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Quantification of gastric mucosal microcirculation as a surrogate marker of portal hypertension by spatially resolved subdiffuse reflectance spectroscopy in diagnosis of cirrhosis: a proof-of-concept study

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Abstract

Background and Aims: Portal pressure can be used to identify patients with chronic liver disease who have progressed to cirrhosis. Portal pressure can also provide accurate prognostication for patients with cirrhosis. However, there are no practical means for assessment of portal pressure. Although it is well established that the gastric mucosal blood supply increases in patients with cirrhosis, this has been difficult to quantify reproducibly. Our group has developed a novel spectroscopic technology called spatially resolved subdiffuse reflectance spectroscopy (SRSRS), which enables quantification of mucosal microcirculation. We aim to ascertain if quantification of the gastric mucosal microcirculation with SRSRS correlates with clinical evidence of portal hypertension.

Methods: Patients undergoing EGD for clinical indications had 10 measurements taken in the endoscopically normal gastric fundus via SRSRS probe to assess the microcirculation. Cases were defined as patients with cirrhosis (n = 18), and controls were those without evidence of liver disease (n = 18); this was corroborated with transient elastography.

Results: The blood volume fraction ($P = .06$) and subdiffuse reflectance ($P = .02$) from a shallow depth in the gastric fundus were higher in patients with cirrhosis than those without. These markers were combined to yield an overall optical marker that can differentiate patients with cirrhosis from controls with a sensitivity of 72% and specificity of 94% (area under receiver operating curve, 0.82).

Conclusions: Spectroscopic quantification of gastric fundal mucosal microcirculation is a promising surrogate of clinical correlates of portal hypertension. This approach may represent

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a less-intrusive surrogate biomarker for liver disease prognostication and potentially response to therapy.

INTRODUCTION

Chronic liver disease has increased rapidly in the United States by 31% between 2000 and 2015.[1,2] Deaths from cirrhosis, which is the result of progression of chronic liver disease, have increased by 65% from 1999 to 2016, and cirrhosis is the tenth leading cause of death among Americans.[3] Cirrhosis is a heterogeneous clinical entity ranging from clinically asymptomatic patients (compensated cirrhosis) to those with severe, often irreversible or life-threatening adverse events such as jaundice, variceal bleeding, ascites, and hepatic encephalopathy (decompensated cirrhosis).[4] Portal hypertension is the main driver of hepatic decompensation, and its severity correlates with decompensating events including development of varices and variceal bleeding.[4]

Portal pressure mirrors the progression of liver disease and can be estimated by an invasive technique: hepatic venous pressure gradient (HVPG).[4–6] In general, individuals without cirrhosis have an HPVG ≤5 mm Hg and in those with cirrhosis, HVPG is >5 mm Hg. Those with HVPG ≥10 mm Hg are considered to have clinically significant portal hypertension, and the development of varices and decompensating events occurs after this threshold. In a precision medicine approach to management of cirrhosis, patients with clinically significant portal hypertension are the main target for therapy with portal hypertensive agents.[4,6] Antiportal hypertensive therapies, specifically β-blockers that reduce portal pressure, have been shown to improve overall mortality in this group.[7] HPVG has been suggested as a surrogate biomarker for antiportal hypertensive treatments, such as the emerging group of antifibrotic agents.[6]

However, HVPG is an invasive, expensive, and operator-dependent test that is not routinely performed.[8] Response to portal hypertensive therapy is not measured due to lack of surrogates for HVPG. Even management of varices, a life-threatening portal hypertensive adverse event, remains suboptimal because β-blockers are empirically titrated to heart rate and not HVPG.[9] Therefore, development of an easy-to-use surrogate for HVPG that can be used for stratification of cirrhosis and as a platform for rapid clinical evaluation of existing and upcoming antiportal hypertensive agents is important. Portal hypertension has manifestations throughout the GI mucosa exemplified by portal hypertensive gastropathy (PHG). Unfortunately, PHG or other endoscopic manifestations of portal hypertension correlate modestly with portal pressure and because it is a semiquantitative and subjective measure, it is imprecise for research and clinical applications.[10–14]

