

Psychomotor Speed From Minimal Hepatic Encephalopathy Testing Is Associated With Physical Frailty In Patients With End-stage Liver Disease



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Introduction

- Physical frailty is strongly correlated with reduced cognitive function not only in the elderly but also in patients with end-stage liver disease (ESLD)^{1,2}
- The Stroop Color and Word test is a neuropsychological test that assesses the ability to inhibit the cognitive interference that occurs when the processing of one stimulus impedes the simultaneous processing of a second stimulus (the Stroop effect).³ A smartphone-based version of the Stroop test—Stroop EncephalApp—has been validated in the United States for screening and diagnosis of minimal hepatic encephalopathy (HE)^{4,5}
- Physical frailty is highly prevalent in ESLD, particularly among patients with HE.⁶ The Liver Frailty Index (LFI), a performance-based measure of physical function combining grip strength, chair stands, and balance, is a validated frailty assessment tool for patients with cirrhosis and ESLD⁷
- While the LFI comprises tests of physical performance, it might conceivably also capture the contributions of cognitive impairment to physical frailty in ESLD

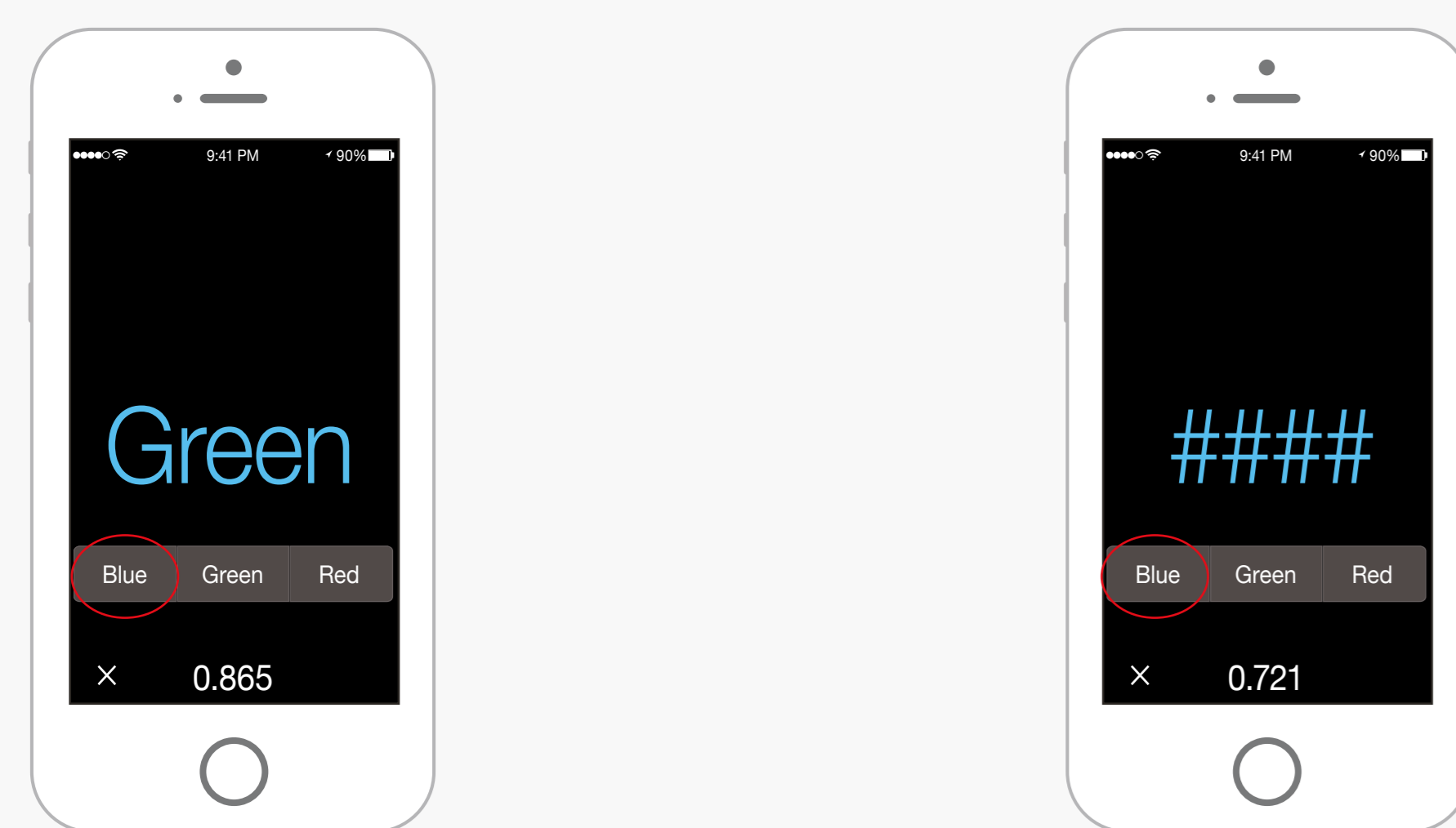
Aim

- To assess the relationship between cognitive impairment (assessed with Stroop EncephalApp) and physical frailty (assessed with LFI) in cirrhosis

