ORIGINAL ARTICLE - HEPATOLOGY (CLINICAL)

A novel smartphone scleral-image based tool for assessing jaundice in decompensated cirrhosis patients

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Abstract

Background and Aim: Serum bilirubin is an established marker of liver disease. Reliable tools for non-invasive assessment of jaundice in cirrhosis patients, at risk of clinical decompensation, are highly desirable. While smartphone-based imaging has been described in neonatal jaundice, it has not been investigated in advanced cirrhosis patients.
Methods: We included 46 hospitalized patients with acute cirrhosis decompensation and jaundice. Scleral images using an Android smartphone were taken to derive "Scleral Color Values (SCV)," which were matched with same day serum bilirubin measurements. In 29 patients, repeat SCV and bilirubin measurements were performed over time. We analyzed the relationship of SCV and its dynamics with serum bilirubin, clinical scores, and patient outcomes.
Results: Of 46 patients, 26 (57%) had alcoholic hepatitis as the decompensation precipitant. Seven patients died during admission; a further 12 following hospital discharge. SCV had an excellent linear correlation with serum bilirubin (rho = 0.90, $P < 0.001$); changes in SCV and serum bilirubin across different time points, were also closely associated (rho = 0.77, $P < 0.001$). SCV correlated significantly with CLIF Consortium Acute Decompensation score (rho = 0.38, $P < 0.001$) and grade of Acute-on-Chronic Liver Failure (rho = 0.42, $P = 0.039$). SCV was higher in patients who died, however, not significantly (86.1 [IQR 83.0–89.7] vs 82.3 [IQR 78.5–83.3], $P = 0.22$). The associations of SCV with clinical parameters mirrored those of serum bilirubin.
Conclusion: Smartphone-based assessment of jaundice shows excellent concordance with serum bilirubin and is associated with clinical parameters in acute cirrhosis decompensation. This approach offers promise for remote assessment of cirrhosis patients at-risk of decompensation, post hospital discharge.

Introduction

Serum bilirubin is an important measure of liver function in acute and chronic liver disease including cirrhosis, reflected in its significance as part of clinical scores such as the model for end-stage liver disease (MELD) score, for the assessment of severity and prognosis in cirrhosis.[1,2] Patients with decompensated cirrhosis, defined by the onset of clinical signs including jaundice, ascites, hepatic encephalopathy, and/or portal hypertensive related bleeding, require timely, regular follow-up for these complications, especially post hospital discharge. The current standard of care for such clinical reviews, include blood sampling, to aide detection of new complications and to guide appropriate management.[3] However, increasing pressures on an over-burdened healthcare system may challenge this traditional mode of practice, and this

has been further exacerbated by the COVID-19 pandemic, which necessitated telephone consultations to be instituted.[4] Thus, options to assess a patient remotely are highly desirable, and we recently performed a study of digital home management in patients with advanced cirrhosis, showing good feasibility and utility of a smartphone monitoring approach.[5] Assessment of the patients' bilirubin levels reflecting jaundice as an indication of acute decompensation, without bringing the patient to the hospital, would add a new dimension to remote monitoring for better patient care.

The visible scleral and conjunctival jaundice is not reliably quantifiable by the naked eye[6,7] but processed scleral imaging has shown good potential. In this regard, smartphone technology with its ubiquitous adoption and intuitive use, including easy and high-quality image capture, presents an obvious choice of device to assist specialist assessment for remote hepatological care. We

have previously developed an algorithm to screen for neonatal jaundice, based on scleral images obtained by a smartphone camera, and demonstrated excellent correlation between the smartphone camera-derived measurements and serum bilirubin comparable to modern transcutaneous bilirubinometers.[8] Several studies have explored the usability of scleral imaging in adults to assess jaundice; however, these were generally small in size and provided scarce information on causes of jaundice and severity of liver disease studied.[9–12] Furthermore, no previous study has focused on the validity of smartphone-based methods specifically in patients with cirrhosis and acute decompensation, where bilirubin levels commonly are beyond $10\times$ upper limit of normal.