Our multidisciplinary group of hepatologists/gastroenterologists have developed novel techniques to assess gut mucosal circulation in a quantitative and depth-selective manner, exploiting the pathognomonic absorption spectra of hemoglobin.[15] We have shown that measuring gut mucosal blood content can predict neoplasia in the colon and esophagus via field carcinogenesis.[16–18] We hypothesize that precise measurements of gut mucosal circulation with a novel spectroscopic technology, spatially resolved subdiffuse reflectance spectroscopy (SRSRS), may serve as a surrogate for HVPG. SRSRS has an advantage over

other optical techniques in its practicality (ease of manufacturing, low cost), facilitating potential bench to bedside transition. In this pilot study, we compared SRSRS measurements of the gastric fundic mucosa in patients with cirrhosis with those without cirrhosis. Patients were identified by the presence or absence of clinical markers of portal hypertension as surrogates.

METHODS

SRSRS technology

Our group developed the SRSRS probe to quantify in vivo tissue structure and microvasculature.[19] The probe consists of 4 optical fibers arranged in a linear array, held by a custom-made glass ferrule. The fibers have a center-to-center spacing of 60 μm. One fiber acts as a white-light illumination source, and the next 3 fibers collect backscattered light at 3 unique source detector separations (SDSs): 60, 120, and 180 μm (Fig. 1A). Notably, these SDS values are less than a transport mean free path, indicating that they are subdiffuse. This results in the SRSRS probe targeting the shortest photon paths that preserve information about the microvasculature and tissue ultrastructure (structures <~200 nm). A combination of 2 optical markers measured by the SRSRS probe were used in this study: the blood volume fraction and the relative subdiffuse reflectance. The blood volume fraction is calculated by fitting the reflectance spectrum measured by the probe between 500 and 700 nm to the absorption spectra of hemoglobin using algorithms developed previously.[20] The blood volume fraction quantifies the volume fraction of tissue sampled by the probe that is composed of blood vessels. Increased blood volume fraction indicates that blood vessels are occupying more space in the tissue (volume). Subdiffuse reflectance is a relative measure of the most subdiffuse scattering measured by the probe between 630 and 700 nm to avoid the effects of hemoglobin absorption below 630 nm. Subdiffuse reflectance is calculated as $I_{60\ \mu m}/(I_{60\ \mu m} + I_{120\ \mu m} + I_{180\ \mu m})$ where $I_{60\ \mu m}$, $I_{120\ \mu m}$, and $I_{180\ \mu m}$ are the sum of measured reflectance from the 3 fibers of the probe at 3 unique SDSs.[20] In other words, increased relative subdiffuse reflectance indicates a relative increase in the light collected by the channel with the shortest SDS (60 μm) relative to the total amount of scattered light collected by all 3 channels. From a biological perspective, an increase in the relative subdiffuse reflectance corresponds to an increase in the variance of the mass-density of tissue structures, which may be a consequence of altered microvasculature. Monte Carlo simulations have shown the SRSRS probe is sensitive to structures as small as 25 nm and as large as 10 μm and is primarily sensitive to depths up to ~300 μm (Supplementary FIgs. 1 and 2, available online at www.giejournal.org).

The SRSRS measurement unit consists of a mobile cart with a broad-band xenon light source, CPU, monitor, calibration equipment, and fiber optic probe (Fig. 1B). The automatic calibration system and system design have been described in detail previously.[21] The probe is passed through the accessory channel of the endoscope and advanced to its tip. Figure 1C shows the SRSRS probe traversing the accessory channel of the endoscope.

Patients

This single-center pilot study comparing patients with cirrhosis with those without was performed at Boston Medical Center (Boston, Mass, USA). The study was approved by the Institutional Review Board of Boston Medical Center and all patients provided consent to participate in the study.

