liver-related events (SLEs) when their grade changed from green to amber (Mantel-Cox, $P = 0.006$) to red (Mantel-Cox, $P = 0.013$). No significant differences in survival were observed due to worsening of any LTLT grade over time. (), Green–green; (), green–amber; (), green–red; (), amber–amber; (), amber–red; (), red–red; (), green–green-censored; (), green–amber-censored; (), green–red-censored; (), amber–amber-censored; (), amber–red-censored; (), red–red-censored.

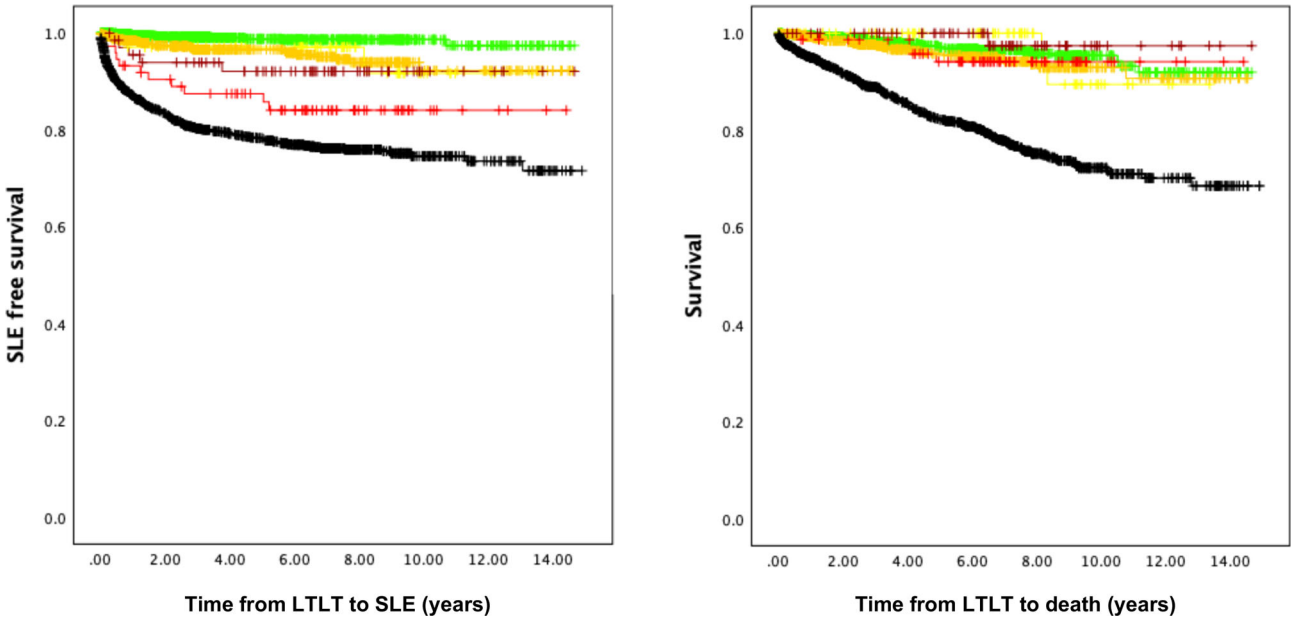


Figure 3 Kaplan–Meier graphs for development of serious liver-related events and mortality in groups whose liver traffic light test (LTLT) grades improved over the follow-up period. Significantly more patients developed serious liver-related events (SLEs) if they remained red compared to improving to amber (Mantel-Cox, $P = 0.004$); no differences were observed on changing from amber to green. Significantly fewer patients died if their grade changed from red to amber (Mantel-Cox, $P < 0.001$) or green (Mantel-Cox, $P = 0.001$). (), Green–green; (), amber–green; (), amber–amber; (), red–green; (), red–amber; (), red–red; (), green–green-censored; (), amber–green-censored; (), amber–amber-censored; (), red–green-censored; (), red–amber-censored; (), red–red-censored.

