

PRE-TRANSPLANT HEPATIC ENCEPHALOPATHY (HE) IS ASSOCIATED WITH HE IN PATIENTS WITH RECURRENT CIRRHOSIS AFTER LIVER TRANSPLANTATION

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Summary

Background. We hypothesized that patients with recurrent cirrhosis are more likely to develop post-transplant HE if they had pre-transplant HE.

Methods. We evaluated patients who developed cirrhosis after transplantation (1987 to 2023 at a tertiary transplant center) who also developed West-Haven stage 2 or greater HE. Patients with ALF were excluded. Post-transplant HE patients were matched using a case control design to post-transplant cirrhosis patients without post-transplant HE.

Results. 194 patients developed post-transplant cirrhosis; 78/194 (40%) developed post-transplant HE. The most common cause of post-transplant cirrhosis was HCV, and among all patients with cirrhosis post-transplant, HE developed approximately 7 years after liver transplantation (median [IQR]: 6.8 [11] years). In the 78 patients with HE after transplant, pre-transplant HE was identified in 31 (40%) patients. Patients with HE pre-transplant developed post-transplant HE faster than those without HE pre-transplant (4 years vs 9 years; log-rank test: $p < 0.05$). In patients with post-transplant cirrhosis but without post-transplant HE, pre-transplant HE was identified in 8 (7%) patients (8/116 vs 31/78 who had HE pretransplant, $p < 0.001$). In multivariable analysis, the strongest predictor of post-transplant HE was HE pre-transplant (OR = 10.8, 95% CI 4.0-33.6, $p < 0.001$).

Conclusions. Patients with post-transplant cirrhosis who develop HE are more likely to have had pre-transplant HE, suggesting intrinsic biological factors in HE pathogenesis – perhaps related to mesenteric shunts or perhaps the microbiome. The data raise the possibility that patients who had HE pre-transplant who develop cirrhosis after liver transplantation may benefit from prophylactic lactulose/rifaximin.

Key words: liver, transplantation, outcome, pathogenesis, decompensation

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Abbreviations

CDW: clinical data warehouse

OLT: orthotopic liver transplant

EV: esophageal varices

GV: gastric varices

HE: hepatic encephalopathy

HCC: hepatocellular carcinoma

HRS: hepatorenal syndrome

HCV: hepatitis C virus

MUSC: Medical University of South Carolina
MELD: model for end-stage liver disease
MASH: metabolic dysfunction-associated steatohepatitis
OLT: orthotopic liver transplant
SBP: spontaneous bacterial peritonitis

INTRODUCTION

Hepatic encephalopathy (HE) affects up to 40% of patients with cirrhosis and is a significant cause of morbidity and mortality¹⁻³. Liver transplantation remains a major treatment modality for cirrhosis patients with decompensating events, including HE⁴. A small proportion of transplant patients develop recurrent cirrhosis after liver transplantation, and thus are at risk for further decompensating events, including HE⁵.

The pathogenesis of HE in patients who develop cirrhosis after liver transplantation is likely similar to the pathogenesis of HE pre-transplantation – though the precise pathophysiologic mechanisms of HE in either situation are incompletely understood. Known mechanisms of pre-transplant HE include increased portal pressure and portosystemic anastomoses^{1,6,7}, disruption in ammonia metabolism⁸⁻¹³, blood-brain barrier alterations¹², genetic factors¹⁴, and small intestinal bacterial overgrowth (SIBO)¹⁵⁻¹⁸. Given that many mechanisms implicated in HE pathogenesis are extra-hepatic, and considering the efficacy of lactulose and rifaximin – mainstays of HE therapy targeting small bowel bacteria^{16,19-23} – it is possible that once cirrhosis develops, extra-hepatic factors play a significant role in HE pathogenesis.

Here, we hypothesized that cirrhosis patients with HE pre-transplant are more likely to develop HE after liver transplantation than those without HE pre-transplant. Therefore, we examined cirrhosis patients with recurrent cirrhosis after liver transplantation to predict the development of post-transplant HE.

