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The qEEG-TIPS score: development of a predictive model for recurrent overt hepatic encephalopathy after elective TIPS

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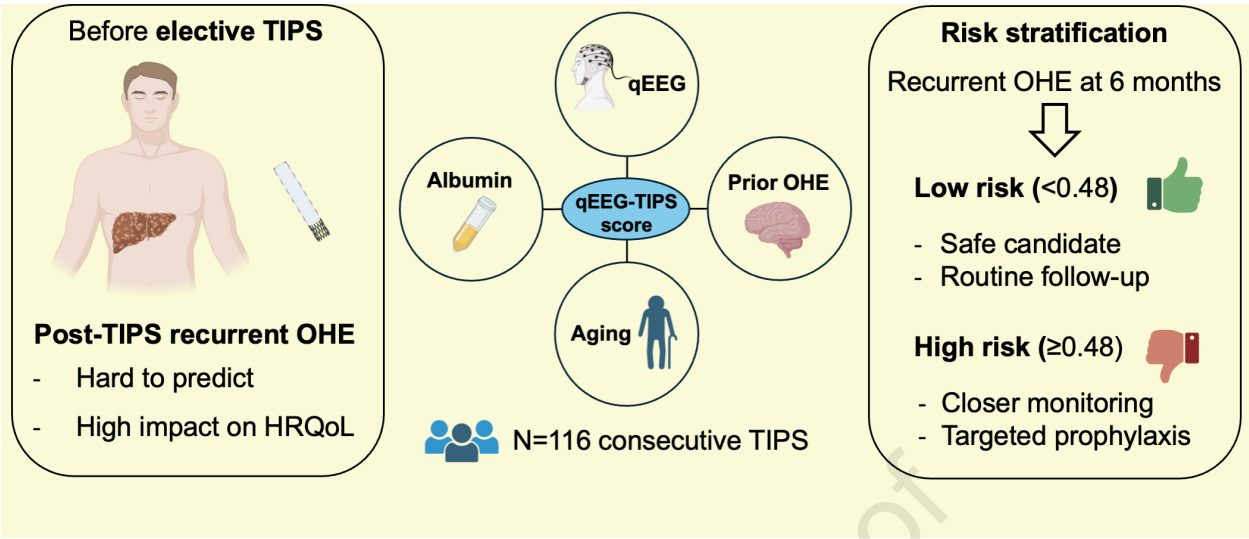

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Title: The qEEG-TIPS score: development of a predictive model for recurrent overt hepatic encephalopathy after elective TIPS

Short title: A qEEG-based model for post-TIPS recurrent HE

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Authors contributions:

AC: Writing – Review & Editing; **AP:** Data Curation. **ASVM:** Data Curation. **AZ**: Formal analysis, Writing – Review & Editing. **CC**: Investigation. **DS**: Methodology, Software, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Visualization. **FA**: Investigation. **FC**: Investigation. **FM**: Data Curation. **FSci**: Data Curation. **FS**: Conceptualization, Methodology, Writing – Review & Editing, Project administration, Supervision, Funding acquisition. **FV:** Writing – Review & Editing. **LZ**: Data Curation, Investigation, Writing – Review & Editing. **MB**: Investigation, Data Curation. **MG:** Writing – Review & Editing. **MS**: Data Curation. **RMC**: Data Curation. **SM:** Data Curation, Investigation, Supervision, Writing – Review & Editing. **TG**: Data Curation.

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Abstract

Background & Aims: Overt hepatic encephalopathy (OHE) continues to be the primary complication following transjugular intrahepatic portosystemic shunt (TIPS). It significantly impairs patients' health-related quality of life (HRQoL), particularly in its recurrent and persistent forms, and may outweigh the benefits of the procedure. This study aimed to develop and internally validate a prognostic score incorporating quantified-EEG (qEEG) to predict the risk of post-TIPS recurrent OHE at 3 and 6 months.

Methods: We prospectively enrolled 161 consecutive patients with cirrhosis undergoing elective TIPS for refractory/recurrent ascites or secondary prophylaxis of variceal bleeding. All patients underwent qEEG assessment by validated spectral analysis criteria prior to TIPS placement. A multivariable Cox regression model was constructed to estimate the risk of recurrent OHE. Model performance was evaluated using time-dependent ROC curves, calibration plots, decision curve analysis (DCA), and internal validation via bootstrap resampling (B=1500).

Results: Independent predictors of recurrent OHE included age, serum albumin, prior OHE history, and qEEG alterations, which were incorporated into the novel qEEG-TIPS score. The time-dependent AUCs were 0.76 (95% CI: 0.70-0.82) and 0.80 (95% CI: 0.76-0.85) at 3 and 6 months, respectively. The score identified high-risk patients with a significantly greater incidence of recurrent OHE at 6 months (48% vs 8% in low-risk patients, $p<0.001$). Internal validation yielded an optimism-corrected C-index of 0.74 (95% CI: 0.69-0.84), indicating mild overfitting but good predictive stability. DCA supported the clinical utility of the model.

Conclusions: The qEEG-TIPS score demonstrated good discrimination and calibration in predicting short-term risk of recurrent OHE after TIPS. This tool may assist in risk stratification and guide personalized management before and after TIPS.

Impact and implications

- Recurrent overt hepatic encephalopathy (OHE) is the primary complication of TIPS in patients with cirrhosis, markedly reducing quality of life, increasing healthcare burden, and complicating clinical decision-making.

- This study introduces and internally validates the *qEEG-TIPS score*, a novel, non-invasive tool integrating quantified EEG with clinical variables to predict the short-term risk of recurrent OHE after elective TIPS.

- These findings hold particular relevance for patients, hepatologists, and transplant teams as they enable more personalized risk assessment prior to TIPS and may guide decisions on prophylaxis, patient selection, and post-procedural monitoring.

- If externally validated, the qEEG-TIPS score could enhance clinical pathways by identifying high-risk patients for targeted interventions, supporting more cost-effective and patient-centered TIPS management strategies.