Table 2 Area under curves (AUCs) for the continuous liver traffic light test (LTLT) variable and enhanced liver fibrosis (ELF) score for mortality and the prediction of serious liver-related events (SLE) in a subgroup of 1225 individuals

Event	Positive, *n*	Negative, *n*	Continuous LTLT AUC (95% CI)	ELF score AUC (95% CI)
SLE	68	1157	0.84 (0.80–0.89)	0.82 (0.77–0.87)
Cirrhosis	67	1158	0.84 (0.79–0.89)	0.82 (0.76–0.87)
Varices	24	1201	0.86 (0.79–0.93)	0.83 (0.75–0.91)
Ascites	13	1212	0.89 (0.82–0.96)	0.88 (0.81–0.94)
Death	21	1204	0.77 (0.63–0.91)	0.84 (0.74–0.95)

CI, confidence interval.

86%, PPV of 0.21, and NPV of 0.98 (LTLT in this cohort: sensitivity 75%, specificity 77%, PPV 0.16, NPV 0.98) (Table S4).

Discussion

Importance of the study. The LTLT has proven to be a good predictive model of mortality and SLE incidence in this validation cohort composed of both primary and secondary care patients with various etiologies of liver disease (*Fig.* 4).[5] Patients with a red LTLT had a 30% likelihood of developing esophageal varices or being admitted to hospital with cirrhosis, liver failure, or ascites after a median interval of approximately 3 years. Analysis of the implications for an individual moving up or down with regard to LTLT grades demonstrates clinical relevance in determining a patient's increased or decreased risk of developing an SLE or death. The continuous LTLT was as accurate in predicting an SLE as the ELF test, currently recommended by the United Kingdom's National Institute for Health and Care Excellence for the noninvasive staging of liver fibrosis for individuals with NAFLD.[9] The LTLT utilizes the same mechanized assays for HA and P3NP as the ELF test, with the addition of platelet count. Therefore, for future studies, it will be possible to calculate an LTLT result alongside ELF in any patient for whom a complete blood count is available. As the LTLT algorithm, unlike the ELF test, is not patented, this may extend applicability.

Study strengths and limitations. The main strength of this study is that it utilized pseudoanonymized sequential LTLT NHS clinical assay results, and as such, it did not require subjects to give informed consent and thus represents the real-life