Methods

- Patients with cirrhosis of any etiology (with or without hepatocellular carcinoma) who were listed for liver transplant were enrolled into this observational study at 3 US clinical centers (University of California, San Francisco; University of Pittsburgh Medical Center; and Baylor University Medical Center). Patients presenting with overt HE or color blindness were excluded
- On study entry, patients were assessed for frailty (LFI), minimal HE (Stroop EncephalApp), and overt HE (modified orientation log [MO-log] and Clinical Hepatic Encephalopathy Staging Scale [CHESS])
- In the Stroop test, subjects are simultaneously presented with 2 conflicting stimuli (a word stimulus and a color stimulus) and are required to successfully complete 2 tasks: an easier “Off”-state task and a more difficult “On”-state task:
 - In the Off-state task, the subject views a neutral stimulus (####) presented in red, green, or blue, one at a time, and has to respond as quickly as possible by touching the matching word (“Red,” “Green,” or “Blue”) displayed at the bottom of the screen (Figure 1)
 - In the On-state task, the subject is presented with discordant-colored words (eg, the word “Green” is presented in blue, and the correct answer is “Blue”) (Figure 1)
 - Outcomes are expressed as the total time needed to complete 5 correct runs (each comprising 10 presentations) in the Off state (Off-time) and in the On state (On-time)

FIGURE 1 The Stroop EncephalApp Evaluates Psychomotor Speed and Cognitive Alertness by Measuring the Time Required to Correctly Identify a Series of Symbols and Printed Words of Different Colors



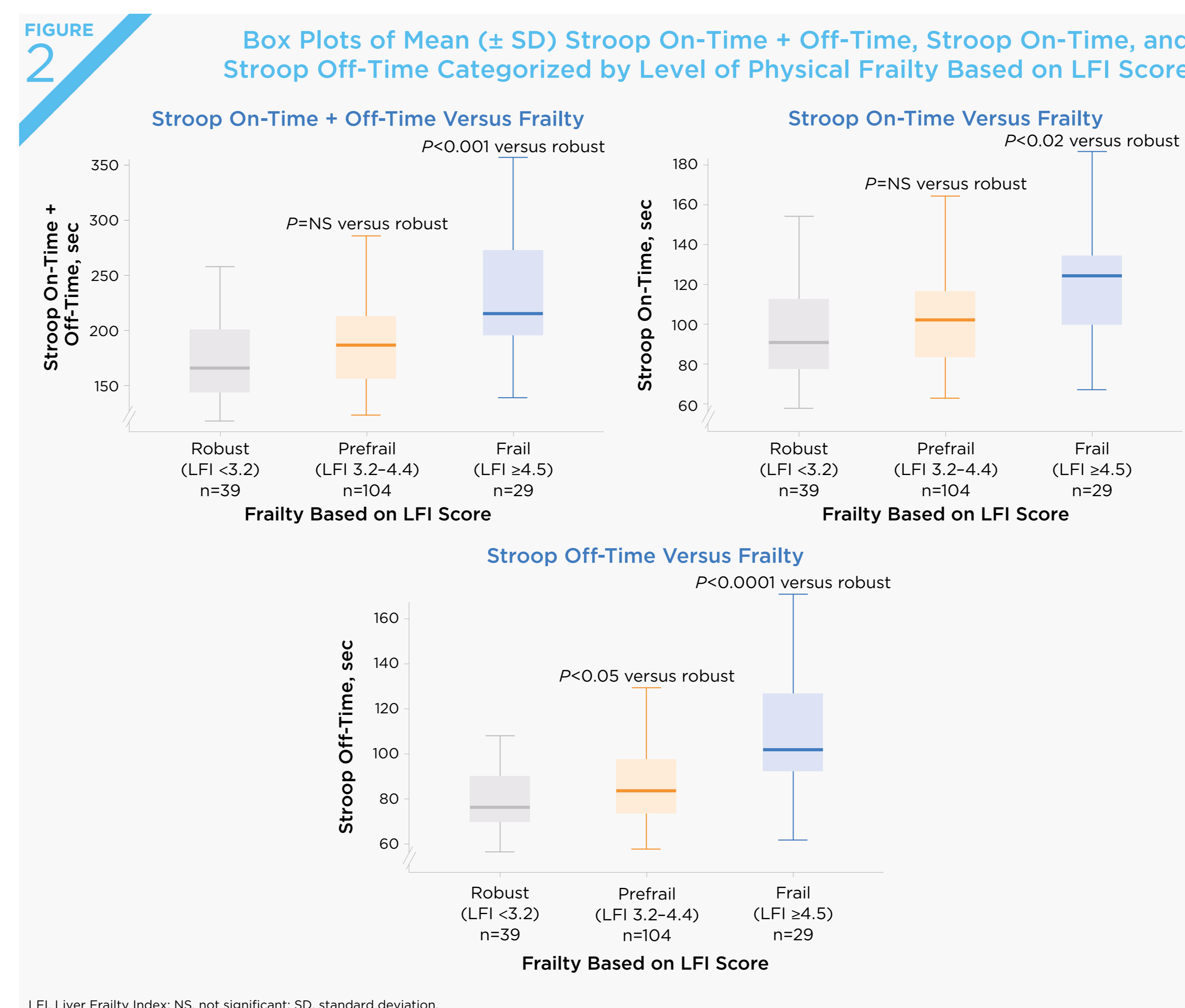
On-state task: subjects are instructed to tap the button (“Blue,” “Green,” or “Red”) corresponding to the font color rather than the meaning of the presented word as quickly and accurately as possible.