Cases

We recruited patients with documented cirrhosis (ultrasonography, cross-sectional imaging, or transient elastography findings) who were undergoing standard of care EGD for variceal screening. Patients were excluded if they had acute variceal bleeding, history of variceal banding, history of surgical or interventional radiology interventions to the portal circulation, such as transjugular intrahepatic portosystemic shunt, splenectomy, or splenic vein embolization, or occlusive portal vein thrombosis. Patients with visible upper GI lesions, such as ulcers and tumors, were excluded.

Controls

Controls were patients undergoing EGDs without cirrhosis. We performed transient elastography on controls to exclude unrecognized cirrhosis. The most common indications for EGD on controls were dyspepsia and abdominal pain. Patients were excluded if visible GI lesions, such as ulcers or tumors, were detected.

Procedural details

The SRSRS probe was calibrated before use for each patient with a custom-designed optical fixture containing 2 calibration standards: flat field for normalizing different channels and white standard for removing the effect of the illumination lamp. In addition, an ambient measurement (probe light turned off) was subtracted from each in vivo measurement to remove the effect of the endoscope lamp.[21]

Each study participant underwent a standard of care EGD under conscious sedation or monitored anesthesia care. The fiberoptic probe was inserted into the accessory channel of the endoscope and extended to 1 cm from the tip of the endoscope (Fig. 1C). Our primary site was the gastric fundus and 10 readings were taken in close proximity to each other (2 cm) in the endoscopically normal mucosa. Each measurement is estimated to take about 250 milliseconds. Measurements were averaged to perform biomarker calculations. The average mean standard deviation of measurements from the same patient was 26.3% of the mean. Exploratory measures were taken from the esophagus, antrum, and duodenal bulb. The rest of the EGD was then completed as per standard of care.

Data analyses

Data were transferred to the Northwestern University Biomedical Engineering Department for processing and analysis. Data exclusion criteria were implemented to ensure robust biomarker calculations. To be included in the final analysis, each in vivo measurement had to have complete calibration measurements, including proper ambient measurements. In addition, the reflectance spectra had to fit to a physical model of tissue scattering.[20,22]

Specifically, measured scattering is fit using least squares fitting to the equation: $I_{measured} = I_{scattering} \times e^{-\mu_a}$ where $I_{measured}$ is the measured signal, $I_{scattering}$ is the theoretical pure scattering spectrum and μ_a is the optical absorption due to hemoglobin, which can be further decomposed into physiologic parameters such as the blood volume fraction using techniques described previously.[20] The sum of squares error (SSE) was required to be less than 2× the average SSE of all spectra. Any measurement not meeting these criteria was determined to be an aberrant measurement (eg, hardware failure, improper calibration, poor tissue contact, or damaged tissue). In addition, any patient whose biomarker values were outside the range [Q1 – 1.5(Q3 – Q1), Q3 + 1.5(Q3 – Q1)], where Q1 and Q3 are the 25th and 75th percentiles, were excluded from the analysis.

Spectroscopic parameters were compared between patients with cirrhosis and those without using the Mann-Whitney rank sum test. Parameters showing significant differences were combined by logistic regression to create a composite measure. At various cut-off values on the receiver operating characteristic curve, the sensitivity and specificity of the composite measure were determined in differentiating patients with cirrhosis from controls. Demographic information was described using means and standard deviations (where normally distributed) and frequency statistics. MATLAB software (R2018a, MathWorks Inc, Natick, Mass, USA) and SAS software (Version 9.4, Cary, NC, USA) were used for statistical analyses.

RESULTS

Tissue phantom studies

To validate the ability of SRSRS to accurately measure optical properties, we measured liquid tissue phantoms with optical properties covering the full range of expected values encountered in vivo. The experimental results were compared with Monte Carlo tissue modeling simulations to verify accurate modeling of the optical properties and probe collection geometry (Supplementary Fig. 1 and supplementary fig. 2).[23,24] Using validated simulations, we investigated the size and depth sensitivity of SRSRS.[25] Probability density functions from depth investigation simulations are shown in Figure 2. In general, if each of the 3 collection fibers samples a broad range of depths, the calculated expected value for a single photon would be ~150, ~230, and ~285 μm, respectively.