In this study, we tested the correlation of a novel Scleral Color Value (SCV), (obtained by an Android smartphone and post-processing image algorithm analysis), with serum bilirubin levels in jaundiced patients with decompensated cirrhosis. We hypothesized there would be close concordance between serum bilirubin and SCV, as well as mapping to changes in bilirubin levels. Furthermore, we assessed if there were significant associations between the SCV parameter of jaundice and clinical scores, as well as outcome, and whether these matched the expected associations and prognostic importance of serum bilirubin.

Methods

Study design and participants. In this prospective study, we consecutively included 46 hospitalized patients with cirrhosis and acute decompensation. Inclusion criteria were age > 18 years, cirrhosis diagnosed either histologically or based on clinical, radiological and biochemical criteria, jaundice defined as serum bilirubin > 80 μmol/L and acute decompensation (increasing jaundice, ascites, hepatic encephalopathy, kidney injury or variceal bleeding) with no improvement of clinical state within the first 72 h, as assessed by the treating clinician. There were no exclusion criteria other than inability or refusal to informed consent.

Ethics for this study was granted as an amendment for a nested sub-study, to an ongoing biomarker trial in decompensated cirrhosis-The DASIMAR study (amendment 6). The DASIMAR study was approved by the local governing Research Ethics Committee (London – Harrow; REC Ref: 08/H0714/8), and the participants provided written informed consent in accordance with the Declaration of Helsinki.

Imaging was performed at the bedside by the investigators every 4 to 7 days until discharge, the interval depending on the patient's condition and bilirubin dynamics, that is, a longer interval was applied if bilirubin was unchanged within 4 days after the latest image capture. During admission, serum bilirubin was measured daily using a standard hospital bio-assay as part of routine patient management. All patients were followed for readmissions using patient records until orthotopic liver transplantation (OLT) or death, or until censored study end in March 2021.

Imaging

Image capture. For consistency during this pilot study, one dedicated Samsung S8 phone was used for all image capture. A custom-developed app was used to take the images. For each requested capture, a flash followed by no-flash image was collected in quick succession, and saved in a raw, unprocessed format. The flash turned on when the app was opened to avoid startling the subject, and a custom diffuser was placed over the flash to reduce its intensity. The subject was then asked to look to one side and images were captured of the exposed sclera. After capture, the app allowed a review of the captured flash/no-flash image-pair to ensure good image quality, and to use the subtracted signal to noise ratio (SSNR) metric[13] to check that there was sufficient difference in intensity between flash and no-flash images. The total time needed to perform imaging was < 5 min.

Image analysis. Image analysis was performed on a computer using code written with MATLAB software (MathWorks r2020b). For each capture session, one image pair was selected based on: the clarity of the sclera in the images, the alignment, and a sufficient difference in intensity between the flash and no flash images using the SSNR metric.[13] The entire exposed sclera region was then selected in both images. The selected regions of interest were automatically filtered to exclude blood vessels and regions of reflection (one post-processing image quality reviewer – M. N. H.). The color values were extracted from the raw images and then subtracted to account for changes in ambient light between different capture sessions.[13] A one-time calibration step was performed to produce results that were independent of the capture device[13]; this consisted of capturing images of a chart containing patches of known color and applying automated processing to generate a conversion to a device-independent color space. This procedure ensures that same color value will be reported for the same object using different phone cameras.[13] The conversion was applied to the subtracted data producing a new metric referred to throughout this manuscript as the Sclera Color Value (SCV).

Statistical analysis. Student's *t*-test and Mann–Whitney tests were used for comparison of normally and non-normally distributed variables between the groups, respectively. We used the χ^2-test or Fisher's exact test to assess differences in proportions. The correlation between SCV and serum bilirubin, as well as changes in these measures was analyzed using Pearson's correlation, while associations between SCV/bilirubin with clinical scores were assessed by Spearman's correlation. We used the non-parametric receiver operating characteristics (ROC) analysis to assess the performance of SCV, bilirubin and other measures to predict death or OLT, and tests of equality of areas under the ROC curve (AUROCs) for comparison of SCV with other parameters.

