

ORIGINAL ARTICLE

Speech patterns and enunciation for encephalopathy determination—A prospective study of hepatic encephalopathy

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Abstract

Hepatic encephalopathy (HE) is a complication of cirrhosis that benefits from early diagnosis and treatment. We aimed to characterize speech patterns of individuals with HE to investigate its potential to diagnose and monitor HE. This was a single-center prospective cohort study that included participants with cirrhosis with HE (minimal HE [MHE] and overt HE [OHE]), cirrhosis without HE, and participants without liver disease. Audio recordings of reading, sentence repetition, and picture description tasks were obtained from these groups. Two certified speech-language pathologists assessed speech rate (words per minute) and articulatory precision. An overall severity metric was derived from these measures. Cross-sectional analyses were performed using nonparametric Wilcoxon statistics to evaluate group differences. Change over time in speech measures was analyzed descriptively for individuals with HE. The study included 43 total participants. Speech results differed by task, but the overall pattern showed slower speech rate and less precise articulation in participants with OHE compared to other groups. When speech rate and precision ratings were combined into a single speech severity metric, the impairment of participants with OHE was more severe than all other groups, and MHE had greater speech impairment than non-liver disease controls. As OHE improved clinically, participants showed notable improvement in speech rate. Participants with OHE demonstrated impaired speech rate, precision, and speech severity compared with non-liver disease and non-HE cirrhosis. Participants with MHE had less pronounced impairments. Speech parameters improved as HE clinically improved. **Conclusion:** These data identify speech patterns that could improve HE diagnosis, grading, and remote monitoring.

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INTRODUCTION

Hepatic encephalopathy (HE) is defined as a reversible cognitive dysfunction caused by hepatocellular dysfunction and/or portosystemic shunting.^[1] Early identification and treatment of HE can improve quality of life, decrease readmissions, and reduce mortality.^[2–6] HE diagnosis and staging can be challenging, as the symptoms are nonspecific. Asterixis emerges only in later stages and is present in other conditions, while lab tests like blood ammonia have inadequate positive predictive value.^[7–11] Gold-standard clinical grading systems, such as the West Haven criteria,^[1] are limited by high interrater variability.^[12] Valid and reliable tools to diagnose and stage HE would improve its clinical care.

Changes in speech are often clinically apparent in HE, particularly in individuals with overt HE (OHE), defined as West-Haven criteria grade ≥ 2 HE. Speech changes may arise as a result of altered neurotransmission, cerebral edema, and/or blood–brain barrier disruption.^[13] This raises the possibility that more subtle changes in speech may be apparent in grade 1 HE or minimal hepatic encephalopathy (MHE). Distinctive speech patterns are linked to many other conditions that affect the nervous system, including Parkinson's disease, depression, and amyotrophic lateral sclerosis (ALS).^[14,15] Given the altered speech patterns seen in HE and the success of applying speech analysis to other diseases, it may be feasible to identify distinctive speech patterns that can assist in the diagnosis or grading of minimal or overt HE.

The objectives of this prospective clinical study were to assess the association between speech rate, precision, and overall severity with the presence and severity of HE and to determine whether changes in speech correlate with degree of severity. The hypothesis of this investigation was that distinctive speech patterns would differentiate patients with and without HE and that speech patterns would improve in individuals as HE resolved.

METHODS

Study setting

This prospective cohort study was performed within the University of North Carolina (UNC) health system. The UNC Institutional Review Board approved this project (#18–2151).

OHE participants

Participants aged 18–75 years were recruited during a hospitalization for OHE, defined by West-Haven criteria grade 2 or 3 HE^[1] diagnosed by a trained clinician.

Exclusion criteria included critical illness (e.g., mechanical ventilation, shock requiring vasopressors, renal failure requiring hemodialysis), presence of a nasogastric tube or other device that might affect speech, non-English primary language, severe hearing or vision loss, pregnancy, recent heavy alcohol use or psychoactive drugs that could impair mental status or speech, significant electrolyte abnormalities, or severe neuropsychiatric disorders. These exclusion criteria were chosen to exclude participants with alternative causes of altered mental status, which may be associated with abnormalities in speech. Given OHE participants' impaired mental status, consent was provided by their designated power of attorney or legal next of kin.