Off-state task: subjects are instructed to tap the button (“Blue,” “Green,” or “Red”) corresponding to the font color of the presented symbol as quickly and accurately as possible.

- Stroop On-time (a measure of response inhibition and psychomotor speed), Stroop Off-time (primarily a measure of psychomotor speed), and their combinations were analyzed separately to better characterize the contributions of cognitive processing via response inhibition (On-time minus Off-time) and psychomotor speed (Off-time). Expected Stroop EncephalApp values (US-based population norms) were obtained from www.encephalapp.com
- LFI represents the aggregate score of gender-adjusted handgrip strength, chair stand, and balance tests and is generated using an online calculator (<https://liverfrailtyindex.ucsf.edu>), with a higher LFI score indicating greater frailty
 - LFI = $(-0.33 \times \text{gender-adjusted grip strength}) + (-2.529 \times \text{number of chair stands per second}) + (-0.04 \times \text{balance time}) + 6$
- Classification of frailty (robust, prefrail, and frail) was based on established LFI score cutoffs, with “robust” defined as an LFI score of <3.2, “prefrail” as an LFI score between 3.2 and 4.4, and “frail” as an LFI score of ≥ 4.5 ⁸
- Pearson correlation and multivariable linear regression models were used to identify factors underlying variability in Stroop EncephalApp parameters

Results

- Of 207 patients enrolled in the study, 172 patients (mean \pm standard deviation) age 58 \pm 10] years) with Child-Pugh class A (32%) or class B/C (68%) cirrhosis underwent Stroop and LFI evaluation
- Evaluated patients were predominantly White (93%) and male (59%). The main etiologies of cirrhosis were alcohol abuse (37%) and nonalcoholic steatohepatitis (25%)
- Of the 172 patients tested, 97% had normal mentation (MO-log score ≥ 23), 81% had minimal HE, and none had overt HE (CHESS ≥ 3); however, 69% of patients had prior overt HE
- Neurocognitive dysfunction as indicated by Stroop On-time + Off-time, Stroop On-time, and Stroop Off-time increased across LFI frailty categories (Figure 2). Stroop On-time + Off-time showed a linear relationship with LFI score ($\rho = 0.28$, $P < 0.001$) (Figure 3) of similar magnitude to that observed for age ($\rho = 0.29$, $P < 0.001$) and education ($\rho = -0.24$, $P < 0.002$) (Figure 3)
- The correlation between Stroop EncephalApp time modality and LFI score was strongest for Off-time ($\rho = 0.37$, $P < 0.0001$), intermediate for On-time ($\rho = 0.20$, $P < 0.01$), and weakest for On-time minus Off-time ($\rho = -0.05$, $P = 0.5$), suggesting that psychomotor speed was the main factor driving the association between neurocognitive and physical function (Figure 4)
- Multivariable analysis with adjustment for age, education, and gender indicated that Stroop On-time + Off-time ($\beta = 15.4$, $P < 0.02$) and Stroop Off-time ($\beta = 9.0$, $P = 0.001$) were the only Stroop EncephalApp parameters significantly associated with LFI score (Table 1)



LFI, Liver Frailty Index; NS, not significant; SD, standard deviation.