All data are expressed as means ± standard deviations (SD), medians with interquartile range (IQR) or proportions, and *P*-values ≤ 0.05 were considered statistically significant. STATA version 14.0 ®StataCorp LP was used for data analysis. There were no missing values in the dataset.

Results

Patient characteristics and clinical outcomes. The characteristics of patients at baseline and their outcomes are shown in Table 1. Briefly, the majority of the patients were male; the

Table 1 Patient characteristics

		n = 46
Male : female		32:14
Age (years)		49 ± 12
Serum bilirubin (μmol/L)		177 (89–352)
Child–Pugh score		10.5 (9–12)
MELD-Na score		26 (21–29)
CLIF AD score		56 (49–63)
Cirrhosis etiology (*n*, %)	Alcohol	34 (74%)
	NASH	4 (9%)
	HCV	2 (4.3%)
	AIH	2 (4.3%)
	PSC	2 (4.3%)
	Unknown	1 (2%)
	Secondary biliary cirrhosis	1 (2%)
Decompensating event (*n*, %)	Alcoholic hepatitis	26 (57%)
	Infection	8 (17.5%)
	AIH flare	1 (2%)
	DILI	1 (2%)
	Dehydration	1 (2%)
	Bleeding	1 (2%)
	Unknown	8 (17.5%)
Length of hospital stay (days)		17 (8–34)
Need for intensive care (*n*, %)		10 (22%)
Development of ACLF (*n*, %)		15 (33%)
Total death (*n*, %)		19 (41%)
In-hospital death (*n*, %)		7 (17%)
Death or OLT within 28 days (*n*, %)		5 (11%)
Death or OLT within 90 days (*n*, %)		17 (37%)

Data presented as means ± standard deviations for normally distributed variables, medians (interquartile range) for non-normally distributed variables, or proportions.
MELD-Na score, Model for End-Stage Liver Disease – sodium score; CLIF-C AD score, CLIF Consortium Acute Decompensation score; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; DILI, drug-induced liver injury; ACLF, acute-on-chronic liver failure; OLT, orthotopic liver transplantation.

dominant cirrhosis etiology was alcohol (74%); and the most common factor precipitating decompensation and admission was alcoholic hepatitis (AH) (57%). The patients had severe disease as denoted by high median Child-Pugh, MELD-Na and CLIF Consortium Acute-Decompensation score (CLIF-C AD) scores. After discharge, the patients were followed for a median of 86 (IQR 21–279) days. A total of 19 patients (41%) died within the study duration; of these, seven patients died in-hospital, and further 12 died during follow-up. Four patients received OLT, all following discharge after their initial admission. Ten patients required support in the intensive therapy unit, with a median stay of 14.5 (IQR 8–41) days, and 15 fulfilled the criteria for acute-on-chronic liver failure (ACLF) during the course of their admission. Five patients died or received OLT within 28 days, and 17 within 90 days from the date of the initial admission.

Image quality and post-processing analysis. Before study initiation, a series of test images were performed. Fourteen sets of images were collected, these were used purely for assessing image quality and app usability, and the data was not included in the results presented here. The version of the app for these test images did not include a review-step immediately after capture, including the use of the SSNR metric, and a marked improvement in image quality was seen when it was subsequently added for the main study. Moreover, during the test image capture before the study began, it was observed that images very commonly contained specular reflection and large amounts of blood vessels on the sclera. An automatic filtering function was introduced to remove these pixels from image analysis, which improved consistency of the results. Very good overall image quality was thereby achieved, with only 3% of early patient image sets having to be excluded from analysis. Also, provided the automatic check of SSNR passed and the sclera was visible and in focus, results were found to be minimally affected by image pair choice. Once images were transferred to a computer for processing, bilirubin estimates on a per-patient basis were produced in < 5 min.