Non-OHE participants

Two groups of non-OHE controls aged 18–75 years provided consent and were enrolled in the outpatient setting: (1) non-OHE cirrhosis and (2) non-liver disease controls. The non-OHE group consisted of participants with cirrhosis who were receiving care at UNC hepatology outpatient clinics and had no current or prior HE diagnosis or treatment. These participants were further divided into those with MHE and non-HE cirrhosis based on the results of Stroop Encephalapp, a validated tool for the detection of MHE.^[16,17] To define MHE, population-based norms for Stroop Encephalapp were used.^[18] Non-liver disease controls were patients receiving care at UNC outpatient clinics with no clinical, laboratory, or radiologic evidence of liver disease.

Data collection

Baseline characteristics were extracted from the electronic health record, including age, sex, race, ethnicity, body mass index, smoking status (none/current/former), diabetes, alcohol intake, and years of education. For participants with cirrhosis, additional data extracted included the etiology of cirrhosis, Model for End-Stage Liver Disease–Sodium score, and Child-Pugh score. For patients with OHE, the potential precipitating cause of OHE was determined via chart review.

At enrollment, participants with OHE were administered the Mini-Mental State Exam (MMSE), a validated tool to screen for cognitive impairment,^[19] and HE was graded by study staff using the West-Haven Criteria.^[1] Speech recordings were obtained from all participants at the time of enrollment. Participants were asked to answer a set of scripted questions about HE symptoms, repeat words and sentences of varying length, prolong a vowel, count from 1 through 20, repeat syllables (pa, ta, ka) rapidly and steadily to determine diadochokinetic rate and rhythm, complete the Modern Cookie Theft Picture task to evaluate

connected speech,^[20] and read a standardized text out loud—The Caterpillar Passage.^[21,22] These three speaking tasks were chosen because they are associated with different cognitive and motor demands. Sentences are primarily sensitive to motor impairment and, to a lesser extent, working memory. In contrast, the reading task and picture description have a greater cognitive load, with the picture description allowing for easier interpretation of results in the context of language and literacy differences. This speech sample was audio recorded on an Apple iPad, using a Sennheiser clip-on condenser microphone.

West-Haven grading, MMSE, and voice recordings were performed every day of hospitalization until clinical resolution of OHE (defined as West Haven grade <2 and MMSE >25). Repeat assessments of participants with OHE were performed during any readmission to UNC Hospitals for HE and at 3 months after the index admission.

During the enrollment visit for non-liver disease controls, non-HE cirrhosis and individuals with MHE, all assessments were performed including MMSE, Stroop Encephalapp, and standardized speech recordings. Participants with MHE and non-HE cirrhosis had repeat assessments performed at 3 months after index enrollment visit.

Speech analysis

Speech metrics assessed included speech rate, perceptual rating of articulatory imprecision, and a computed metric combining the two former measures. Speech rate, defined as the number of words produced per minute of talking time, was measured by a blinded analyst. Perceptual ratings of articulatory imprecision were completed independently for all participants by two certified speech-language pathologists with expertise in neurologic communication disorders (authors AJ and KLH). Ratings were completed in sets by sample type (e.g., sentences, reading, picture description), with samples from different groups disguised, mixed, and randomized to reduce possible bias. A five-point Likert scale was used (1 = no imprecision, 2 = equivocal/questionable imprecision, 3 = mild imprecision, 4 = moderate imprecision, 5 = severe imprecision). Samples were presented and ratings recorded using Alvin3 software.^[23] Interrater reliability of the ratings was determined by percentage of samples within 1 rating scale point. According to this criterion, the raters were reliable for 99% of the picture description samples, 91% of reading samples, and 93% of sentences. No rating differed by more than 2 rating points. Because of the overall high reliability, the two listeners' ratings were averaged for each speech sample.

Overall speech severity was calculated as the summed Z scores of speech rate and speech precision,

with Z scores computed with reference to the mean and SD measures of the non-liver disease control group. For the overall speech severity metric, higher numbers represent greater impairment (e.g., speech rate less than the healthy mean and imprecision ratings greater than the healthy mean), and lower numbers represent less impairment.

Speech rate, precision, and overall severity were chosen because they are sensitive to dysarthria, which is a clinical feature of OHE. Based on a blinded initial review of the recorded speech samples, it was the impression of authors AJ and KLH that the dysarthria type was ataxic. This type is known to affect primarily the speech dimensions of articulatory precision and speech timing. Additionally, speech rate is sensitive to cognitive impairment and degree of cognitive effort, which are both affected by HE.