Patients

We enrolled 48 patients in the study who met all inclusion and exclusion criteria. Of these, 12 patients were excluded due to suboptimal data quality (related to measurements and/or calibrations) leaving 18 cases (patients with cirrhosis) and 18 controls (patients without cirrhosis) for the final analysis. Two patients were excluded due to incorrect calibration before measurement, 5 patients were excluded due to variability in the signal, and 5 patients were excluded because they were outliers. The demographic characteristics of the patients are shown in Table 1. Of the cases, 17% (3/18) patients had varices and 61% (11/18) had PHG. EGD did not reveal any other significant findings (ulcers, neoplasia, etc). The cause of cirrhosis was predominantly alcohol (44%), hepatitis C (33%) alone or in combination with alcohol (11%); only 2 patients had other causes.

SRSRS biomarker analysis

SRSRS analysis of the endoscopically normal gastric fundal mucosa at the shallow depth was used to analyze the blood volume fraction. This was higher in patients with cirrhosis but did not meet statistical significance ($P = .06$) (Fig. 3A). We also assessed the average blood volume radius and although it increased by ~10% in patients with cirrhosis, this was not significant ($P = .35$) (Fig. 3B). The calculated subdiffuse reflectance biomarker mirrored the blood volume fraction with a modest increase but achieved statistical significance ($P = .02$) as shown in Figure 3C.

The blood volume fraction and subdiffuse reflectance measurements were combined to yield an overall optical marker. This was strikingly different in patients with cirrhosis compared with those without ($P < .0009$) (Fig. 4A). When this combined marker was used for diagnostics, the area under the receiver operator characteristic curve was 82%, which would yield a sensitivity of 72.2% and specificity of 94.4% to differentiate patients with cirrhosis from those without (Fig. 4B). There was some suggestion of improved performance in patients with varices although this exploratory analysis must be interepreted with caution given the limited number of patients with varices.

DISCUSSION

This initial proof-of-concept study establishes that SRSRS can be used to differentiate patients with cirrhosis from those without. Specifically, a combination a spectroscopic biomarker (that integrates the blood volume fraction and subdiffuse reflectance) measured at the gastric fundus at shallow depth can distinguish patients with cirrhosis with promising performance characteristics. The power of the SRSRS approach is in its simplicity and clinical robustness; it is easy to manufacture and use in endoscopy by gastroenterologists.

Although SRSRS can yield myriad spectroscopic data, to minimize the risk of overfitting we analyzed 3 biomarkers from a shallow depth (blood volume fraction, average blood vessel radius, and relative subdiffuse reflection). The blood volume fraction is calculated gauging the percentage volume of tissue analyzed by probe that is blood. Although these data may represent either increased vessel size or vessel number, we did note an increase in average blood vessel radius,[26] albeit with high variance, suggesting that it may be multifactorial (vasodilation plus either increased influx or decreased efflux of blood in the microcirculation) (Fig. 3B). Relative subdiffuse reflectance measures the heterogeneity of structures in tissue. These are likely the tissue correlates to the tissue organizational consequences (eg, cytoskeleton changes, collagen matrix organization, etc), which may potentially be the consequences of altered microcirculation.[22]

Quantification of gut mucosal blood flow appears to be a logical biomarker for HVPG. It is established that cirrhosis, and its key pathophysiologic consequence, portal hypertension, leads to increased blood flow in the gut via the portal venous system, which extends from capillaries of the gut to the hepatic sinusoids. This increase in blood flow to the gut mucosa (gastropathy, duodenopathy, colopathy) is characterized by dilated capillaries and veins in the mucosa and submucosa, without significant inflammation. Most, but not all, studies show that the visual appearance of portal gastropathy correlates with