Concordance of Scleral Color Value and serum bilirubin. SCV showed an excellent linear correlation with serum bilirubin ($r = 0.90$, $P < 0.001$, Fig. 1). This association seemed to lose linearity with SCV not increasing in parallel, with the few very high serum bilirubin values well over 500 μmol/L (Fig. 1). Twenty-nine patients had at least two SCV measurements, and 15 at least three measurements, with a median interval of 9 days from first reading to the last. The changes in SCV and serum bilirubin between the different time points in individual patients were also significantly associated ($r = 0.77$, $P < 0.001$, Fig. 2).

SCV associations with clinical scores and outcomes. Clinical correlates of SCV and serum bilirubin are shown in Table 2. SCV mirrored the significant associations of bilirubin with CLIF-C AD score (rho = 0.38, $P < 0.001$, Fig. 3), the length of hospital stay (rho = 0.38, $P = 0.01$), and ACLF grade in patients who developed ACLF (rho = 0.42, $P = 0.039$, Fig. 4). Baseline SCV and serum bilirubin had similar non-significant associations with death or OLT both at 28 and 90 days.

Both baseline SCV and serum bilirubin were higher in patients who died during admission, however, not significantly. Nevertheless, we performed ROC analysis to assess the predictive potential of SCV and bilirubin for in-hospital mortality, and compared it to the established clinical scores: Child-Pugh, MELD-Na and CLIF-C AD. We restricted this analysis to patients who had their first SCV measured within 3 days of admission ($n = 24$) to secure using a true baseline value of bilirubin and the clinical scores for prognostication of the admission outcome. In this analysis, SCV had an AUROC of 0.71 (95% CI 0.49–0.94), which was not inferior to serum bilirubin, Child–Pugh, MELD-Na and CLIF-C AD scores (Table 3).

Patients with AH as the decompensation precipitant, who often present with severe jaundice, constituted more than half of the cohort ($n = 26$), and had higher SCV than patients with other precipitating factors (87.5 [IQR 81.9–89.2] *vs* 79.4 [IQR 77.2–84.3], $P < 0.001$); the same was the case for serum bilirubin
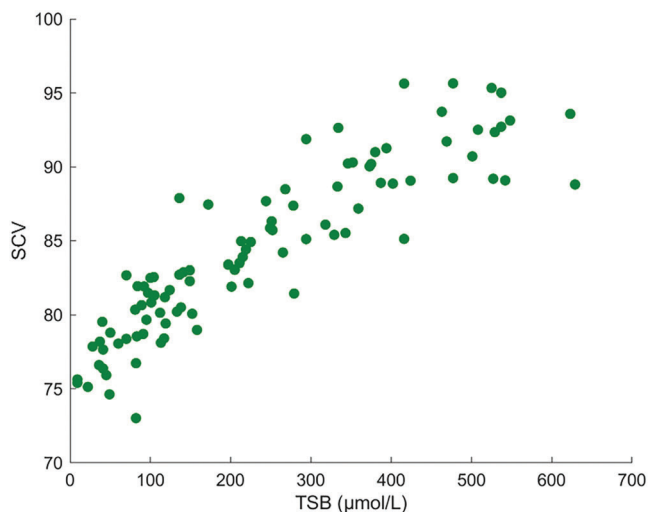
Figure 1 Association between smartphone-extracted Scleral Color Value (SCV) and total serum bilirubin (TSB). $r = 0.90$, $P < 0.001$.
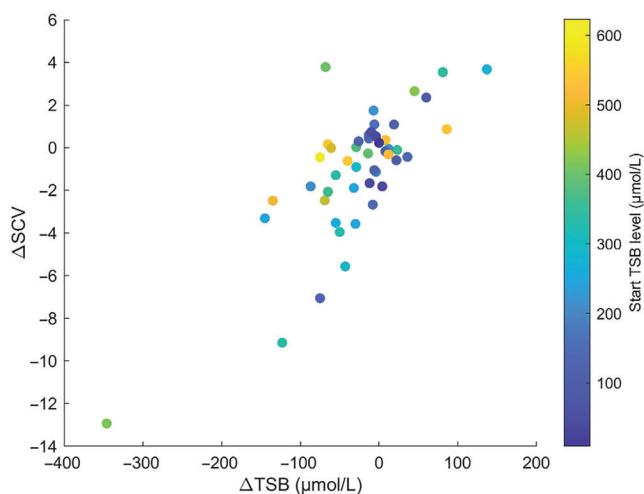

Figure 2 The relationship between changes in smartphone-extracted Scleral Color Value (SCV) and total serum bilirubin (TSB) for pairs of data collected from patients at different timepoints. Dot placement denotes the association between ΔSCV and ΔTSB, while dot color reflects baseline level of TSB. $r = 0.77$, $P < 0.001$.