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Introduction

The introduction of covered stents and refined patient selection criteria have expanded transjugular intrahepatic portosystemic shunt (TIPS) use and improved its therapeutic efficacy in patients with cirrhosis. Nevertheless, the development of overt hepatic encephalopathy (OHE) remains the most frequent and clinically significant shunt-related complication[1]. While the association between post-TIPS OHE and mortality is controversial[2–5], its detrimental impact on health-related quality of life (HRQoL) is well established. A single episode of OHE may be considered acceptable in light of the clinical benefits of TIPS, including improved survival and effective management of portal hypertension-related complications[6]. However, recurrent and persistent OHE significantly worsens outcomes, leading to frequent hospitalizations, increased caregiver burden, and substantial HRQoL deterioration[7–9]. In such cases, the benefit-risk profile of TIPS may become less favorable, highlighting the importance of careful pre-procedural risk stratification. Although several risk factors for post-TIPS OHE have been identified, the ability to accurately predict its occurrence remains limited[10–13]. As a result, conveying each patient's personal risk becomes challenging for clinicians, particularly for recurrent OHE. Given its clinical impact, there is a clear need for reliable predictive models to estimate risk before TIPS, improving patient selection, pre-procedural management, and post-TIPS follow-up. Previous studies have demonstrated a high prevalence of quantitative electroencephalography (qEEG) abnormalities in patients with cirrhosis in the absence of OHE. Notably, these alterations were significantly associated with the subsequent onset of OHE[14]. These findings suggest that qEEG could serve as a valuable tool for improving the prediction of recurrent OHE after TIPS. Here, we report that the qEEG-TIPS score we developed reliably predicts the short-term risk of recurrent OHE following TIPS.

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Patients and methods

Patients

We prospectively enrolled consecutive patients with cirrhosis undergoing elective TIPS with expanded-polytetrafluoroethylene covered stent-grafts (ePTFE-SGs) from February 2015 to February 2024 at our referral center in Modena, Italy. Inclusion criteria were diagnosis of cirrhosis (clinical history, histological findings, or compatible imaging) and indication for TIPS as secondary prophylaxis of variceal bleeding and/or treatment of recurrent/refractory ascites. Exclusion criteria included: standard clinical contraindications to TIPS as stated in the Italian Consensus conference on TIPS[11] (e.g., Child-Pugh score >11, serum bilirubin >5 mg/dL, severe organic renal failure [serum creatinine >3 mg/dL], heart failure, moderate-to-severe pulmonary hypertension [mean pulmonary artery pressure >35 mmHg], recurrent/persistent OHE despite treatment, uncontrolled sepsis); non-cirrhotic portal hypertension; hepatocellular carcinoma (HCC) beyond Milan criteria; diagnosis of neurological or psychiatric disorders; ongoing substance misuse or psychoactive treatment; and failure to provide written informed consent. The study was approved by the local Ethics Committee and adhered to the Declaration of Helsinki (PR: 93/12; 585/2024).

At TIPS placement, anonymized data were collected using a standardized electronic form, including demographics (age, sex), clinical information (liver disease etiology, TIPS indication, OHE history within 12 months, comorbidities, ongoing treatments), and laboratory results on the day of TIPS (hemoglobin, INR, bilirubin, creatinine, albumin, AST/ALT, ammonia, sodium, CRP). Liver disease severity was evaluated by Child-Pugh and MELD-Na scores. Patients were clinically assessed on the day of TIPS to confirm preserved orientation and absence of asterixis according to West Haven criteria. EEG was recorded within 48 hours before the elective TIPS.

As an additional post hoc analysis, pre-procedural contrast-enhanced computed tomography (CT) scans routinely performed for TIPS planning were reviewed to assess the presence of spontaneous portosystemic shunts (SPSS). CT images were available for 157 out of 161 patients (97.5%). Image analysis was independently performed by two expert radiologists (C.C. and F.C.), who were blinded to clinical outcomes. SPSS assessment was conducted on portal venous phase acquisitions as previously described[15]. According to previously published criteria, a diameter ≥8 mm was used to define large SPSS[16]. The presence of large SPSS was then included as an additional candidate predictor in exploratory univariable analyses for recurrent OHE.

EEG Assessment

Resting, eyes-closed EEGs were acquired in the morning with a digital EEG system (Galileo MIZAR S NT, EB Neuro, Italy). Signals were recorded using a 21-channel pre-mounted electrode cap positioned according to the International 10-20 System. Interelectrode impedance was maintained <5 kΩ. Data were sampled at ≥256 Hz, with high-pass filters at 0.5 and 1.6 Hz, a low-pass filter at 70 Hz, and a 50 Hz notch filter. EEG recordings (European Data Format, EDF) were anonymized and sent to two experts (Z.L. and M.S., who were blinded regarding any clinical and laboratory information) for spectral analysis. Z.L and M.S. independently selected 60-100 seconds of artifact-free EEG recordings, and then compared and agreed on the final selection. Spectral analysis was performed on the P3-P4 derivation. For EEG classification, we considered the mean frequency weighted by the power of each frequency band (i.e., the mean dominant frequency [MDF]) and the relative power of the theta and delta bands[14]. Details are reported in Table S1.

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TIPS placement

TIPS was performed after overnight fasting, under mild conscious sedation (midazolam and fentanyl), with non-invasive vital sign monitoring, as previously described[12,17]. Hemodynamic assessment was performed before and immediately after the deployment of the ePTFE-SGs. Portocaval pressure gradient (PCPG) was calculated as the difference between portal vein pressure, measured at the portal vein trunk, and inferior vena cava pressure, registered at the level of the SG ending. In our center, SPSS embolization was performed only in the presence of hepatofugal flow at the portal trunk during post-TIPS portography, which did not occur in any patient of the present cohort. Tracings were recorded using a digital manometer (PowerLab, ADInstruments, USA) and analyzed via LabChart 8 (ADInstruments, USA). SG type and dilation diameter, together with both PCPG measured before and immediately after TIPS opening, were collected.