METHODS

Study population and design

We examined consecutive liver transplant patients who underwent liver transplantation for cirrhosis and were followed between January 1, 1987 and December 31, 2023 at the Medical University of South Carolina (MUSC). Cirrhosis patients were identified using the MUSC Clinical Data Warehouse (CDW) based on ICD-9 and ICD-10 codes as described²⁴. The diagnoses of cirrhosis (both pre- and post-transplant) were validated through a review of the medical record. Complete liver transplant data were abstracted. The study included patients older than 18 years

old. Patients who died within one year after transplant were excluded. The study adhered to guidelines for good clinical practice and was approved by the MUSC institutional Review Board.

Data abstraction and definitions

We evaluated the development of HE after liver transplantation in patients with recurrent post-transplant cirrhosis. The diagnosis of cirrhosis was made based on liver histology demonstrating advanced fibrosis (bridging of broad bands) and/or clinical complications of portal hypertension. Patients with F4 fibrosis on histology were classified as having cirrhosis, while F1 to F3 fibrosis were classified as having cirrhosis only if complications of portal hypertension were present. For patients without liver biopsy results, the diagnosis of cirrhosis was made based on imaging findings consistent with cirrhosis, along with the presence of complications of elevated portal pressure including ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), varices, or HE. Cirrhosis, both pre- and post-liver transplantation, was required for a diagnosis of recurrent post-transplant cirrhosis.

After identifying patients with recurrent post-transplant cirrhosis, we evaluated for development of HE pre and post-transplant. HE was initially identified using ICD-9/10 codes and lactulose or rifaximin administration²⁵, and subsequently validated by review of the medical record. It is standard practice to use the West Haven criteria grading system to assess the severity of HE, and we evaluated for the development of West-Haven stage 2 or greater HE. Patients with reasons for altered mental status other than HE were excluded². Lastly, patients with acute liver failure were excluded.

Sensitivity analysis

Given the advent of direct-acting antivirals for the treatment of HCV and the reduction in HCV-related recurrent cirrhosis, we performed a sensitivity analysis to examine the robustness of the data. We evaluated for the development of recurrent cirrhosis in all patients who underwent liver transplantation for HCV vs. non-HCV related cirrhosis. We compared patients with post-transplant HE with recurrent HCV cirrhosis to post-transplant HE patients with non-HCV recurrent cirrhosis, and evaluated these patients for a history of pre-transplant HE.

Statistical analysis

Post-transplant HE patients with recurrent post-transplant cirrhosis were compared using a case control design to those without post-transplant HE, but with recurrent post-transplant cirrhosis. To predict the likelihood of developing post-transplant HE, binary logistic regression was used to perform bivariate and multivariable analyses.

The variables examined were pre-transplant HE, age, sex, MELD-Na, acute or chronic graft rejection, and recurrent hepatitis C virus (HCV) cirrhosis after liver transplant. Patients with multiple liver transplants were excluded in the regression analyses.

The study's primary endpoint was the rate of HE occurrence after liver transplantation, and the secondary endpoint was the identification of independent predictors of post-transplant HE. Kolmogorov-Smirnov tests were completed to examine variable distributions. Continuous variables were presented as means with standard deviations for normally distributed data, while other variables were shown as medians with interquartile ranges. Discrete variables were expressed as proportions. Chi-square tests or Fisher's Exact tests were completed for discrete variables as appropriate. Continuous variables were analyzed using t-tests or Mann-Whitney U based on normality of distributions. Kaplan-Meier analysis was performed to compare the time to post-transplant HE development between those with and without pre-transplant HE. Cox proportional hazard models were used to calculate hazard ratios (HRs) and their associated 95% confidence intervals (95% CI). Statistical analyses were performed using R, version 4.4.1 Beagle Scouts (R Core Team). P-values less than 0.05 were considered to be statistically significant.

RESULTS

Clinical characteristics

During the study period, 1,537 adult patients underwent liver orthotopic liver transplantation (OLT). Of these, 72 patients transplanted for acute liver failure (ALF) and 223 patients transplanted for diseases other than cirrhosis were excluded (Fig. 1). Of the remaining 1,242 patients who underwent transplantation for cirrhosis, 1,076 patients survived 1 year after liver transplantation (1 year liver graft survival: 87%). Over a mean (SD) follow-up period of 19.2 (6.7) years, 194/1,242 (16%) patients developed post-transplant cirrhosis, with 180/194 (93%) biopsy-proven cases (173/180 with F4 fibrosis, 7/180 F2 or F3 fibrosis with clinical features of cirrhosis). Of the 194 patients with post-transplant cirrhosis, 78/194 (40%) patients developed post-transplant HE. Post-transplant HE patients were typically elderly Caucasian males with HCV-mediated recurrent cirrhosis (Tab. I). The median (IQR) MELD-Na score was 21 (13), with a range of 6 to 40. In the control group of patients with post-transplant cirrhosis, but without post-transplant HE, baseline characteristics and MELD-Na score were not statistically significantly different, except that HCV mediated recurrent cirrhosis was more common