Table 2 Associations of Scleral Color Value and serum bilirubin with clinical scores and outcomes

	SCV	Serum bilirubin
Length of stay	rho = 0.38, $P = 0.01$	rho = 0.34, $P = 0.02$
CLIF-C AD score	rho = 0.38, $P < 0.001$	rho = 0.35, $P < 0.001$
Development of ACLF	86.1 [82.3–89.1] *vs* 81.9 [78.5–88.5], $P = 0.15$	294 [136–402] *vs* 119 [83–352] µmol/L, $P = 0.26$
ACLF grade†	rho = 0.42, $P = 0.039$	rho = 0.35, $P = 0.025$
In-hospital death	86.1 [83.0–89.7] *vs* 82.3 [78.5–83.3], $P = 0.22$	318 [141–333] *vs* 149 [83–387] µmol/L, $P = 0.45$
Death/OLT within 28 days	83.0 [82.9–86.1] *vs* 83.4 [79.4–88.9], $P = 0.90$	205 [141–318] *vs* 158 [89–352] µmol/L, $P = 0.62$
Death/OLT within 90 days	81.1 [80.7–83.1] *vs* 83.4 [79.4–88.9], $P = 0.92$	141 [89–333] *vs* 197 [95–359] µmol/L, $P = 0.92$

†In patients who developed ACLF during admission ($n = 15$).
SCV, of Scleral Color Value; CLIF-C AD score, CLIF Consortium Acute Decompensation score; ACLF, acute-on-chronic liver failure; OLT, orthotopic liver transplantation.

(306 [IQR 119–402] *vs* 100 [IQR 65–224] µmol/L, $P = 0.002$). In AH patients, both SCV (87.9 [IQR 86.1–88.7] *vs* 87.2 [81.5–89.2], $P = 0.77$) and serum bilirubin (318 [IQR 141–333] *vs* 294 [IQR 101–477] µmol/L, $P = 0.77$) were only

slightly higher in patients who died in-hospital compared with those discharged; however, SCV in this subgroup remained significantly associated with CLIF-C AD score (rho = 0.33, $P = 0.012$).

Figure 3 Relationship between smartphone-extracted Scleral Color Value (SCV) and CLIF Consortium Acute Decompensation (CLIF-C AD) score. *n* = 93; rho = 0.38, *P* < 0.001.
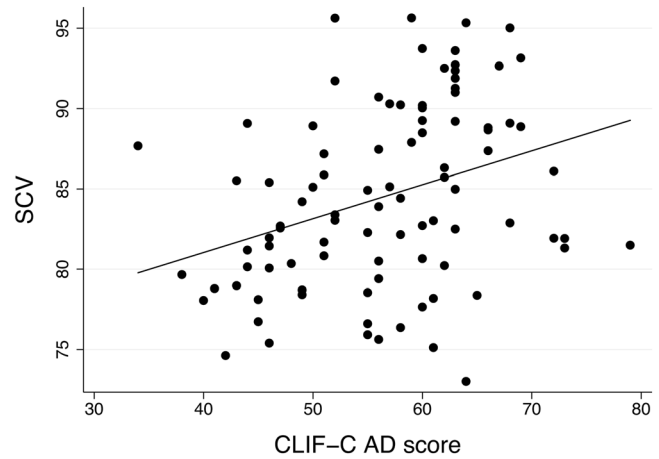