Follow-up

Patients were prospectively followed by a dedicated medical team. At baseline, only those with prior OHE received prophylaxis with non-absorbable disaccharides (e.g., lactulose). Upon discharge, patients and caregivers were instructed to promptly report any mental status changes, especially lethargy, apathy, behavioral changes, or disorientation. One-week post-discharge, caregivers were contacted for early symptom monitoring and an outpatient evaluation was arranged where needed. Follow-up visits were scheduled at 3, 6, and 12 months, or until death or liver transplantation (LT). HE episodes were graded by West Haven criteria, with grade ≥2 denoting OHE[18,19]. Recurrent post-TIPS OHE was defined as ≥2 episodes within 6 months despite treatment; persistent OHE as continuous

impairment unresponsive to therapy. Management followed EASL guidelines[18,19], using lactulose ± rifaximin and addressing precipitating factors. After the first OHE episode, lactulose was titrated to 2-3 bowel movements daily; rifaximin was added for recurrent OHE secondary prophylaxis.

Statistical analyses

This observational study aimed to investigate the prognostic value of qEEG in patients undergoing elective TIPS, with a focus on the development of recurrent OHE. The primary objective was to develop and internally validate a clinical score to estimate the risk of post-TIPS recurrent OHE at 3 and 6 months. Exploratory analyses were performed to evaluate the prognostic performance of the score for time-to-first OHE, moderate-to-severe OHE (West-Haven grade 3–4), and transplant-free survival (TFS). Full details of these analyses were reported in the Supplementary Results.

All analyses were conducted and reported in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement[20]. A formal a priori sample size calculation was not performed, as patient inclusion was based on a predefined time window and the availability of qEEG assessment at our center. Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Data are presented as mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate. Comparisons between groups were performed using the Student's t-test or Wilcoxon rank-sum test, according to variable distribution. Categorical variables are presented as counts and percentages and compared using the chi-squared test or Fisher's exact test. Correlations between qEEG parameters and biochemical values were assessed using Spearman's rank correlation. Time-to-event

data were summarized using Kaplan–Meier curves. Patients who died or underwent LT before the end of follow-up were censored at the day of death/LT. Differences in recurrent OHE incidence were assessed using log-rank tests. A multivariable Cox proportional hazards model was developed to estimate the risk of recurrent OHE after TIPS. Candidate predictors were selected based on clinical relevance and prior evidence (age, gender, TIPS indication, history of OHE, normal/altered qEEG, albumin, bilirubin, INR, creatinine, serum sodium, ammonia, post-TIPS PCPG <10 mmHg, PCPG drop >50%, presence of large SPSS). Backward stepwise elimination was applied using Akaike's Information Criterion (AIC) to derive the most parsimonious model. A two-sided p-value <0.05 was considered statistically significant. The proportional hazards assumption was evaluated using Schoenfeld residuals for each covariate and globally. Model discrimination was assessed using time-dependent Area Under the receiver operating characteristic Curve (AUC) at both 3 and 6 months post-TIPS. Calibration was assessed visually using calibration plots at 3 and 6 months. In addition, logistic recalibration was used to estimate the calibration intercept (i.e., calibration-in-the-large) and calibration slope at both timepoints[21]. Internal validation was performed using bootstrap resampling with 1,500 iterations[22]. Optimism-adjusted performance estimates were obtained, including the corrected C-index (derived from Somers' Dxy), Brier score, calibration slope, R^2, and the discrimination index D[23]. The final model was graphically represented through a nomogram, allowing point-based estimation of the risk. The clinical applicability of the nomogram was evaluated using decision curve analysis (DCA). Cumulative incidence of recurrent OHE was additionally assessed using a competing risks framework, with death and LT as competing events. Kaplan–Meier estimates were reported for consistency with the Cox-based prediction model; results were comparable between approaches, with competing events having minimal impact over the short follow-up. Statistical analyses were conducted using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) within the RStudio environment.

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Results

Characteristics of patients and qEEG analysis

From the 247 patients screened for recruitment, 161 patients were included in the final analysis (Fig. S1). Baseline characteristics of patients are shown in Table 1 and missing data are detailed in Table S1. TIPS was placed for secondary prophylaxis of variceal bleeding in 93 patients (58%) and for recurrent/refractory ascites in 68 (42%). Median pre-TIPS PCPG decreased from 22 mmHg (IQR 7) to 14 mmHg (IQR 5) immediately after TIPS ($p<0.001$), with 79% of patients treated with under-dilated TIPS (dilation diameter ≤7 mm). The median interval between qEEG assessment and TIPS was 1 day (IQR: 6 days). Abnormal (i.e., slowed) qEEG was identified in 40% of patients, including 32% with grade 1, 5% with grade 2, and 3% with grade 3 slowing (Table S2). qEEG alterations greater than grade 1 were uncommon (observed in only 8% of patients). Accordingly, all subsequent analyses grouped any degree of qEEG abnormality into a single category (n = 65). Patients with altered qEEG were older and exhibited more advanced liver disease, as reflected by progressive slowing of qEEG activity with the increase of Child-Pugh class (Table S2). They were more frequently referred for TIPS due to recurrent/refractory ascites and had elevated serum CRP and ammonia levels. By contrast, no significant differences were observed in terms of liver disease etiology, prior history of OHE, or PCPG, either before or after TIPS placement (Table 1). Although not statistically significant, patients without prior OHE had a higher prevalence of normal qEEG compared with those with a history of OHE (63% vs. 44%; $p = 0.08$) (Table S3). As shown in Fig. S2, MDF values were significantly correlated with several clinical and biochemical variables. Specifically, MDF was inversely associated with age ($R = –0.21$; $p=0.01$), MELD-Na score ($R = –0.22$; $p=0.008$), creatinine ($R = –0.20$;

p=0.02), CRP (R = –0.32; p<0.001), and ammonia levels (R = –0.30; p=0.001), while a positive correlation was observed with albumin levels (R = 0.21; p=0.011).