Statistical analysis

Intergroup comparisons for all measures at baseline were performed for groups via Kruskal-Wallis and Wilcoxon signed-rank tests, with pairwise comparisons among groups using multiple Wilcoxon tests. Intraparticipant assessment of change over time was performed descriptively. Finally, we performed subgroup analyses of baseline speech metrics among patients with MHE who subsequently developed OHE after enrollment using nonparametric Wilcoxon tests for the comparisons.

RESULTS

The study included 43 participants (15 non-liver disease controls, 6 non-HE cirrhosis, 13 MHE, and 9 OHE) enrolled from December 12, 2018, to January 31, 2020. In total, participants provided 103 separate days of voice recordings. Baseline characteristics are included in [Table 1](#).

Between-group differences in speech rate

Cross-sectional comparisons of speech rate can be found in [Figure 1](#). Overall speech rate was fastest for the sentence repetition task, followed by reading and picture description. In the sentence repetition task, the OHE group (median, 124 words/min; 95% confidence interval [CI], 91–149) was significantly slower compared with MHE (median, 167 words/min; 95% CI, 157–178; $p < 0.01$), non-HE cirrhosis (median, 170 words/min; 95% CI, 149–209; $p < 0.01$), and non-liver disease controls (median, 165 words/min; 95% CI, 155–206; $p < 0.01$). There were no other significant differences between groups. Similarly, for the

TABLE 1 Demographic and clinical characteristics of study participants^a

	Non-liver disease controls (n = 15)	Non-HE cirrhosis (n = 7)	Cirrhosis, MHE (n = 12)	OHE (n = 9)
Age, median (IQR)	62 (45–64)	54 (49–57)	59 (54–64)	54 (46–60)
Female (%)	11 (73%)	4 (57%)	4 (33%)	3 (33%)
BMI, median (IQR)	28 (24–32)	28 (22–38)	26 (24–30)	30 (28–36)
Race/ethnicity				
Black	5 (33%)	0 (0%)	3 (25%)	1 (11%)
White/Hispanic	0 (0%)	0 (0%)	0 (0%)	0 (0%)
White/non-Hispanic	10 (67%)	7 (100%)	9 (75%)	9 (89%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Education (years), median (IQR)	15 (14–18)	14 (14–16)	12 (12–15)	12 (11–14)
Diabetes	2 (13%)	3 (43%)	3 (25%)	3 (33%)
Smoking				
Current	1 (7%)	2 (29%)	6 (50%)	0 (0%)
Prior	1 (7%)	1 (11%)	3 (25%)	4 (44%)
Etiology of Cirrhosis (%)				
HCV	–	3 (43%)	6 (50%)	1 (11%)
HBV	–	0 (0%)	1 (8%)	0 (0%)
ALD	–	1 (14%)	0 (0%)	3 (33%)
HCV + ALD	–	0 (0%)	3 (25%)	1 (11%)
NASH	–	3 (43%)	0 (0%)	4 (44%)
AIH	–	0 (0%)	2 (16%)	0 (0%)
Other	–	0 (0%)	0 (0%)	0 (0%)
MELD-Na, median (IQR)	–	8 (6.5–8)	7.5 (7–10.5)	18 (16–25)
Child-Pugh score, median (IQR)	–	5 (5–5)	5 (5–5)	11 (9–13)
Precipitating factor for HE (%)				
Nonadherence to lactulose/ rifaximin	–	–	–	6 (67%)
Sepsis/Infection	–	–	–	1 (11%)
TIPS	–	–	–	1 (11%)
GI bleeding	–	–	–	0 (0%)
AKI/dehydration	–	–	–	1 (11%)

Abbreviations: AIH, autoimmune hepatitis; AKI, acute kidney injury; ALD, alcohol-related liver disease; BMI, body mass index; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; MELD-Na, Model for End-Stage Liver Disease–Sodium; NASH, nonalcoholic steatohepatitis; TIPS, transjugular intrahepatic portosystemic shunt.

^aBased on data at the time of enrollment.

reading task (i.e., Caterpillar passage), speech rate was slower for OHE (median, 48 words/min; 95% CI, 25–110) compared with MHE (median, 153 words/min; 95% CI, 135–172; $p < 0.01$), non-HE cirrhosis (median, 151 words/min; 95% CI, 141–165; $p < 0.05$), and non-liver disease controls (median, 164 words/min; 95% CI, 154–189; $p < 0.01$). For the Cookie Theft task, the OHE group was significantly slower (median, 62 words/min; 95% CI, 26–109) than all other groups, including MHE (median, 155 words/min; 95% CI, 135–166; $p < 0.01$), non-HE cirrhosis (median, 136 words/min; 95% CI, 105–174; $p < 0.05$), and healthy control (median, 131 words/min; 95% CI, 117–171; $p < 0.01$).