HVPG.[10–14,27] The grading of PHG is semiquantitative and subjective and thus imprecise for research and clinical applications. Earlier studies (from the 1990s) with reflectance spectrophotometry have demonstrated enhanced gut mucosal perfusion in cirrhosis, and it changes with antihypertensive medications and transjugular portosystemic shunts.[14,28,29] However, a single study that demonstrated correlation of gut mucosal perfusion with visual appearance of portal gastropathy found that it did not correlate with HVPG.[14] Previous attempts at quantification of gut mucosal circulation with older spectroscopic technologies have been studied as surrogates for portal pressure with mixed and unconvincing results. Although the data showed that the microcirculation was decreased in the fundus in these patients, these were based on flow and not content.[30,31] Flow would be affected by changes in resistance (eg, tortuous vessels). Furthermore, SRSRS has many more facets (detection of oxygenation status, tissue microarchitecture) that can be used in future studies.

Identifying patients with increased portal pressures is critical for developing demise-prevention strategies. Nonselective β-blockers are the mainstay for prevention of esophageal variceal hemorrhage. However, there is emerging evidence that targeting portal hypertension with nonselective β-blockers can also affect decompensation and deaths from nonvariceal causes. In the landmark PREDESCI study, nonselective β-blockers were able to prevent decompensation in a rigorous randomized controlled trial in patients even with small varices.[7] The major benefit was from reduction in ascites rather than simply prevention of GI bleeding. Furthermore, Turco et al[32] performed a meta-analysis of clinical trials and noted that patients with cirrhosis who responded to treatment with nonselective β-blockers (based on reductions in HVPG) had a reduced risk of events, death, or liver transplantation. In another study, pooled longitudinal data from the simtuzumab trial (a monoclonal antibody against lysyloxidase like 2) in patients with compensated cirrhosis related to nonalcoholic steatohepatitis showed that changes as low as 1 mmHg in HVPG, irrespective of the study arm, were associated a 15% risk of liver-related clinical outcomes, including decompensation, demonstrating the importance of reduction in portal pressure in predicting outcomes.[33] These studies underscore the paramount importance of developing more practical measures of HPVG.

The SRSRS system is a state of the art, fully automated optical spectroscopy system designed by our group to be used in clinical settings, with minimal technical training.[21] The system is designed to reduce variability in optical signals due to established factors such as pressure, angle of contact, and time of contact of the optical probe with the mucosa. The salient factors include an automated calibration tool, optical contact sensor for automated in vivo signal acquisition, and a methodology for real-time in vivo probe calibration correction, which ensure robustness of all measurements.

There are several limitations that need to be acknowledged. As this is a pilot study, the number of patients is modest. Because this was the first clinical trial of the SRSRS, endoscopist familiarity with optimal use of the technology (eg, calibration and mucosal contact) was sometimes inadequate. This may have contributed to the exclusion of 12 patients. Comparing the first 10 patients with the last 10 patients, the attrition rate declined from 40% to 10%. The learning curve was small given the low number of procedures per endoscopist (48 procedures performed by 9 endoscopists). We noted that a short inservice

training can ensure adequate performance. Thus, the SRSRS technology is physician friendly, an important requisite for implementation in clinical practice. For this proof-of-concept study, we only used 2 biomarkers to mitigate concerns of overfitting. In future studies, the performance will be evaluated in a larger cohort of patients with different causes of cirrhosis, and it is expected to improve with the development of algorithms with more biomarkers along with assessment of different penetration depths (current depth was empirically chosen at ~150 μm). Inflammation and neoplasia can affect mucosal blood flow, therefore the performance of SRSRS for quantification of portal hypertension in the presence of these conditions will also need to be explored. Our focus was on the gastric fundus (based on the prevalence of PHG), but this does not preclude other sites as being more diagnostic, albeit this would likely require experimenting with several penetration depths (given the distinct mucosal thickness). Finally, although measurement of portal pressure would have been more rigorous, HVPG is impractical, expensive, and invasive (hence the clinical impetus for this approach). We used transient elastography to determine liver stiffness, a parameter used routinely in clinical practice with a high performance for diagnosis of cirrhosis.[34,35] In addition, our cases are likely to have portal hypertension because they had a median liver stiffness of 28 kPa (interquartile range, 21–32 kPa), which is above the threshold for cirrhosis (11–12.5 kPa)[35] and suggests clinically significant portal hypertension (20–25 kPa).[4]