in non-HE group. Acute or chronic rejection episodes occurred at similar rates in patients with and without post-transplant HE (post-transplant HE: 27/78 (35%) vs no post-transplant HE: 29/116 (25%), $p = 0.15$). Brain MRI was performed in 21 of 78 post-transplant HE patients, and did not show a structural lesion in any patient. Of the 26 recurrent cirrhosis patients with multiple liver transplants (out of 194 total), 21 (81%) experienced post-transplant HE, and of these, 18 (86%) developed HE after their second liver transplant.

Clinical outcomes

In the 78 patients with HE after transplant, pre-transplant HE was identified in 31 (40%) patients. In patients with post-transplant cirrhosis but without post-transplant HE, pre-transplant HE was identified in 8 (7%) patients (8/116 vs 31/78 who had HE pretransplant, $p < 0.001$). Ammonia levels were not significantly associated with the development of post-transplant HE. Overall, following liver transplantation for cirrhosis, post-transplant cirrhosis developed at a median of 6.4 years (IQR: 9.1), and post-transplant hepatic encephalopathy at a median of 6.8 years (IQR: 11).

To better understand the timing of post-transplant HE development in patients with pre-transplant HE versus those without pre-transplant HE, we performed a Kaplan-Meier analysis in post-transplant HE patients (Fig. 2). In this analysis, over a follow up of 10 years after liver transplantation, patients with pre-transplant HE developed post-transplant HE more rapidly than those without pre-transplant HE (Fig. 2; median time to post-transplant HE: 4 years [IQR: 8] vs 9 years [IQR: 5]; HR: 1.74; 95% CI: 0.995–3.036; log-rank test: $p < 0.05$).

HE pre-transplant HE as a predictor of post-transplant HE

We next wished to identify clinical features that are associated with post-transplant HE development in patients with recurrent cirrhosis after transplant. Therefore, we performed a binary logistic regression analysis (as in Methods) (Tab. II). Predictor variables examined included the following: pre-transplant HE, age, sex, MELD-Na, acute or chronic graft rejection, and recurrent HCV post-transplant cirrhosis. Of these variables, pre-transplant HE, female sex, and MELD-Na were significant predictors of post-transplant HE (Tab. II). The strongest predictor of HE post-transplant was pre-transplant HE (OR = 10.8, 95% CI 4.0–33.6, $p < 0.001$) (Tab. II).

Sensitivity analysis

Given the reduction in HCV cirrhosis after the advent of direct acting antiretrovirals, we evaluated patients who underwent liver transplantation for non-HCV cirrhosis, and compared these to those who underwent transplantation