Incidence of OHE

The one-year incidence of at least a single episode of OHE reached 41% (95% CI: 33-48), while the incidence of recurrent and persistent OHE was 24% (95% CI: 17-31) (Fig. 1), and 9% (95% CI: 4-13), respectively (Fig. S3). Corresponding cumulative incidence functions in a competing risks framework were provided in Fig. S4. The incidence of post-TIPS recurrent OHE remained stable during the study period (Fig. S5 and Table S4). Most events occurred early, largely within the first 3 months after TIPS. A primary trigger was identified in 91% of first post-TIPS OHE episodes and managed accordingly. The most common triggers were dehydration (57%), infections (22%), constipation (9%), and gastrointestinal bleeding unrelated to portal hypertension (3%). Among patients who developed post-TIPS OHE, 52% subsequently experienced recurrent episodes. As shown in Fig. S6, 63% of those with recurrent OHE had three or more episodes within the first 6 months after TIPS.

Development of a clinical score to estimate the risk of post-TIPS recurrent OHE

A multivariable Cox proportional hazards model was developed to estimate the individual risk of recurrent OHE following TIPS. Four baseline variables were independently associated with the outcome: age, baseline serum albumin, history of OHE, and altered qEEG at baseline (Table 2). The model demonstrated good discrimination (Harrell's C-index: 0.76) and fulfilled proportional hazards assumptions. Using the coefficients of the

multivariable model, we derived a composite linear predictor and developed the qEEG-TIPS score, which provides individualized estimates of the risk of recurrent OHE at 3 and 6 months. The nomogram (Fig. 2) visually integrates the four predictors into a single tool, allowing clinicians to easily compute patient-specific risk. The corresponding predicted probabilities are based on the baseline survival function estimated from the cohort. Decision curve analysis (Fig. 3) confirmed that the qEEG-TIPS score yields a higher net clinical benefit than “treat all” or “treat none” strategies across a wide range of threshold probabilities, supporting its potential usefulness in guiding post-TIPS management. For practical application, we also created an interactive web-based calculator that allows clinicians to obtain individualized risk estimates at the bedside (https://tipsscores.shinyapps.io/RecOHE/). All details and extended performance metrics are reported in the Supplementary Results.

Risk subgroups

To define a high-risk subgroup, the optimal cut-off for the LP of the qEEG-TIPS score was identified using the Youden Index. A threshold of 0.48 was determined, corresponding to an AUC of 0.79 (95% CI 0.70-0.88), with a sensitivity of 75% (95% CI: 65-83) and specificity of 77% (95% CI: 68-84) (Fig. S7). Based on this threshold, 107 patients were classified as low risk (qEEG-TIPS score <0.48), and 54 as high risk (qEEG-TIPS score ≥0.48). Kaplan–Meier analysis revealed a significantly higher incidence of recurrent OHE in the high-risk group ($p<0.001$, Fig. 4). Specifically, the estimated 3- and 6-month risks of recurrent OHE were 33% (95% CI 19-45) and 48% (95% CI 32-61) in the high-risk group, compared to 5% (95% CI 1-9) and 8% (95% CI 3-13) in the low-risk group. The qEEG-TIPS score demonstrated high negative predictive values at both timepoints (NPV at 3 months: 93% [95% CI 90-95]; NPV at 6 months: 90% [95% CI 87-93]), indicating strong ability to

identify patients at low risk of recurrent OHE. Positive predictive values were modest (PPV at 3 months: 32% [95% CI 25-38]; PPV at 6 months: 44% [95% CI 37-51]), which is expected given the relatively low event rate.

Discrimination, calibration and internal validation of qEEG-TIPS score

At 3 and 6 months after TIPS, the time-dependent AUCs were 0.76 (95% CI 0.70-0.82) and 0.80 (95% CI 0.76-0.85), respectively, indicating good discriminatory performance at clinically relevant time points (Fig. 5). Model calibration was satisfactory, with calibration plots showing close agreement between predicted and observed probabilities of recurrent OHE, particularly across the low- and intermediate-risk ranges (Fig. S8). Calibration intercepts at 3 and 6 months were 0.143 and 0.225, respectively, suggesting a slight underestimation of absolute risk, while calibration slopes were 0.870 and 1.084, indicating modest miscalibration with minimal overfitting. Internal bootstrap validation (1500 resamples) yielded an optimism-corrected C-index of 0.74 (95% CI 0.69–0.84), compared with an apparent C-index of 0.76, supporting good predictive stability. The optimism-corrected calibration slope was 0.915 (95% CI 0.685-1.154), further confirming acceptable calibration. Overall predictive accuracy was supported by Brier scores of 0.109 at 3 months and 0.129 at 6 months. Full validation metrics are reported in Table S5.

Subgroup analysis in patients without prior episodes of OHE

In the subgroup of patients without a prior history of OHE (n = 136), age, serum albumin, and altered qEEG remained independently associated with the risk of post-TIPS recurrent OHE. Under-dilated TIPS (≤7 mm) placement emerged as a significant protective

factor. Model discrimination remained satisfactory in this subgroup, with a time-dependent AUC of 0.76 (95% CI 0.64-0.88) at 3 months and 0.79 (95% CI 0.68-0.90) at 6 months. Details were reported in Supplementary Results.