In summary, quantification of gastric fundal mucosal circulation by SRSRS can differentiate patients with cirrhosis from those without and is simple, feasible, and safe during endoscopy. This was a proof-of-concept study, and further refinement of the technology will undoubtedly improve performance, including biomarkers, and determine appropriate gut mucosal location. From a clinical deployment perspective, this approach could be used in a standard EGD, using ultrathin endoscopes (potentially with the patient not under sedation) or by targeting more readily accessible mucosa (eg, rectal mucosa).[28] Our long-term vision would be to use SRSRS for both risk stratification of cirrhosis and as a companion biomarker for therapeutics to ascertain whether a particular intervention (eg, nonselective β-blocker or emerging agent such as an antifibrotic) is effective, bringing the era of personalized medicine into the care of patients with cirrhosis.[36]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

HVPG	hepatic venous pressure gradient

PHG	portal hypertensive gastropathy
SDS	source detector separation
SRSRS	spatially resolved subdiffuse reflectance spectroscopy

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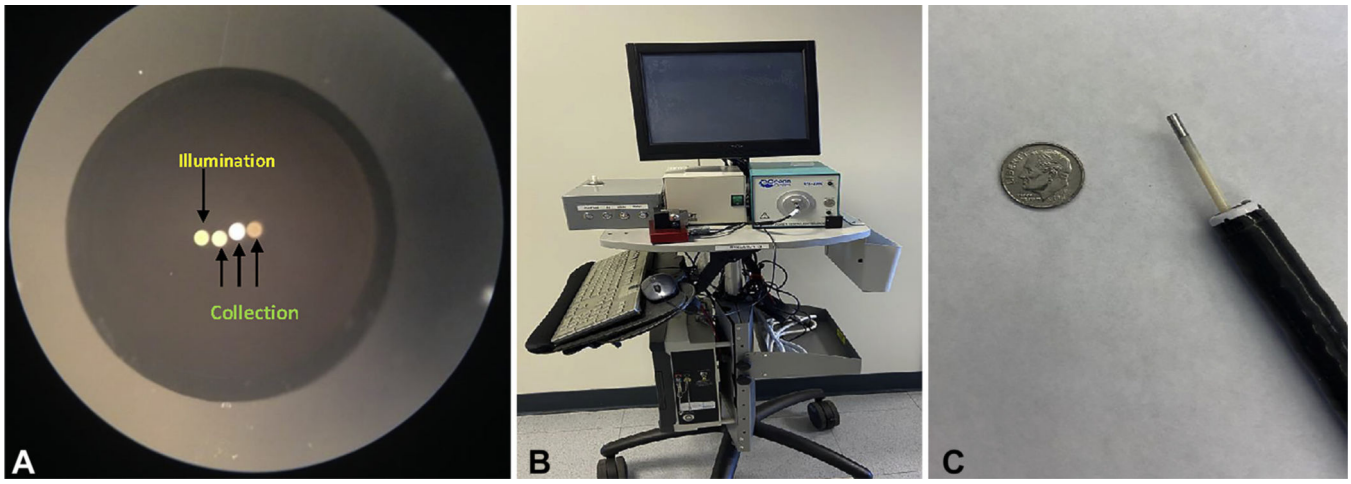

Figure 1.

Spatially resolved subdiffuse reflectance spectroscopy (SRSRS) instrumentation and probe. **A,** SRSRS optical fiber arrangement. **B,** SRSRS instrumentation, including the spectrophotometer and central processing unit (CPU). **C,** The SRSRS probe in the accessory channel of the endoscope.