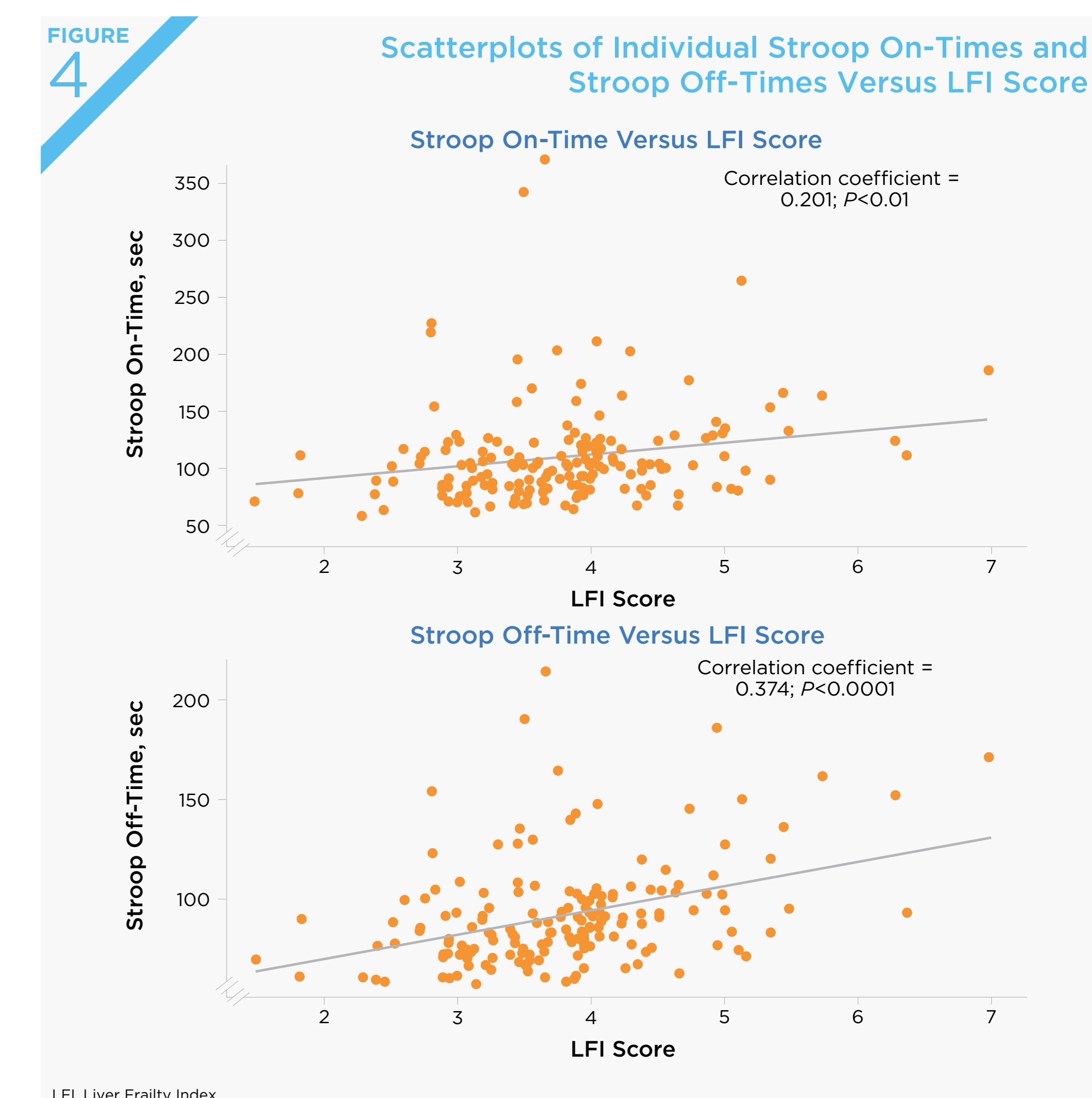
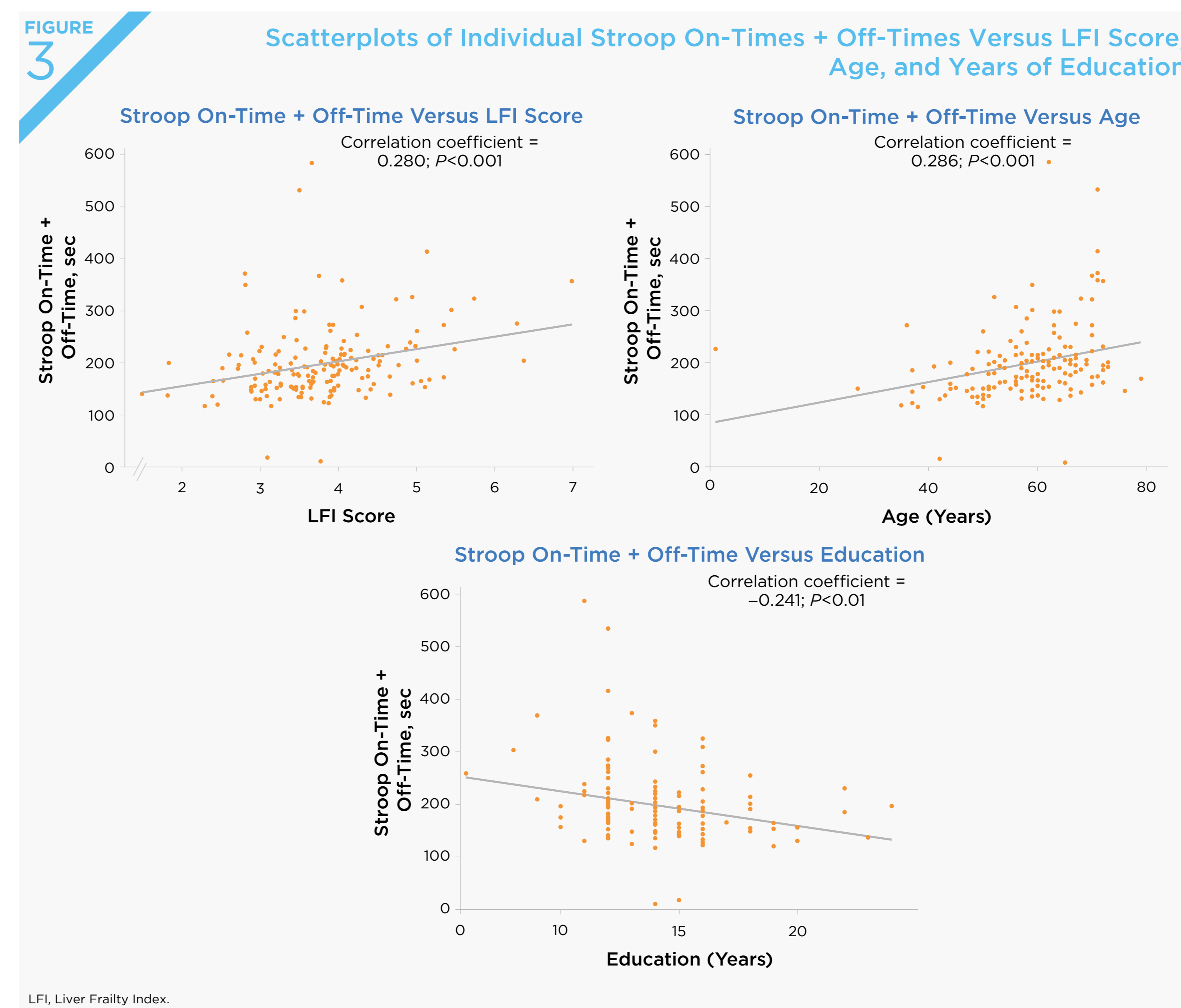