Figure 4 Relationship between smartphone-extracted Scleral Color Value (SCV) and the grades of acute-on-chronic liver failure (ACLF). rho = 0.42, *P* = 0.039.
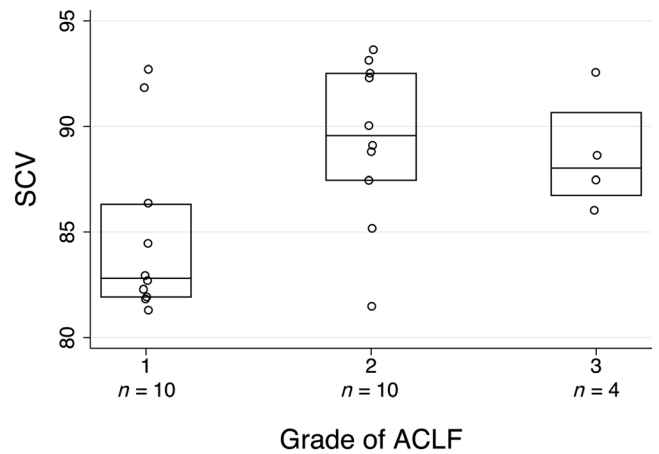
Table 3 Areas under the receiver operating characteristics curve with 95% confidence intervals for the prediction of in-hospital death by Scleral Color Value, total serum bilirubin, and Child–Pugh, MELD-Na and CLIF-C AD scores

SCV	0.71 (0.49–0.94)	*P*†
Serum bilirubin, μmol/L	0.71 (0.49–0.94)	1.0
Child–Pugh score	0.64 (0.42–0.86)	0.56
MELD-Na score	0.67 (0.41–0.94)	0.83
CLIF-C AD score	0.56 (0.41–0.88)	0.56

†*P*-value as compared with SCV using the by tests of equality of areas under the receiver operating characteristics curve.
SCV, Scleral Color Value, MELD-Na score, model for end-stage liver disease – sodium score; CLIF-C AD score, CLIF Consortium Acute Decompensation score.

Discussion

In this first study of non-invasive assessment of jaundice in advanced cirrhosis using smartphone-image analysis, we define a novel parameter, SCV, which is derived from scleral conjuctival imaging. SCV shows excellent concordance with serum bilirubin in hospitalized, acutely decompensated, cirrhosis patients. We demonstrate SCV mirrors the associations of bilirubin with clinical scores for severity of cirrhosis and decompensation, as well as admission-related parameters and temporal changes.

SCV showed a very strong linear cross-sectional correlation with serum bilirubin levels, which supported our hypothesis of accurate, smartphone-based, non-invasive assessment of jaundice in cirrhosis. Notably, the strength of the association between SCV and bilirubin levels appeared to be weaker at very high bilirubin levels of considerably greater than 500 μmol/L (×30 of normal upper reference-limits). However, this potential limitation is unlikely to impact the utility of the technology in detecting new cirrhosis decompensation, given that even far lower bilirubin levels (approx. 200 μmol/L) are used to define liver failure for ACLF criteria and need for urgent intervention.[14,15] Beyond this threshold, other end-organ factors are more impactful in defining outcomes. We also demonstrated good concordance of the changes in bilirubin and SCV over time, supporting the contention of the potential of such technology to monitor patients at-risk of acute cirrhosis decompensation. However, not all patients had serial measurements of SCV, and validation of the dynamic associations of SCV and bilirubin in future studies is warranted. Telemedicine and telemonitoring are promising tools in the management of liver disease.[5,16,17] Most patients with cirrhosis have smartphones and are willing to use them in their disease management,[18] and we

recently performed a study of remote management in patients with advanced cirrhosis, showing excellent patient engagement as well as fewer and shorter hospital readmissions and less unplanned abdominal fluid drains than in a control group.[5] Thus, integrating smartphone-based jaundice assessment into remote-home monitoring for advanced cirrhosis patients would add value and complement other digital markers of liver complications. In particular, this approach would help identify patients in the community in need of further investigation and possible hospitalization, and help focus the efforts of healthcare providers on the patients most at need. However, the time interval for detecting changes and their magnitude, require further evaluation and validation in larger cohorts.