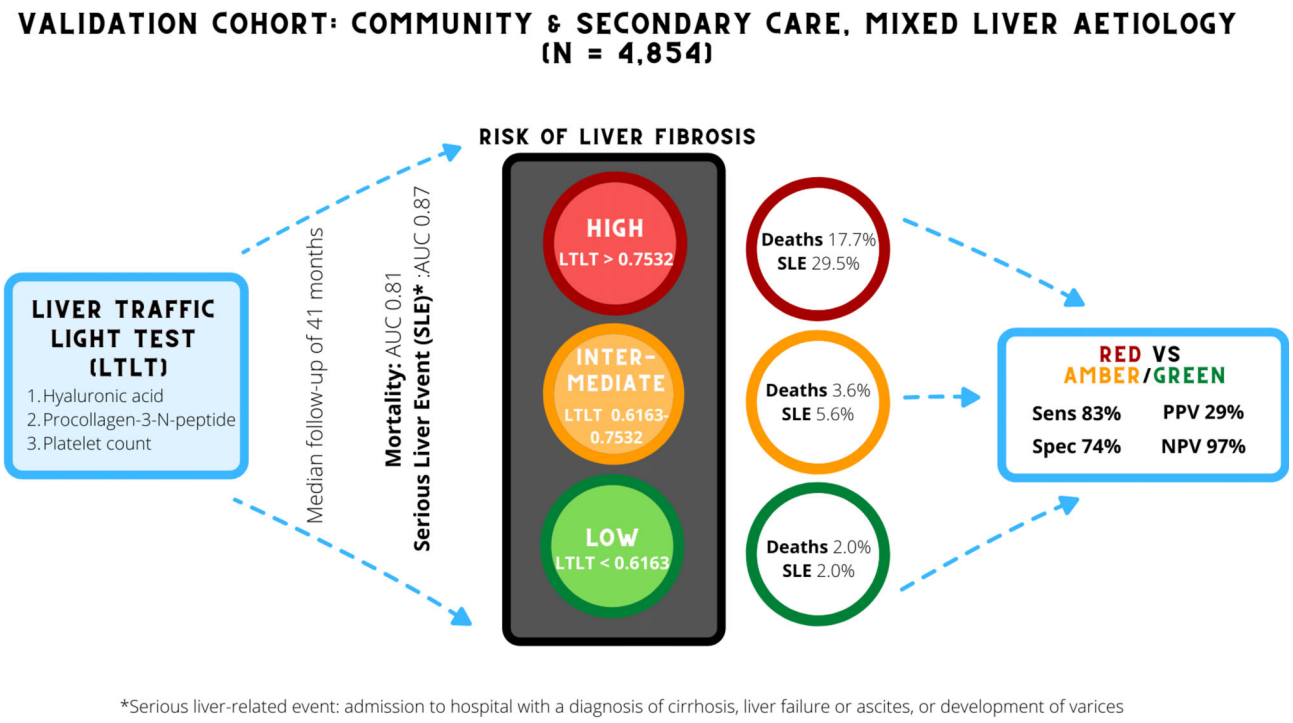


Figure 4 Graphical summary of this study.

performance of the LTLT in a mixed primary and secondary care setting. The outcomes used as the reference standard in this study represent real-life clinical consequences (SLEs and mortality), that is, the things that ultimately matter in terms of preventing a first decompensating event or a tragic death.

The fact that we used routinely collected NHS clinical data is also the main limitation because we were reliant on these systems to provide the required clinical data, and as a result, the data are not of the same standard as would be found in a consented research study. NHS clinical coding is comprehensive when patients are admitted, so the outcome data used to determine SLEs were accurate. Unfortunately, however, NHS diagnostic coding is not applied to outpatient clinics. While the requesting physician is required to indicate relevant clinical details on the test request form, human nature is such that some information was missing. We combined all available sources of information but were unable to ascertain the etiology of suspected liver disease or the underlying reason for the test request in 512 (11%) cases.

In our follow-up cohort, 33 and 18% of individuals scored red and amber grades, respectively, whereas in the community, the prevalence of liver fibrosis would be lower. In the community LOCATE study, the prevalence of a red test in selected subjects with risk factors for liver disease was 21%.[7] The higher prevalence of fibrosis in this study is a consequence of the fact that our cohort is comprised of patients already suspected of having liver disease. As a result of this spectrum bias, predictive values for survival and SLEs would be lower in a community population with a lower risk for liver fibrosis. Indeed, Hagström *et al.* identified that the predictive values of the aspartate aminotransferase (AST) to platelet ratio index (APRI) (AUC 0.670), FIB-4 (AUC 0.702), and NAFLD fibrosis scores (AUC 0.624) were modest with regard to the prediction of cirrhosis and its complications in the general population.[10] However, the LTLT was specifically designed for use in individuals with underlying risk factors for liver disease, and the strong results obtained in this study will be clinically useful in this setting for ruling out liver fibrosis (NPVs > 97%).

Finally, we regret that we were unable to provide a cost-effectiveness analysis for the LTLT compared to other diagnostic algorithms as accurate costing data were not available to us. While the FIB-4 score, APRI, and AST to alanine aminotransferase ratio are cheaper, the LTLT may prove to be more cost-effective depending on its diagnostic performance in relation to these other tests. Results of this analysis would be highly informative for service providers.

Comparison to existing literature. These data validate our original findings derived from a significantly smaller cohort of 641 patients with a mean follow-up of 46 months (range 13–89 months),[5] compared to 4854 participants, and a mean follow-up time of 55 months (range 1–181 months) for this study. Our original paper showed that the LTLT predicted survival with an AUC of 0.85 (0.78–0.91), and a red score was associated with a greater risk of the death and the development of ascites and varices compared to an amber result.[5] Our findings also support the results of a preliminary analysis published by our group, which identified a Spearman rank correlation coefficient of 0.90 between a red LTLT score and an ELF test >10.5 in 597 participants.[7]