Between-group differences in speech imprecision

Comparisons of speech imprecision between groups can be found in [Figure 2](#). Overall imprecision was worst for the reading task, followed by sentence repetition task and picture description. For the sentence repetition task, participants with OHE (median, 2.2; 95% CI, 1.6–3.1) were significantly more imprecise than non-liver disease controls (median, 1.1; 95% CI, 1.0–1.2; $p < 0.0001$), and non-HE cirrhosis (median, 1.2; 95% CI, 1.1–1.4; $p < 0.01$), but a comparison to participants with MHE was not significant (median, 1.6; 95% CI, 1.4–2.0). Additionally, the MHE control group had significantly

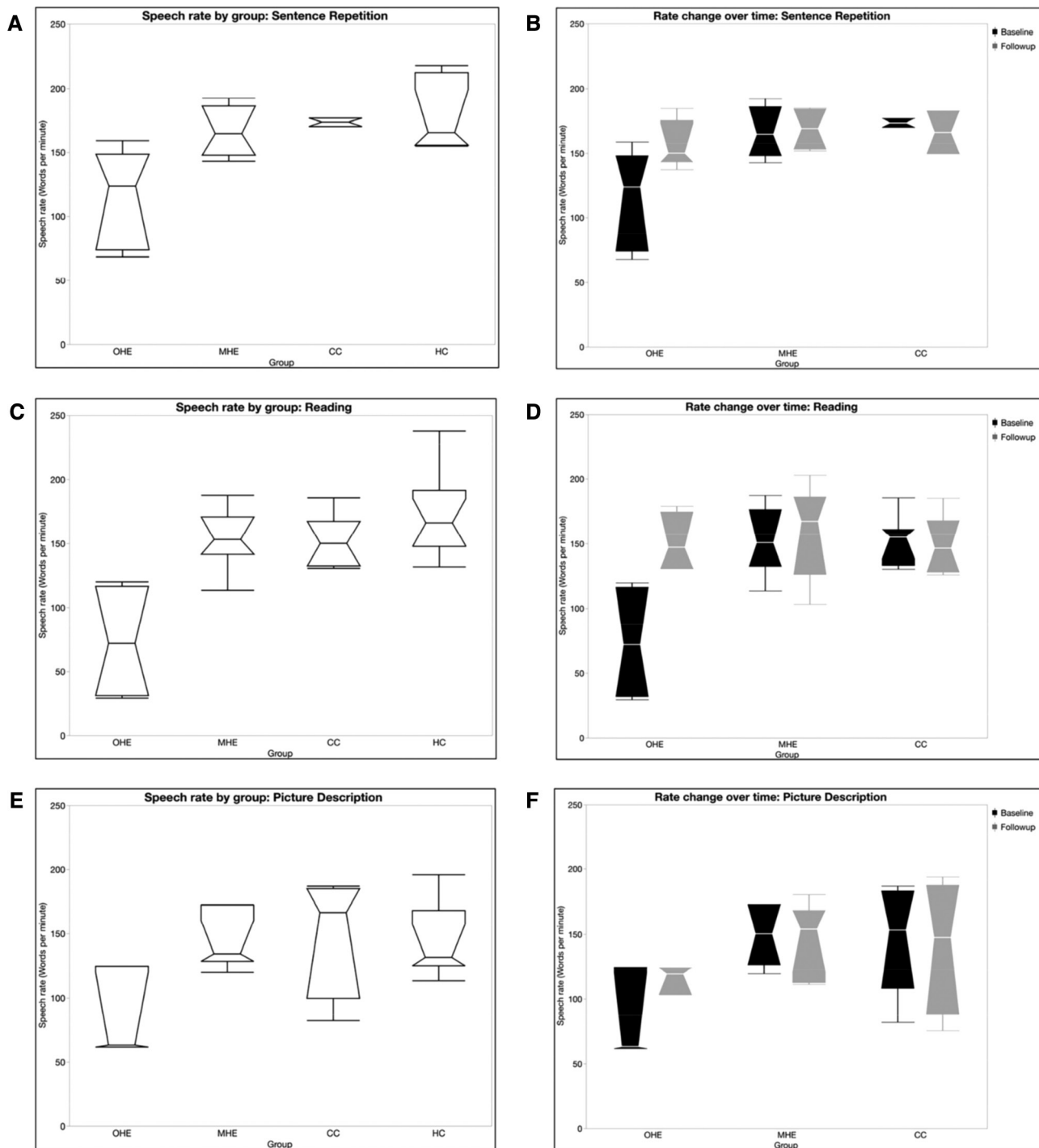


FIGURE 1 Baseline speech rate (words per minute) and change in speech rate in overt hepatic encephalopathy (OHE), minimal hepatic encephalopathy (MHE), non-hepatic encephalopathy (HE) cirrhosis controls (CC), and non-liver disease controls (HC). Baseline speech rate and change in speech rate in sentence repetition task (A,B), reading task (C,D), and picture description (E,F).

lower precision compared with non-liver disease controls ($p < 0.01$) and non-HE cirrhosis ($p < 0.05$); all other comparisons were not significant ($p > 0.05$). For the reading task, participants with OHE (median, 3; 95% CI, 1.8–3.4) had lower precision than non-liver disease controls (median, 1.5; 95% CI, 1.1–1.7; $p < 0.01$). There were no statistically significant differences between the MHE (median, 2; 95% CI, 1.3–2.5) and cirrhosis groups

(median, 1.5; 95% CI, 1.1–2.2; $p < 0.05$), and all other comparisons were also nonsignificant. For the Cookie Theft task, the OHE (median, 2; 95% CI, 0.5–3.9) and MHE (median, 2; 95% CI, 1.4–2.6) groups were significantly less precise than non-liver disease controls (median, 1; 95% CI, 0.9–1.2; $p < 0.05$). The non-HE cirrhosis group (median, 1; 95% CI, 0.9–1.6; $p > 0.05$) did not differ from any other group.