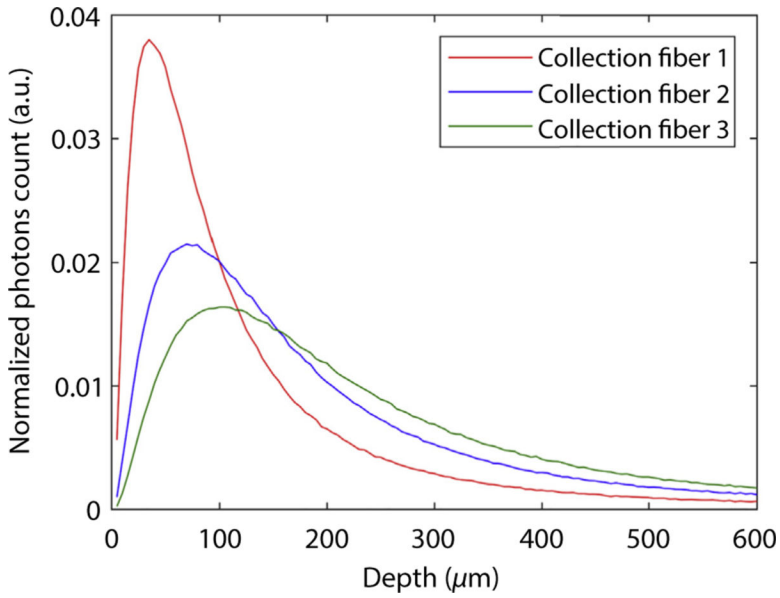

Figure 2.

Penetration depth of spatially resolved subdiffuse reflectance spectroscopy (SRSRS) probe fibers. The probability density function for the depths sampled by the 3 fibers. This demonstrates that although each fiber samples a broad range of depths, the calculated expected value for a single photon (photon origination depth) would be ~150, ~230, and ~285 μm for the 3 fibers.

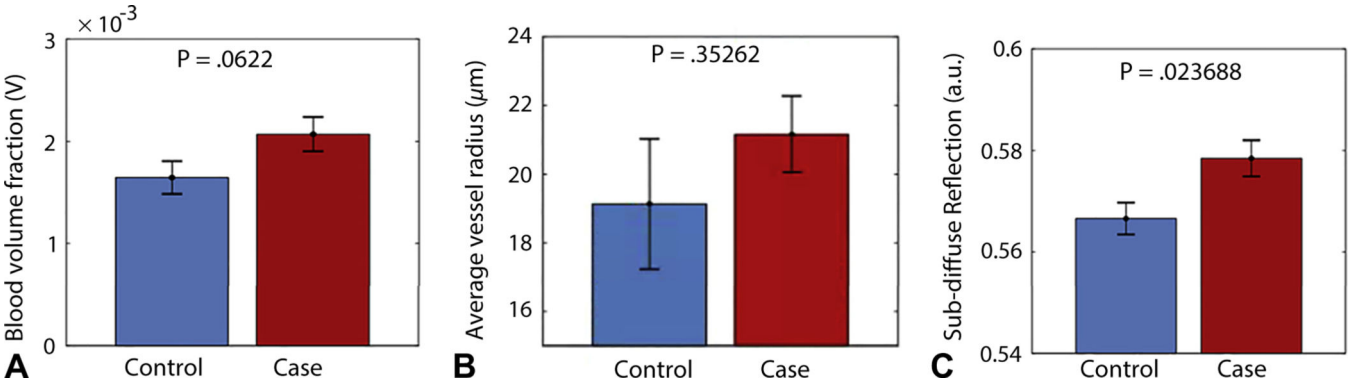

Figure 3.

Spatially resolved subdiffuse reflectance spectroscopy (SRSRS) biomarkers in the fundus of the stomach with cases (cirrhotics) and controls. **A,** Blood volume fraction; **B,** blood vessel radius; **C,** subdiffuse reflectance in controls (patients without cirrhosis) and cases.