Table 3 Studies assessing the prognostic capabilities of noninvasive liver tests for survival and development of an serious liver-related events (SLE)

Study	No. participants	Liver etiology	Noninvasive liver test	AUC SLE (95% CI)	AUC mortality (95% CI)
LTLT	4854	Mixed	Continuous LTLT	0.87 (0.85–0.89)	0.81 (0.78–0.84)
Pang *et al.*, 2014	2052	Mixed	FibroScan	0.80 (0.75–0.85)	
Vergniol *et al.*, 2011	1457	HCV	FibroScan		0.82 (0.68–0.90)
			FibroTest		0.80 (0.69–0.87)
			APRI		0.66 (0.55–0.75)
			FIB4		0.75 (0.63–0.83)
Vergniol *et al.*, 2014	1025	HCV	FIB4		0.82 (0.74–0.89)
			APRI		0.80 (0.70–0.88)
			FibroScan		0.81 (0.72–0.89)
Berenguer *et al.*, 2015	903	HIV/HCV	FIB4	0.75 (0.72–0.78)	0.79 (0.76–0.83)
V. de Ledinghen *et al.*, 2013	600	HBV	FibroTest		0.82 (0.71–0.89)
			FibroScan		0.80 (0.70–0.87)
de Vries *et al.*, 2017	534	PSC	ELF score		0.80 (0.75–0.85)†
Parkes *et al.*, 2010	457	Mixed	ELF score	0.87 (0.81 to 0.92)	
Boursier *et al.*, 2016	452	NAFLD	APRI		0.54 (0.46–0.61)
			FIB4		0.70 (0.64–0.75)
			HepaScore		0.73 (0.67–0.79)
			FibroMeter		0.79 (0.74–0.83)
			FibroScan		0.72 (0.66–0.78)
Boursier *et al.*, 2014	373	HCV	APRI	0.86 (0.81–0.90)	0.87 (0.79–0.93)‡
			FIB4	0.88 (0.83–0.92)	0.91 (0.85–0.95)‡
			FibroTest	0.84 (0.78–0.90)	0.86 (0.77–0.93)‡
			HepaScore	0.81 (0.73–0.88)	0.89 (0.81–0.95)‡
			FibroMeter	0.87 (0.81–0.92)	0.88 (0.80–0.95)‡
Angulo *et al.*, 2013	320	NAFLD	NAFLD fibrosis score	0.86 (0.80–0.92)	0.70 (0.62–0.78)†
			APRI	0.80 (0.73–0.86)	0.63 (0.53–0.72)†
			FIB4	0.81 (0.76–0.87)	0.67 (0.58–0.76)†
			BARD	0.73 (0.66–0.80)	0.66 (0.58–0.74)†
Kim *et al.*, 2014	170	HBV	ELF score	0.80 (0.73–0.89)	
			FibroScan	0.73 (0.65–0.82)	
Robic *et al.*, 2011	150	Mixed	FibroScan	0.84 (0.75–0.92)	
Sebastiani *et al.*, 2015	148	NASH	APRI	0.89 (0.82–0.96)	
			FIB4	0.89 (0.83–0.95)	
			NAFLD fibrosis score	0.77 (0.69–0.91)	
Trembling *et al.*, 2012	81	ALD	ELF score	0.81 (0.71–0.90)	

†Death/liver transplantation.

‡Liver-related deaths.

ALD, alcohol-related liver disease; APRI, AST to platelet ratio; AUC, area under curve; CI, confidence interval; ELF, enhanced liver fibrosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LTLT, liver traffic light test; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis; SLE, serious liver-related event.