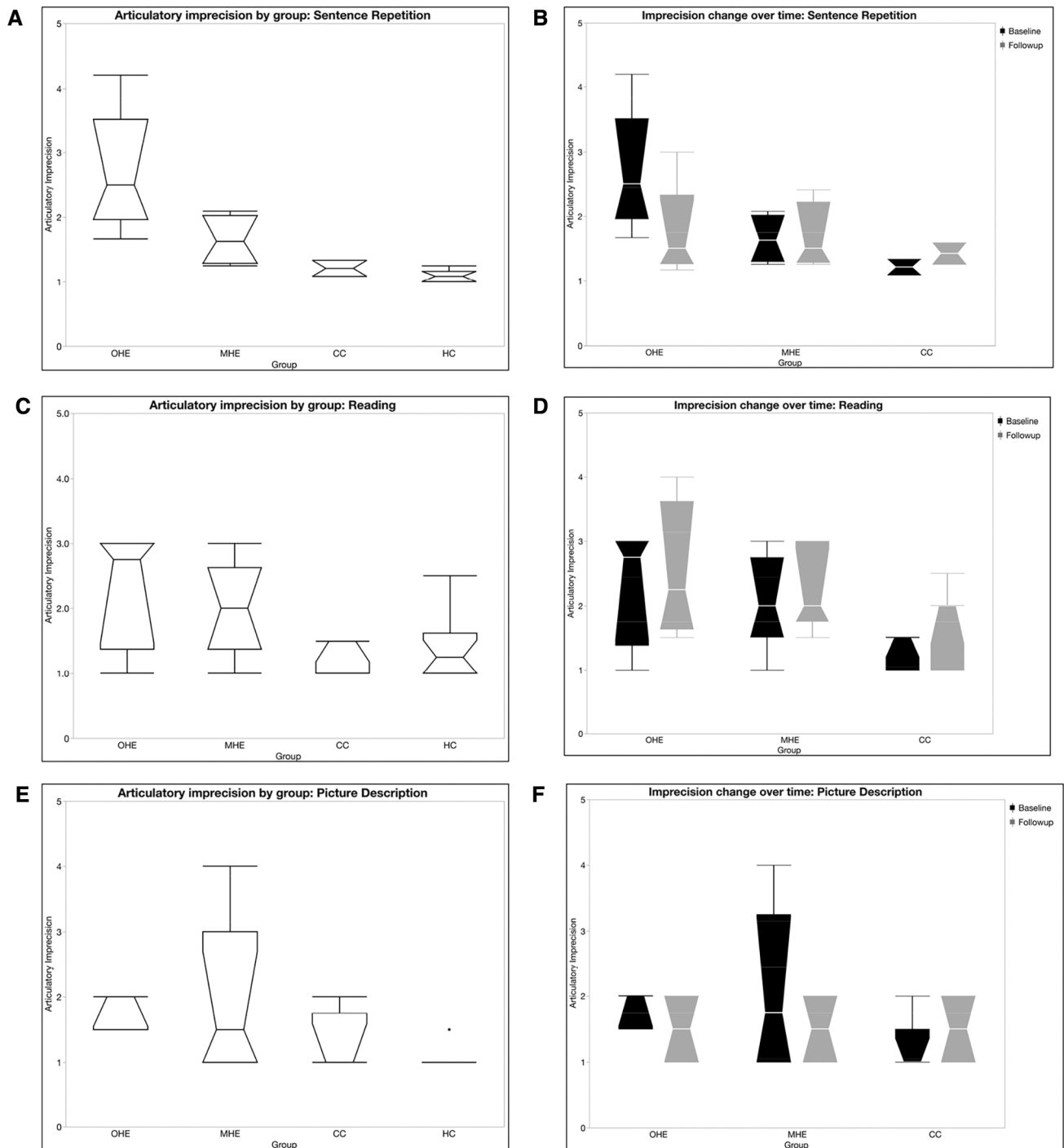


FIGURE 2 Baseline speech imprecision and change in speech imprecision in OHE, MHE, non-HE CC, and HC. Baseline speech imprecision and change in speech imprecision in sentence repetition task (A,B), reading task (C,D), and picture description (E,F).

Between-group differences in overall speech severity

Speech severity comparisons among groups can be found in [Figure 3](#). For the sentence task, speech severity was significantly worse for OHE (median, 13.1; 95% CI, 6.4–22.5) and MHE groups (median, 5.2; 95% CI, 3.6–9.0; $p < 0.05$) compared with non-HE cirrhosis (median, 0.9; 95% CI, 0.0–2.5; $p < 0.01$)

and non-liver disease controls (median, 0.0; 95% CI, –1.7 to 1.7; all comparison $p < 0.01$). For the reading task, severity was worse for OHE (median, 6.4; 95% CI, 2.9–8.2) compared to participants with MHE (median, 2; 95% CI, 0.0–3.1; $p < 0.05$), non-HE cirrhosis (median, 1.0; 95% CI, 0.0–2.0; $p < 0.05$), and non-liver disease controls (median, 0.2; 95% CI, –0.8 to 0.8; $p < 0.001$); no other comparisons were significant. For the Cookie Theft task, participants with