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Discussion

Post-TIPS OHE significantly impacts patients' and caregivers' quality of life[7]. Recurrent OHE leads to frequent hospitalizations, placing a substantial burden on caregivers and healthcare systems[24–26]. Managing recurrent and persistent OHE can be especially challenging and frustrating for clinicians, particularly in patients who are ineligible for LT. Multiple risk factors contributing to post-TIPS OHE have been suggested, including advanced age, renal dysfunction, hyponatremia, impaired liver function, and sarcopenia - many of which also overlap with those implicated in OHE during the natural course of cirrhosis[1,11]. Existing predictive models have shown suboptimal discrimination and limited clinical applicability, offering modest support for personalized risk communication or for the implementation of tailored prophylactic strategies[27–32]. Notably, the highest incidence of OHE occurs within the first months after TIPS, a phase characterized by increased susceptibility to precipitating factors due to the systemic and hepatic hemodynamic alterations induced by portal systemic shunting. This susceptibility likely contributes to the poor predictive capacity for OHE, complicating clinical decision-making. Given the great impact of recurrent OHE and the complexity of its management, we selected post-TIPS recurrent OHE as our primary outcome. In our study, qEEG performed shortly before TIPS revealed abnormalities in 40% of patients, despite the absence of overt neuropsychiatric symptoms such as disorientation to time or space. This prevalence is consistent with previous findings by Amodio et al[14], who reported qEEG abnormalities in 38% of patients with cirrhosis. Altered qEEG was significantly associated with older age, more advanced liver dysfunction, and systemic inflammation. This evidence reinforces the hypothesis that electrophysiological abnormalities are caused by hepatic impairment and portal hypertension in patients with cirrhosis, even in the absence of previous episodes of OHE[33]. Indeed, in multivariable analysis, alongside established risk factors such as age, serum

albumin levels, and a history of prior OHE episodes, the presence of altered qEEG emerged as an independent predictor of post-TIPS recurrent OHE.

Interestingly, patients with and without prior OHE presented relatively modest differences in qEEG parameters. Several factors may explain this finding, such as the selection of candidates which limits the prevalence of prior OHE, and a possible mitigating effect of secondary prophylaxis with lactulose alone or combined with rifaximin on baseline neurocognitive function.

Notably, qEEG has already shown potential in predictive modeling, improving mortality prediction when added to MELD in patients with cirrhosis[34]. The predictive model derived from these variables, the qEEG-TIPS score, demonstrated good discriminative performance and adequate calibration. It effectively stratified patients into low- and high-risk groups, with the low-risk group exhibiting minimal incidence of post-TIPS recurrent OHE and the high-risk group showing a markedly elevated incidence. Overall, the primary clinical utility of the qEEG-TIPS score lies in supporting confident identification of those patients who can safely undergo TIPS, while for high-risk patients, the model provides clinical value beyond risk stratification by guiding more personalized management strategies. These may include pre-TIPS optimization of modifiable risk factors, targeted prophylactic interventions, procedural strategies aimed at limiting shunt flow, and enhanced post-procedural monitoring. Decision curve analysis confirmed that the model offers a net clinical benefit compared to 'treat-all' or 'treat-none' approaches across clinically relevant threshold probabilities.

This study has several limitations that should be acknowledged. First, the qEEG-TIPS score has not yet undergone external validation. Although internal bootstrap validation showed acceptable optimism-corrected discrimination and calibration, some degree of overfitting cannot be excluded, with a potential tendency toward risk overestimation, as commonly

observed in models derived from relatively small samples. External validation in independent cohorts is therefore essential to confirm generalizability and to allow model recalibration if needed.

Second, standardized psychometric and neurophysiological testing for covert HE was not systematically performed at baseline. In particular, the absence of PHES[19], Critical Flicker Frequency[27], or other validated covert HE assessments precluded both a formal diagnosis of covert HE and a direct head-to-head comparison of the prognostic performance of qEEG with other established tools. Future prospective studies should incorporate multiple covert HE assessments to enable robust comparative evaluation of their diagnostic and prognostic value.

Third, a minority of patients (16%) had a history of OHE and were receiving secondary prophylaxis with non-absorbable disaccharides, which may have influenced both baseline neurophysiological function and post-TIPS outcomes. However, in an exploratory sensitivity analysis restricted to patients without prior OHE, altered qEEG remained an independent predictor of post-TIPS recurrent OHE, while under-dilated TIPS placement emerged as a protective factor. These support the robustness of the model and its applicability to routine clinical practice. Moreover, the growing adoption of small-caliber TIPS, together with increasing interest in dedicated low-diameter stent grafts, suggests that the present cohort closely reflects contemporary interventional strategies.

Fourth, nutritional status and body composition, including sarcopenia, were not systematically assessed and therefore could not be evaluated as potential modifiers of post-TIPS OHE risk. Given the emerging evidence on this association, future studies with predefined body composition assessments are warranted.

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Lastly, although the qEEG-TIPS score relies on objective qEEG parameters, limited availability of EEG equipment and the need for specialized expertise in quantitative interpretation may restrict its widespread implementation. Nevertheless, qEEG is a reproducible, patient-independent technique with minimal inter-operator variability. Recent advances in simplified, low-cost wireless EEG systems ("light-EEG")[35] and automated analysis platforms may facilitate broader adoption[33]. Notably, light-EEG has already been successfully implemented in a multicentre clinical trial with centralized analysis[36]. EEG acquisition, including preparation, typically requires 20-30 minutes, while automated analysis for purposes of HE assessment takes approximately 5 minutes, although expert selection of artefact-free segments remains necessary. Future cost-effectiveness analyses will be important to determine whether improved risk stratification offsets the additional resource requirements, both in terms of equipment and personnel training.

In summary, the qEEG-TIPS score provides a straightforward tool for individualized risk stratification of recurrent OHE after TIPS. By combining qEEG data with key clinical variables, the model demonstrated good discriminatory performance and internal validity. If validated externally, it could enhance clinical decision-making, improve candidate selection, and support tailored peri-procedural management to optimize patient outcomes.

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Abbreviations

AIC, Alkaike's Information Criterion; AUC, Area Under the receiver operating characteristic Curve; CRP, c-reactive protein; DCA, decision curve analysis; HCC, hepatocellular carcinoma; ePTFE-SGs, expanded polytetrafluoroethylene covered stent-grafts; HRQoL, health-related quality of life; IQR, interquartile range; LP, linear predictor; LT, liver transplantation; MELD-Na, Model for End-Stage Liver Disease-Sodium; MDF, mean dominant frequency; NNT, numbers needed to treat; NPV, Negative Predictive Value; OHE, overt hepatic encephalopathy; PCPG, portocaval pressure gradient; PHES, the Psychometric Hepatic Encephalopathy Score; PPV, Positive Predictive Value; qEEG, quantitative electroencephalography; SD, standard deviation; SPSS, spontaneous portosystemic shunts; TFS, transplant free survival; TIPS, transjugular intrahepatic portosystemic shunt; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis.