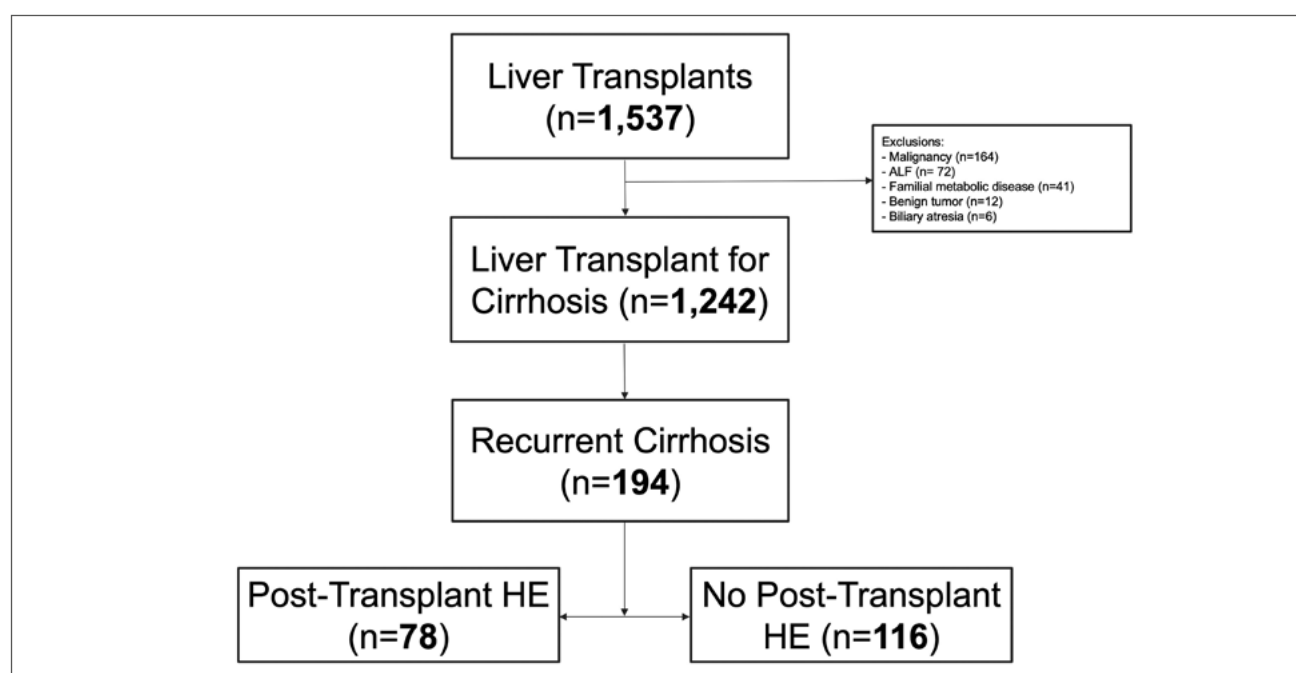


Figure 1. Patients. Shown is a consort diagram of the patients included in the study.

Table I. Clinical characteristics.

	Cases (HE after OLTx) (n) = 78	Controls (No HE after OLTx) (n) = 116	p value
Demographics			
Female, n (%)	36 (46%)	41 (35%)	NS
Age, median (IQR)	59 (21)	63 (16)	NS
Age at transplant, median (IQR)	47 (19)	49 (12)	NS
White, n (%)	57 (73%)	91 (79%)	NS
Black, n (%)	20 (26%)	20 (17%)	NS
Other, n (%)	1 (1%)	5 (4%)	NS
Graft rejection (acute or chronic)	27 (35%)	29 (25%)	NS
Post-transplant cirrhosis etiology			
HCV, n (%)	26 (33%)	59 (51%)	< 0.05
MASH, n (%)	15 (19%)	14 (12%)	NS
Alcohol-associated, n (%)	9 (12%)	12 (10%)	NS
Other, n (%)	28 (36%)	31 (27%)	NS
MELD-Na, median (IQR)	21 (13)	15 (11)	NS

for HCV cirrhosis. Of the 1,242 patients who underwent liver transplantation for cirrhosis, 937 (75%) were transplanted for non-HCV cirrhosis and 305 (25%) for HCV cirrhosis. Recurrent HCV cirrhosis was commonly seen in patients who were transplanted for HCV cirrhosis

(87/305, 29%), but also occurred in patients transplanted for non-HCV recurrent cirrhosis (107/937, 11%). Of the 107 patients with recurrent non-HCV cirrhosis, 45 (42%) developed post-transplant HE; post-transplant HE was observed at a similar rate in patients with recurrent HCV