Importantly, SCV not only had cross-sectional and dynamic associations with serum bilirubin but shared its clinical correlates. Thus, it mirrored the established significant associations of serum bilirubin with clinical parameters such as length of hospital-stay and disease severity scores, and was a moderate predictor of in-hospital mortality, suggesting potential clinical significance. SCV was not associated with the 28-day or 90-day mortality, as was also noted with serum bilirubin. Possible explanations for this null association, as well as for the only moderate prediction of SCV, bilirubin and other clinical parameters for in-hospital mortality, may include the fact that in very advanced cirrhosis decompensation, as in this population reflected by the high median clinical severity scores (MELD-Na = 26 and CLIF-C AD = 56), multiple factors contribute to deterioration and death.[19] This is evident from the current ACLF scoring system that attributes less weight to bilirubin (which is invariably high in inpatients with acute decompensation) and higher weighting to kidney and brain failure. Furthermore, a large proportion of our patients had AH, and although their short-term outcome is associated with bilirubin and its dynamics,[20–22] it may be influenced even more by systemic inflammation[23,24] and the development of multiple organ failure,[25] which is in line with our present findings of weaker associations of SCV and serum bilirubin with outcome in this subgroup of patients. The study's relatively small sample size may also have resulted in too few events to derive statistical significance for correlates of SCV and bilirubin with hard outcomes, despite the advanced disease severity, and a larger powered study would be needed to assess this endpoint. It is important to state that smartphone-based jaundice assessment tools are less likely relevant during acute hospital admission when routine lab tests are available but may provide vital diagnostic insight post-hospital discharge, by determining evolution of jaundice in the community, as an indicator of new clinical deterioration. Furthermore, this approach could potentially be tested in other conditions where assessment of jaundice out of hospital is clinically relevant.

The image capture in our study was performed by several investigators, under variable ambient light conditions, and had to accommodate patient frailty and difficulties with cooperation given their severe disease. Despite this, 97% of the resulting images, after post-capture optimization, were of sufficient quality for analysis and interpretation, highlighting the applicability of this technology in a real-life setting. We also emphasize that the image post-processing (specifically the one-time calibration step using images of a chart containing patches of known colors to generate a conversion to a device-independent color space) applied to generate the data ensures compatibility between different smartphones.[13] Given that the process of image capture is simple and not time-consuming, we assert that most caregivers to cirrhosis patients would be able to perform the assessment. Additionally, self-imaging in more able patients should be possible, given the front-facing camera of the smartphone could also be used for image capture.[13] Image processing for this study was carried out on a computer, but in the future, all processing will be incorporated into the app. The sclera segmentation process is currently not automated but sclera segmentation is an established tool with particular recent focus on achieving high accuracy results using images from smartphones.[26] Automating the segmentation step is, therefore, likely to be feasible, enabling real-time results for point-of-care testing. We estimate that once all processing is incorporated into a future version of the app, a bilirubin estimate should be produced in < 3 min on the phone.

Our study has strengths and limitations. The main strength was the successful deployment of novel technology in a well-defined group of patients with advanced cirrhosis, for real-life testing of non-invasive bilirubin measurement, for potential future application post hospital discharge in advanced cirrhosis. The SCV readings were performed within hours of the serum bilirubin measurements to avoid possible confounding effects associated with fluctuations in bilirubin in a rapidly deteriorating patient. The most significant limitation of the study was the relatively small sample size of the patient population, limiting the post-hoc analysis of prognostic significance of SCV for clinical outcomes. However, given that we performed repeated measurements in many of the patients, the total number of matching-pairs of SCV and serum bilirubin were sufficient to serve the purpose for proof-of-concept, investigating the potential utility of smartphone-based bilirubin assessment.

In conclusion, smartphone-based assessment of jaundice in decompensated cirrhosis we show is feasible and accurate, including for the detection of changes in bilirubin over time. It mirrors not only the levels of bilirubin but also its associations with clinical parameters. Given the high societal penetration of smartphones and the simplicity of image capture, this approach provides a promising tool for future testing in patients with advanced cirrhosis in the community, to monitor for new clinical complications.

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