Table 1: Multivariable Regression Analysis of the Association Between Stroop Time, LFI Score, Gender, Age, and Education

	LFI Score	Male Gender	Age (Years)	Education (Years)
Stroop On-time + Off-time				
Coefficient	15.4	-11.9	1.68	-4.9
P-value	0.018	0.252	0.001	0.015
Stroop On-time				
Coefficient	5.0	-11.6	1.04	-2.8
P-value	0.219	0.078	0.001	0.025
Stroop Off-time				
Coefficient	9.0	-5.7	0.6	-1.9
P-value	0.001	0.142	0.002	0.010
Stroop On-time - Off-time				
Coefficient	-4.0	-5.9	0.5	-0.9
P-value	0.132	0.165	0.019	0.264

LFI, Liver Frailty Index.

Conclusions

- The association between physical and neurocognitive dysfunction in cirrhosis appears to be mainly attributable to reduced psychomotor speed rather than to impaired cognitive processing. Psychomotor slowing in cirrhosis may have central and/or peripheral components, including cognitive control impairment, neuromuscular weakness, and incoordination^{9,10}
- Our findings suggest that comprehensive assessment of minimal HE should include frailty metrics. The demonstrated brain-muscle relationship further supports investigating interventions targeting both physical and cognitive function in ESLD

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