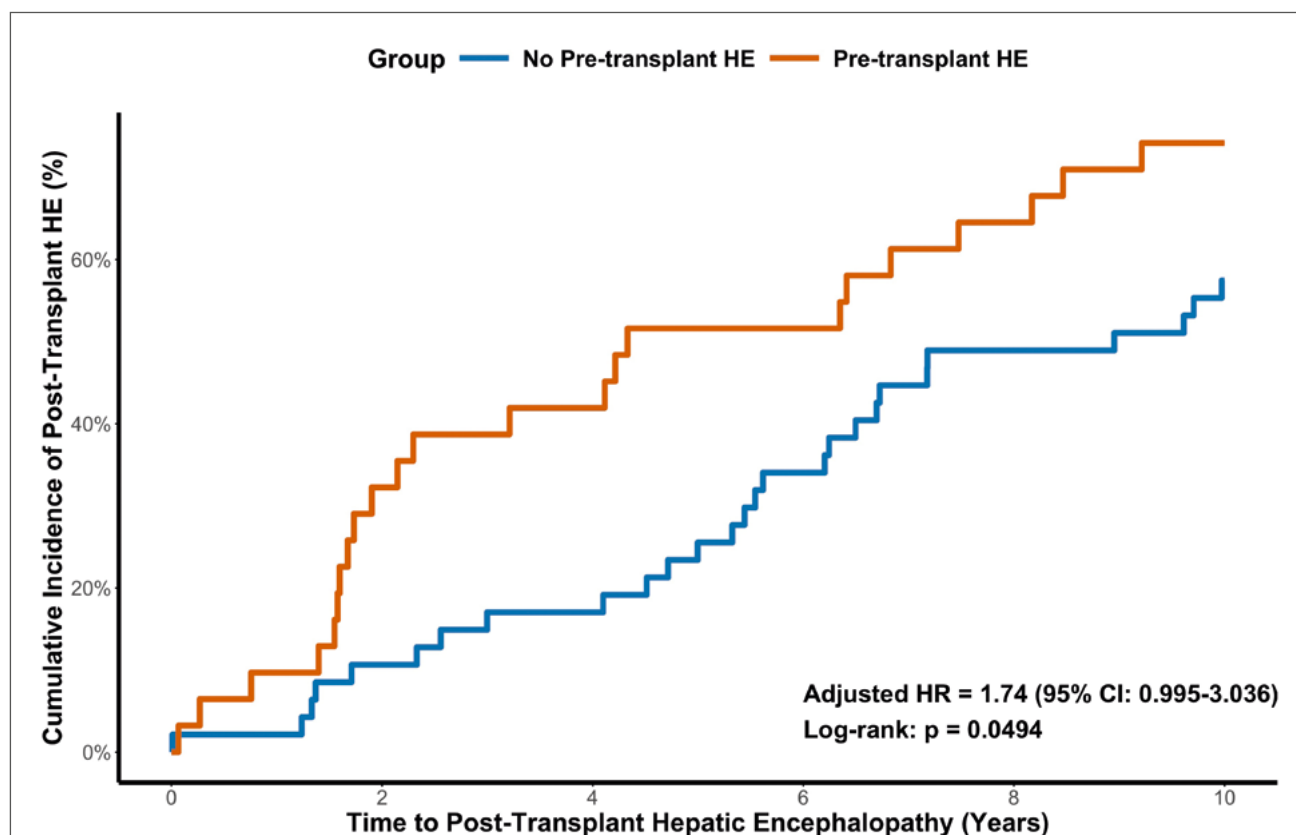


Figure 2. Time to Post-Transplant Hepatic Encephalopathy (HE) Development. Shown is a Kaplan-Meier analysis of the timing of post-transplant HE development in patients with pre-transplant HE versus those without pre-transplant HE.

Table II. Predictors of hepatic encephalopathy after liver transplantation in patients with recurrent cirrhosis*.

	OR	95% CI	p value
HE pre-transplant	10.8	3.95-33.60	< 0.001
Female	3.06	1.40-6.90	< 0.05
MELD-Na	1.05	1.00-1.11	< 0.05
Age	1.01	0.98-1.04	0.61
HCV	0.67	0.30-1.47	0.32
Graft Rejection (Acute or Chronic)	0.37	0.10-1.11	0.09

*Shown is a multivariable regression to evaluate for the development of post-transplant HE in 168 patients with recurrent cirrhosis (n = 26 patients who underwent two or more liver transplants were excluded from the cohort of 194 patients with recurrent cirrhosis).

cirrhosis (33/87 (38%). In the 45 patients with HE after recurrent non-HCV cirrhosis, pre-transplant HE was identified in 17 (38%) patients. In patients with post-transplant HE but with HCV recurrent cirrhosis, pre-transplant HE was identified in 16 (48%) patients (16/33 vs 17/45 who had HE pretransplant, $p = 0.48$).