This study of 4854 patients represents one the largest cohorts to examine the prognostic capabilities of a noninvasive marker of liver fibrosis and is one of few to have included a mixture of liver disease etiologies (*Table* 3, Supplementary Material). FibroScan was also validated in 2052 individuals with a variety of causes of liver disease.[11] Over a median follow-up of 15.6 months, FibroScan achieved a similar prognostic AUC value of 0.80 for the prediction of an SLE. The ELF score has also achieved comparable prognostic AUC values for the prediction of liver outcomes; however, these were obtained in smaller cohorts, the largest of which includes 457 patients over a median follow-up of 7 years (AUC 0.87).[12–14] In a longitudinal study comprising 373 patients with chronic hepatitis C virus (HCV) infection, serum markers performed as follows for the prediction of an SLE: AST to platelet ratio (APRI) (AUC 0.86), FIB-4 (0.88), FibroTest (0.84), HepaScore (0.81), and FibroMeter (0.87).[15] Few studies have analyzed the performance of noninvasive markers for the prediction of individual complications of liver disease.[16,17] The LTLT predicts the development of varices with an AUC of 0.90. This value is comparable to the performance of FibroScan (AUC 0.81), APRI (0.75), and FIB-4 (0.79) for predicting portal hypertension.[18]

The ability of noninvasive liver fibrosis scores to predict overall survival has also been investigated. In a prospective study of 1025 individuals chronically infected with HCV, the prognostic performance of FibroScan (AUC 0.81) and FIB-4 (0.82) was comparable, although FIB-4 was significantly more accurate than APRI (0.80).[19] FibroScan and FibroTest accurately predicted

survival over a 5-year period with AUC values of 0.80 and 0.82, respectively, in a prospective study of 600 individuals with chronic hepatitis B.[20] In 452 NAFLD patients, a reduction in survival was observed as the stage of liver fibrosis progressed using FibroScan and FibroMeter.[21]

Clinical implications. Unlike the ELF test, which utilizes two of the same fibrosis markers, we chose not to patent the LTLT in the hope that this may make it more available to patients. The LTLT could potentially enable primary care physicians to triage patients according to their risk of developing an SLE or mortality, aiding decision-making in terms of optimizing risk factor modification and judging the need for secondary care referral. This selective process would reduce the number of unnecessary referrals to specialists and the number of liver biopsies, which may lower health-care expenditure.

FibroScan is the most extensively validated noninvasive method for detecting liver fibrosis and is recommended as the first-line tool in evaluating cirrhosis in harmful drinkers[22]; however, this is unfeasible due to FibroScan's lack of accessibility in primary care and cost-effectiveness.[23] Conversely, the LTLT has demonstrated feasibility for alcoholic liver disease in primary care and is more widely available.[6] Thus, fewer patients would require referral to secondary care for this indication alone.

When patients were divided according to an improvement or deterioration of their LTLT result over time, those who improved from a red grade had significantly lower mortality rates and SLE incidence than those who did not. No significant differences were observed when patients' grades worsened from amber to red, suggesting it is optimal to aim for, and remain in, the green grade. Similarly, significantly more patients developed SLEs when their grade deteriorated from a green score. These data support the use of the LTLT as a follow-up tool to exemplify the importance of lifestyle modifications. Although all aforementioned noninvasive liver fibrosis test results are similar to those determined in this study, the traffic light grades provide further clinical value in that results can be easily interpreted by physicians and understood by patients, so they may be incentivized to improve their risk factor burden as demonstrated in the ALDDeS study.[6]

The use of noninvasive testing by primary care physicians changed over the course of the study. Practically all the primary care requests other than those from research studies occurred during the final 2 years of this analysis, where they comprised around half of the tests requested. This represents a paradigm shift in the diagnosis of liver disease that we hope will enable more patients with liver fibrosis to be identified earlier. There is a point of reversibility for patients who have yet to develop established cirrhosis, and it is this concept that the LTLT aims to capitalize on. If patients at risk of liver disease in the community are identified and treated earlier, the rising mortality from liver disease may be averted.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Number of tests ordered from primary and secondary care and community-based research studies included in this analysis per study year.
Table S1. Distribution of the study population across different etiologies of liver disease and LTLT grade.
Table S2. Distribution across subgroups according to etiology of liver disease and change in LTLT grade.
Table S3. Distribution of study population according to etiology of liver disease and ELF test results, $n = 1225$.
Table S4. Sensitivity, specificity, and positive predictive and negative predictive values of dichotomous LTLT (red/amber *vs* green) and ELF (≤10.5 *vs* >10.5) tests for mortality and the development of serious liver-related events (SLE), $n = 1225$.