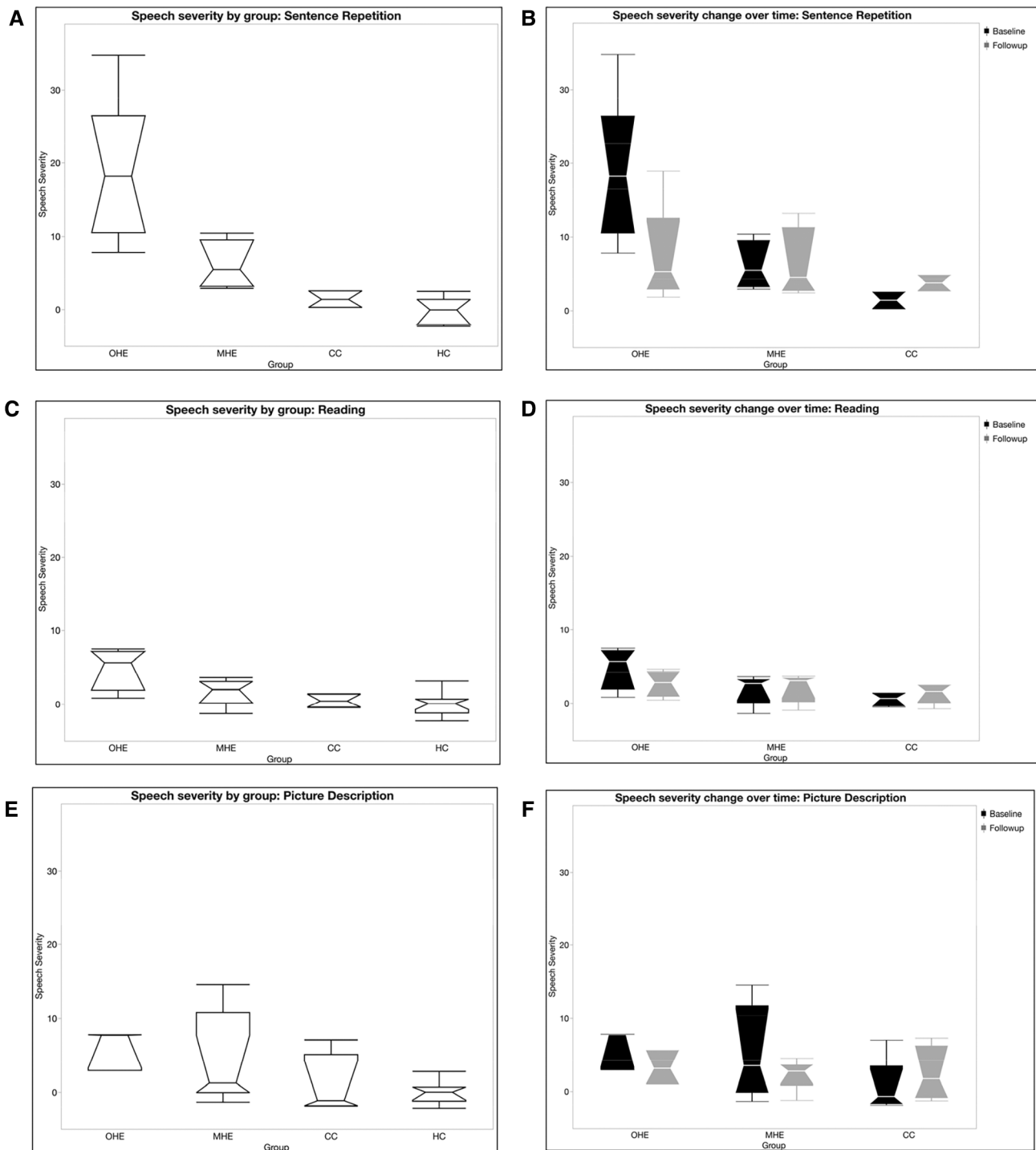


FIGURE 3 Baseline overall speech severity and change in speech severity in OHE, MHE, non-HE CC, and HC. Baseline speech severity and change in speech severity in sentence repetition task (A,B), reading task (C,D), and picture description (E,F).

OHE (median, 7.7; 95% CI, -1 to 18) and MHE (median, 3.7; 95% CI, 1.4–7.5) had worse speech severity compared with non-liver disease controls (median, 0.1; 95% CI, -1.4 to 1.5). In addition, participants with non-HE cirrhosis (median, -0.1; 95% CI, -2.0 to 3.9; $p > 0.05$) were significantly less severe than participants with OHE. No other comparison was statistically significant.

Temporal changes in speech measures among participants with OHE

Speech change from study enrollment (baseline) to follow-up sessions was evaluated descriptively (Figures 1–3). As shown in Figure 1, median speech rate for the OHE group increased from baseline to follow-up in all three tasks, with most notable change

found in the reading task. At follow-up assessment in the outpatient setting, there were no statistically significant differences between speech rate, imprecision, or severity for any of the speech tasks between the MHE and OHE groups. Speech rate was relatively stable for participants with MHE and non-HE cirrhosis. Median articulatory imprecision improved (reduced) over time for the OHE group, but the change was modest and only noted in the sentence repetition task. Similarly, the speech severity was reduced over time for the OHE group but most pronounced in the sentence repetition task. As with articulatory rate, participants with MHE were stable from baseline to follow-up for both articulatory imprecision and speech severity. Participants with non-HE cirrhosis were mostly stable, although articulatory imprecision and speech severity showed slight worsening in the sentence repetition task.

Subgroup analysis of patients with MHE who developed OHE

After enrollment, the 12 patients with MHE were followed for a median of 34 months, and 3 of 12 (25%) developed overt HE at 4, 10, and 35 months after enrollment. There were no statistically significant differences in speech rate, precision, and overall severity for any of the speech tasks at baseline between patients with MHE who did and did not develop OHE.