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References

1. **Saltini D, Indulti F, Guasconi T**, et al. Transjugular Intrahepatic Portosystemic Shunt: Devices Evolution, Technical Tips and Future Perspectives. *Journal of Clinical Medicine*. 2023;12(21):6758. doi:10.3390/jcm12216758

2. Nardelli S, Riggio O, Marra F, et al. Episodic overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt does not increase mortality in patients with cirrhosis. *J Hepatol*. 2024;80(4):596-602. doi:10.1016/j.jhep.2023.11.033

3. Hartl L, Kornfehl A, Reiberger T. Does encephalopathy with early onset after TIPS impact on mortality? *J Hepatol*. 2024;81(6):e269-e270. doi:10.1016/j.jhep.2024.05.035

4. **Kabelitz MA, Sandmann L,** Praktiknjo M, et al. Early Occurrence of Hepatic Encephalopathy Following Transjugular Intrahepatic Portosystemic Shunt Insertion is Linked to Impaired Survival: A Multicenter Cohort Study. *Clin Gastroenterol Hepatol*. Published online March 15, 2025:S1542-3565(25)00203-4. doi:10.1016/j.cgh.2025.01.024

5. Saltini D, Nardelli S, Schepis F. Reconsidering the Relationship Between Early Post Transjugular Intrahepatic Portosystemic Shunt Hepatic Encephalopathy and Mortality: Are We Still Missing Something? *Clin Gastroenterol Hepatol*. Published online May 10, 2025:S1542-3565(25)00376-3. doi:10.1016/j.cgh.2025.04.020

6. Larrue H, D'Amico G, Olivas P, et al. TIPS prevents further decompensation and improves survival in patients with cirrhosis and portal hypertension in an individual patient data meta-analysis. *J Hepatol*. 2023;79(3):692-703. doi:10.1016/j.jhep.2023.04.028

7. Montagnese S, Amato E, Schiff S, et al. A patients' and caregivers' perspective on hepatic encephalopathy. *Metab Brain Dis*. 2012;27(4):567-572. doi:10.1007/s11011-012-9325-7

8. Ladegaard Grønkjær L, Hoppe Sehstedt T, Norlyk A, et al. Overt Hepatic Encephalopathy Experienced by Individuals With Cirrhosis: A Qualitative Interview Study. *Gastroenterol Nurs*. 2018;41(6):468-476. doi:10.1097/SGA.0000000000000286

9. Friis KH, Thomsen KL, Laleman W, Montagnese S, et al. Post-Transjugular Intrahepatic Portosystemic Shunt (TIPS) Hepatic Encephalopathy-A Review of the Past Decade's Literature Focusing on Incidence, Risk Factors, and Prophylaxis. *J Clin Med*. 2023;13(1):14. doi:10.3390/jcm13010014

10. Bai M, Qi X, Yang Z, et al. Predictors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in cirrhotic patients: a systematic review. *J Gastroenterol Hepatol*. 2011;26(6):943-951. doi:10.1111/j.1440-1746.2011.06663.x

11. Fagiuoli S, Bruno R, Debernardi Venon W, et al. Consensus conference on TIPS management: Techniques, indications, contraindications. *Dig Liver Dis*. 2017;49(2):121-137. doi:10.1016/j.dld.2016.10.011

12. **Schepis F, Vizzutti F**, Garcia-Tsao G, et al. Under-dilated TIPS Associate With Efficacy and Reduced Encephalopathy in a Prospective, Non-randomized Study of Patients With Cirrhosis. *Clin Gastroenterol Hepatol*. 2018;16(7):1153-1162.e7. doi:10.1016/j.cgh.2018.01.029

13. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on TIPS. *J Hepatol*. 2025;83(1):177-210. doi:10.1016/j.jhep.2025.01.029

14. Amodio P, Del Piccolo F, Pettenò E, et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. *J Hepatol*. 2001;35(1):37-45. doi:10.1016/s0168-8278(01)00129-5

15. Nardelli S, Riggio O, Turco L, et al. Relevance of Spontaneous Portosystemic Shunts Detected with CT in Patients with Cirrhosis. *Radiology*. 2021;299(1):133-140. doi:10.1148/radiol.2021203051

16. Simón-Talero M, Roccarina D, Martínez J, et al. Association Between Portosystemic Shunts and Increased Complications and Mortality in Patients With Cirrhosis. *Gastroenterology*. 2018;154(6):1694-1705.e4. doi:10.1053/j.gastro.2018.01.028

17. Saltini D, Zanetto A, Schepis F. Sedoanalgesia during TIPS placement:

Journal Pre-proof

Hemodynamic and ethical issues. *J Hepatol*. 2025;82(4):e193-e194. doi:10.1016/j.jhep.2024.11.001

18. American Association for the Study of Liver Diseases, European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol*. 2014;61(3):642-659. doi:10.1016/j.jhep.2014.05.042

19. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. *J Hepatol*. 2022;77(3):807-824. doi:10.1016/j.jhep.2022.06.001

20. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ*. 2015;350:g7594. doi:10.1136/bmj.g7594

21. Van Calster B, McLernon DJ, van Smeden M, et al. Topic Group 'Evaluating diagnostic tests and prediction models' of the STRATOS initiative. Calibration: the Achilles heel of predictive analytics. *BMC Med*. 2019;17(1):230. doi:10.1186/s12916-019-1466-7

22. Steyerberg EW, Bleeker SE, Moll HA, et al. Internal and external validation of predictive models: A simulation study of bias and precision in small samples. *Journal of Clinical Epidemiology*. 2003;56(5):441-447. doi:10.1016/S0895-4356(03)00047-7

23. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15(4):361-387. doi:10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4

24. Chen Z, Babcock A, Sanogo V, et al. Predictors of 30-day readmission and hospitalization costs of patients with hepatic encephalopathy in the US from 2010 to 2014. *Expert Rev Pharmacoecon Outcomes Res*. 2022;22(3):409-415. doi:10.1080/14737167.2021.1927717

Journal Pre-proof

25. Frenette CT, Levy C, Saab S. Hepatic Encephalopathy-Related Hospitalizations in Cirrhosis: Transition of Care and Closing the Revolving Door. *Dig Dis Sci*. 2022;67(6):1994-2004. doi:10.1007/s10620-021-07075-2

26. Wong RJ, Gagnon-Sanschagrin P, Heimanson Z, et al. Real-World Trends and Future Projections of the Prevalence of Cirrhosis and Hepatic Encephalopathy Among Commercially and Medicare-Insured Adults in the United States. *Clin Transl Gastroenterol*. 2025;16(5):e00823. doi:10.14309/ctg.0000000000000823

27. Berlioux P, Robic MA, Poirson H, et al. Pre-transjugular intrahepatic portosystemic shunts (TIPS) prediction of post-TIPS overt hepatic encephalopathy: the critical flicker frequency is more accurate than psychometric tests. *Hepatology*. 2014;59(2):622-629. doi:10.1002/hep.26684

28. Senzolo M, Zarantonello L, Formentin C, et al. Predictive value of induced hyperammonaemia and neuropsychiatric profiling in relation to the occurrence of post-TIPS hepatic encephalopathy. *Metab Brain Dis*. 2019;34(6):1803-1812. doi:10.1007/s11011-019-00490-5

29. Wang Z, Wu YF, Yue ZD, et al. Comparative study of indocyanine green-R15, Child-Pugh score, and model for end-stage liver disease score for prediction of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. *World J Gastroenterol*. 2021;27(5):416-427. doi:10.3748/wjg.v27.i5.416

30. Yang Y, Liang X, Yang S, et al. Preoperative prediction of overt hepatic encephalopathy caused by transjugular intrahepatic portosystemic shunt. *Eur J Radiol*. 2022;154:110384. doi:10.1016/j.ejrad.2022.110384

31. Tuifua TS, Kapoor B, Partovi S, et al. Prediction of Mortality and Hepatic Encephalopathy after Transjugular Intrahepatic Portosystemic Shunt Placement: Baseline and Longitudinal Body Composition Measurement. *J Vasc Interv Radiol*. 2024;35(5):648-657.e1. doi:10.1016/j.jvir.2024.01.012

Journal Pre-proof

32. Tiede A, Stockhoff L, Ehrenbauer AF, et al. Value of systemic inflammation markers for the detection of minimal and prediction of overt hepatic encephalopathy after TIPS insertion. *Metab Brain Dis*. 2024;40(1):58. doi:10.1007/s11011-024-01436-2

33. Montagnese S, Biancardi A, Schiff S, et al. Different biochemical correlates for different neuropsychiatric abnormalities in patients with cirrhosis. *Hepatology*. 2011;53(2):558-566. doi:10.1002/hep.24043

34. Montagnese S, De Rui M, Schiff S, et al. Prognostic benefit of the addition of a quantitative index of hepatic encephalopathy to the MELD score: the MELD-EEG. *Liver Int*. 2015;35(1):58-64. doi:10.1111/liv.12490

35. Schiff S, Casa M, Di Caro V, et al. A low-cost, user-friendly electroencephalographic recording system for the assessment of hepatic encephalopathy. *Hepatology*. 2016;63(5):1651-1659. doi:10.1002/hep.28477

36. Montagnese S, Lauridsen M, Vilstrup H, et al. A pilot study of golexanolone, a new GABA-A receptor-modulating steroid antagonist, in patients with covert hepatic encephalopathy. *J Hepatol*. 2021;75(1):98-107. doi:10.1016/j.jhep.2021.03.012

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Tables

Table 1. Baseline characteristics of the study cohort, stratified by qEEG findings (normal vs. altered).

	Total cohort (N = 161)	Normal qEEG group (n = 96)	Altered qEEG group (n = 65)	p value
Male sex, n (%)	112 (70)	62 (65)	50 (77)	0.117
Median age, y (IQR)	61 (16)	59 (14)	63 (14)	0.014
Etiology of liver disease (%)				0.530
- ALD	60 (37)	36 (38)	24 (37)	
- Viral	46 (29)	28 (29)	18 (28)	
- MAFLD	27 (17)	13 (14)	14 (21)	
- Cholestatic	10 (6)	8 (8)	2 (3)	
- Others*	18 (11)	11 (11)	7 (11)	
TIPS indication, n (%)				0.002
- Recurrent/Refractory ascites	68 (42)	31 (32)	37 (57)	
- II prophylaxis of variceal bleeding	93 (58)	65 (68)	28 (43)	
Prior history of OHE, n (%)	25 (16)	11 (12)	14 (22)	0.119
- II prophylaxis with lactulose	25 (16)	11 (12)	14 (22)	
- II prophylaxis with lactulose + rifaximin	11 (7)	5 (5)	6 (9)	
Large SPSS, n (%)	37 (23)	23 (24)	14 (22)	0.849
Comorbidities:				
- COPD, n (%)	18 (11)	11 (12)	7 (11)	1.000
- CKD, n (%)	15 (9)	11 (12)	4 (6)	0.286
- Diabetes, n (%)	56 (35)	29 (30)	27 (42)	0.177
Biochemical data:				
Albumin, g/dL, ± SD	3.6 ± 0.6	3.7 ± 0.6	3.4 ± 0.6	0.046
Ammonia, µmol/L (IQR)	36.0 (40.0)	30.0 (33.5)	43.5 (29.0)	0.004
Total bilirubin, mg/dL (IQR)	1.30 (1.10)	1.23 (1.14)	1.38 (0.1)	0.365
C-reactive protein mg/L (IQR)	0.70 (1.1)	0.6 (1.0)	0.9 (1.0)	0.010
AST, U/L, (IQR)	33 (19)	33 (19)	34 (16)	0.435
ALT, U/L, (IQR)	23 (15)	23 (15)	22 (16)	0.936
Creatinine, mg/dL (IQR)	0.84 (0.44)	0.81 (0.38)	0.94 (0.51)	0.027
Hemoglobin, g/dl, ± SD	10.5 ± 3.0	10.7 ± 3.4	10.3 ± 2.6	0.192
INR (IQR)	1.36 (0.29)	1.36 (0.25)	1.36 (0.31)	0.594
Serum sodium, mmol/L (IQR)	138 (5)	138 (4)	137 (7)	0.016
Scores:				
Child-Pugh score, n (IQR)	7 (2)	7 (2)	8 (2)	0.014
Child-Pugh class, %				0.031
- A	53 (33)	37 (39)	16 (25)	
- B	90 (56)	53 (55)	37 (57)	
- C	18 (11)	6 (6)	12 (18)	
MELD-Na score (IQR)	13 (6)	12 (6)	14 (7)	0.001
Hemodynamic Assessment				