DISCUSSION

Here, we have shown that the development of HE in patients with post-transplant cirrhosis is strongly associated with a history of HE pre-transplant. After liver transplantation, cirrhosis patients with HE pre-transplant

had nearly an 11 times increased likelihood of developing post-transplant HE. Furthermore, post-transplant HE developed more rapidly after liver transplantation in patients with a history of HE pre-transplant, compared to those without HE pre-transplant (4 vs 9 years). Therefore, given that HE developed in patients with cirrhosis both before and after transplant, and that pre-transplant HE was predictive of post-transplant HE, we speculate that there may be one or more intrinsic factors – which are likely to be extra-hepatic – that are important in HE pathogenesis.

Cirrhosis patients are well known to experience complications including those related to portal hypertension. These complications appear to be related to injury to the liver itself, but also intrinsic biological features (such as the microbiome^{18,26}). In this study, given that recurrent post-transplant cirrhosis patients all had some form of liver injury, and that post-transplant HE developed largely in patients with pre-transplant HE (and at a faster rate than those without), it is likely that the chronic liver injury does not fully explain the development of post-transplant HE. It could be speculated that once cirrhosis develops, intrinsic determinants are important in the pathogenesis of HE.

There appear to be several important biological mechanisms involved in HE pathogenesis. Although these are incompletely understood, important factors specifically include high portal pressure and portosystemic anastomoses/shunting^{1,6,7}, systemic inflammation and oxidative stress^{12,13}, alterations in the blood-brain barrier (e.g., astrocyte dysfunction)¹², and SIBO¹⁵⁻¹⁸, all of which, are thought to increase levels of ammonia in the blood. These findings suggest that elevated ammonia levels due to reduced clearance in cirrhosis do not fully explain the mechanism underlying hyperammonemia in HE. Indeed, ammonia metabolism is also regulated by the small and large bowel²⁷, brain, muscle, and kidney²⁸, and perhaps it is these other organs also contributing to HE development. In particular, gut microbiota alterations in HE link specific bacterial families to inflammation and cognitive impairment¹⁸. Clinically, this has facilitated the development of rapid microbiota-based stool tests that effectively differentiate cirrhotic patients with and without HE²⁶. Remarkably, the study findings align with the mechanisms of microbiota-based stool tests and current frontline agents for HE, namely lactulose and rifaximin, which also work extra-hepatically – and inhibit ammonia-producing bacteria in the gut^{16,19-23}.

We recognize potential limitations in our study. The retrospective study design may lead to potential bias by failure to consider confounding variables (i.e. other causes of post-transplant encephalopathy). However, we went to great measures to exclude such potential confounders through (1) identifying all patients with recurrent post-transplant

cirrhosis (93% biopsy-proven cases) and (2) carefully defining post-transplant HE. Although post-transplant HE has been reported to develop in patients with pre-transplant cirrhosis but without post-transplant cirrhosis, it is likely that other factors are contributing to post-transplant encephalopathy in these patients, given that liver transplantation itself is a known risk factor for altered mental status²⁹. Furthermore, HE is defined by cirrhosis being present. As such, this is one of the first studies to examine post-transplant HE in the important group of cirrhosis patients who also develop recurrent cirrhosis after liver transplantation, thereby mitigating concerns related to other potential causes of encephalopathy.

In conclusion, HE post-transplant is strongly associated with pre-transplant HE, and develops rapidly in these patients once they develop cirrhosis. The data have important clinical implications. For example, patients who undergo liver transplantation who had pre-transplant HE and who develop cirrhosis after transplantation might be monitored carefully for the development of HE, and may even benefit from prophylactic lactulose or rifaximin to prevent post-transplant HE. The data also raise further questions pertaining to the pathogenic factors important in HE.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

AR: contributed to study concept and design, conducted literature review, acquired data, performed statistical analyses, drafted the manuscript, and critically revised the manuscript for significant intellectual content; DR: contributed to study concept and design, drafted the manuscript, critically revised the manuscript for significant intellectual content, and provided supervisory efforts.

Ethical consideration

This study was approved by the Institutional Ethics Committee (please specify name of the Institution: Medical University of South Carolina) (approval number/protocol number 00126018). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was

obtained from each participant/patient for study participation and data publication.

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