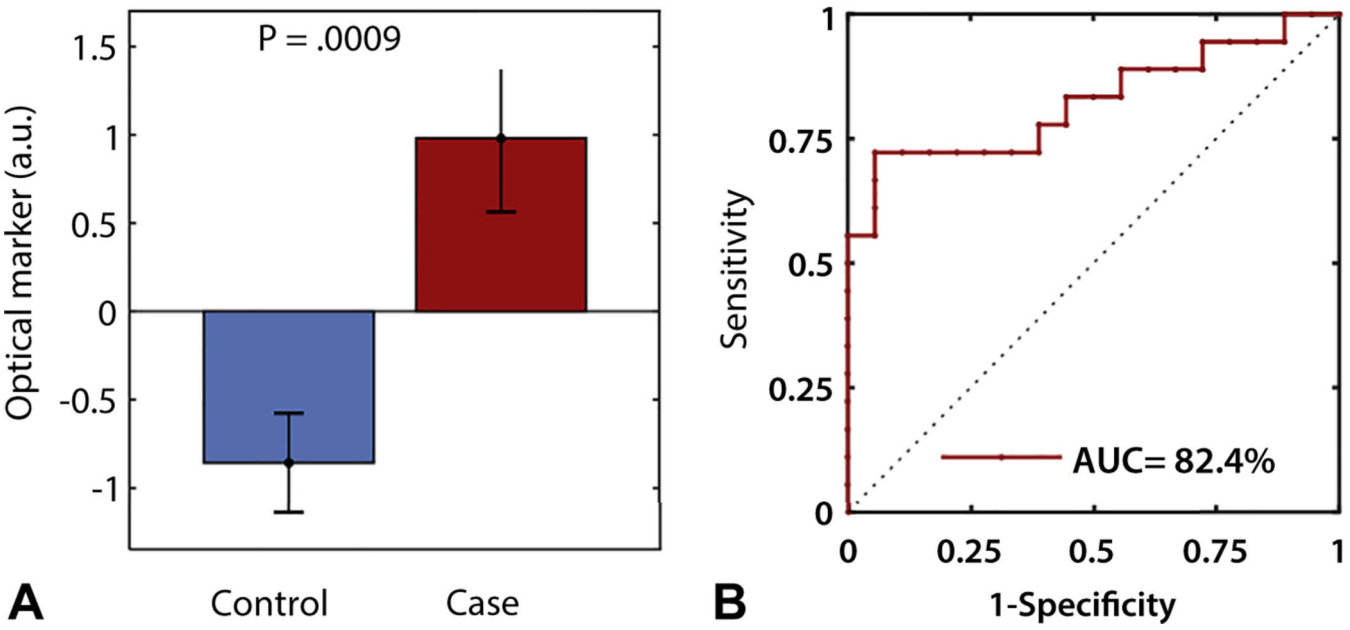

Figure 4.

A, The combination spatially resolved subdiffuse reflectance spectroscopy (SRSRS) biomarker that integrated blood volume fraction and subdiffuse reflectance was significantly different in controls (patients without cirrhosis) compared with cases (patients with cirrhosis). **B,** The combination spectroscopic biomarker had good accuracy (area under the receiver operator characteristic curve [AUC] = 0.82) for the diagnosis of cirrhosis.

TABLE 1.

Characteristics for cases (patients with cirrhosis) and controls

	Case (n = 18)	Control (n = 18)	*P* value
Age (years), mean ± SD	60 ± 10	58 ± 9	.41
Male sex	14 (78)	13 (77)	1.00
Race			
White	12 (67)	9 (50)	.22
Black	6 (33)	6 (33)	
Declined	0 (0)	3 (17)	
Ethnicity			1.00
Hispanic	2 (11)	1 (6)	
Non-Hispanic	16 (89)	17 (94)	
Body mass index (kg/m^2), mean ± SD	33 ± 8	28 ± 7	.07
Active alcohol use	6 (33)	2 (11)	.23
Mean liver stiffness (kPa), median (IQR)	27 (21–32)	4 (3–5)	<.0001

There were no important differences aside from expected differences in measurements from transient elastography (liver stiffness). Values are number (%) except where indicated otherwise.

SD, Standard deviation; *IQR*, interquartile range.