DISCUSSION

In this prospective cohort study, speech rate, precision, and overall severity were significantly impaired in participants with OHE. From the time of initial OHE diagnosis to clinical improvement, participants with OHE demonstrated improvements in all speech measures, with particularly pronounced improvements in speech rate. As may be expected, speech rate, precision, and overall severity after recovery from OHE were similar to patients with MHE. Among participants with MHE with no history of OHE, there were significant impairments in speech precision and overall severity compared with non-HE cirrhosis and non-liver disease controls, but only in the sentence repetition and picture description tasks. These findings suggest that assessing speech patterns could be used to diagnose, grade, or remotely monitor HE. The significantly worse performance of patients with OHE in all speaking tasks is consistent with a diagnosis of dysarthria. The magnification of group differences in the reading and picture description tasks indicate that cognitive factors are also reflected. Based on these results, we recommend using a task that assesses for both motor and cognitive impairment to ensure sensitivity for detecting HE.

This study has several important and potentially clinically relevant findings, including several observations. First, many aspects of speech, including rate, precision, and overall severity, were significantly worse in participants with OHE, and all of these speech metrics improved as the grade of OHE improved. This suggests that speech could be used to monitor patients with known OHE to prompt lactulose titration or evaluation by a clinician. Alternatively, speech metrics could be used as an objective measure of subclinical impairment among hospitalized patients with HE. Second, similar to a recently published study by Bloom et al.,^[24] we found that speech precision and overall severity were significantly worse among participants with MHE compared to non-HE cirrhosis. Our study additionally demonstrates that speech precision and overall severity are impaired in participants with MHE without a history of OHE. Speech recording could therefore be used as part of an easy-to-administer point-of-care screening tool for MHE. Finally, our findings demonstrate that individuals with MHE and OHE often have a decrease in speed or precision, but not always both. There is a natural tradeoff between speed and precision, and individuals with impaired cognitive functions may be able to maintain speech speed while sacrificing precision, or vice versa. Therefore, assessing both speed and precision together is likely to improve our ability to diagnose and monitor HE.

Distinctive speech patterns have been identified in other diseases including Parkinson's disease and ALS.^[14] Additionally, speech analysis has been used to assess for other conditions including depression and suicidality.^[25–30] Findings from this study demonstrate that it may be feasible to develop a tool to predict, diagnose, and stage HE using speech. If our findings are validated in larger samples, speech monitoring could be used as part of a smartphone application for remote use or point-of-care diagnostic tools for use in clinical settings. This could help improve the early diagnosis and treatment of MHE, which could prevent health complications and decrease avoidable emergency-room visits and hospitalizations.

This study is strengthened by its prospective design and assessments by trained clinicians in hepatology and speech-language pathology, which allowed for the accurate measurement of complicated speech metrics such as articulatory precision. However, this study must be interpreted in the context of potential limitations. First, our study was conducted in a single center in the Southeast United States and included participants that speak diverse dialects, which may limit generalizability to other regions.^[31] Second, the distribution of sex was not equivalent across our participant groups, with a much higher proportion of females in non-liver disease controls. Reassuringly, significant differences in speech measures were consistently demonstrated between OHE and non-HE

cirrhosis, which had similar proportions of female participants. Third, we were unable to control for overall health status and non-liver disease comorbidities. However, our inclusion criteria were chosen to be stringent to avoid the inclusion of comorbidities that could affect cognition or speech. Finally, given our small sample size, there is a risk of type II error. However, despite this potential limitation, our results demonstrate statistically significant and clinically meaningful differences between groups.

In conclusion, this study demonstrated that participants with HE had impairments in speech rate, precision, and overall severity. Dramatic changes in speech rate and precision were demonstrated among participants with OHE as they improved clinically, suggesting that speech could be used to monitor HE severity remotely or in hospitalized patients. In sum, these findings provide important early evidence that monitoring of speech is feasible in the inpatient setting and could be used to diagnose, stage, and monitor HE.

AUTHOR CONTRIBUTIONS

Study concept and design: Andrew M. Moon, Hannah P. Kim, Sarah Cook, Renee T. Blanchard, Michael W. Fried, Katarina L. Haley, and Adam Jacks. *Data acquisition:* Andrew M. Moon, Hannah P. Kim, and Sarah Cook. *Data analysis:* Katarina L. Haley, Adam Jacks, and Jennifer S. Shafer. *Data interpretation:* Andrew M. Moon, Hannah P. Kim, Katarina L. Haley, Adam Jacks, Jennifer S. Shafer, and Michael W. Fried. *Manuscript draft and critical revision of the manuscript:* All authors.

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CONFLICT OF INTEREST

Nothing to report.

PRIOR PRESENTATIONS

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