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	Total cohort (N = 161)	Normal qEEG group (n = 96)	Altered qEEG group (n = 65)	p value
Stent-graft type**, n (%)				0.400
- 8 mm	36 (22)	18 (19)	18 (28)	
- 10 mm	31 (19)	19 (20)	12 (19)	
- VCX	94 (58)	59 (62)	35 (54)	
Under-dilated TIPS***, n (%)	127 (79)	77 (80)	50 (77)	0.695
PCPG before TIPS, mmHg (IQR)	22 (7)	22 (7)	22 (7)	0.913
PCPG after TIPS, mmHg (IQR)	14 (5)	14 (4)	13 (5)	0.619
PCPG relative drop, % ± SD	38 ± 14	37 ± 14	39 ± 14	0.358
Post PCPG <10 mmHg, n (%)	20 (12)	11 (12)	9 (14)	0.808
PCPG drop >50%, n (%)	32 (20)	16 (17)	16 (25)	0.232
qEEG parameters				
qEEG to TIPS time, days (IQR)	1 (6)	1 (6)	1 (6)	0.338
MDF, Hz ± SD	9.6 ± 2.3	11.1 ± 1.6	7.7 ± 1.6	<0.001
- Alpha relative power, (%)	30.9 (25.0)	46.2 (20.0)	22.4 (13.6)	<0.001
- Beta relative power, (%)	15.4 (16.4)	26.0 (19.5)	10.7 (6.5)	<0.001
- Delta relative power, (%)	8.8 (8.6)	7.0 (5.8)	10.9 (11.7)	<0.001
- Theta relative power, (%)	27.2 (33.6)	16.5 (12.4)	49.9 (10.5)	<0.001

For data with a normal distribution, results are reported as mean ± standard deviation; for non-normally distributed data, median with interquartile range in brackets is provided. Comparison between “Normal qEEG” and “Altered qEEG” groups were performed using the t-test or Wilcoxon rank-sum test for continuous variables, depending on distribution, and the chi-squared or Fisher’s exact test for categorical variables.

ALD, alcohol-related liver disease; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; COPD, Chronic Obstructive Pulmonary Disease; CKD, chronic kidney disease; MAFLD, Metabolic Dysfunction-Associated Fatty Liver Disease; MDF, Mean Dominant Frequency; MELD-Na, Model for End-Stage Liver Disease-Sodium; OHE, Overt Hepatic Encephalopathy; PCPG, portocaval pressure gradient; qEEG, quantitative electroencephalography; TIPS, Transjugular Intrahepatic Portosystemic Shunt; VCX, VIATORR® Controlled Expansion.

*Others etiologies included autoimmune hepatitis, hemochromatosis, and cryptogenic cirrhosis.

** Stent-graft type refers to the different TIPS-dedicated stents available during the enrollment period: VIATORR® TIPS stent-grafts (VTS) with 8- or 10-mm nominal diameter, and VIATORR® Controlled Expansion (VCX).

*** TIPS were defined “under-dilated” when dilated with an angioplasty balloon-catheter with a diameter less than or equal to 7 mm.

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Table 2. Univariable and multivariable Cox regression analyses for prediction of post-TIPS recurrent OHE.

	Univariable analysis			Multivariable analysis		
Characteristic	HR	95% CI	P value	HR	95% CI	P value
Age, y	1.05	1.02-1.09	0.002	1.04	1.01-1.08	0.026
Albumin, g/dl	0.42	0.24-0.75	0.003	0.47	0.26-0.86	0.015
Altered qEEG	4.37	2.10-9.12	<0.001	2.92	1.35-6.29	0.006
Ammonia, µmol/L	1.01	1.00-1.02	0.043	-	-	-
Creatinine, mg/dL	1.14	0.58-2.23	0.7	-	-	-
INR	1.52	0.40-5.84	0.5	-	-	-
Male sex	0.94	0.46-1.92	0.9	-	-	-
PCPG drop > 50%	0.71	0.33-1.51	0.4	-	-	-
PCPG post-TIPS <10 mmHg	0.91	0.32-2.59	0.9	-	-	-
Prior episodes of OHE	3.11	1.52-6.35	0.002	2.50	1.19-5.25	0.015
Serum sodium, mmol/L	0.98	0.90-1.06	0.5	-	-	-
Large SPSS*	0.90	0.41-1.98	0.8	-	-	-
TIPS indication**	0.43	0.22-0.85	0.015	-	-	-
TIPS under-dilated***	0.51	0.25-1.02	0.059	-	-	-
Total Bilirubin, mg/dL	1.16	0.87-1.53	0.3	-	-	-

Cox proportional hazards regression was used to explore associations between baseline variables and the risk of recurrent OHE after TIPS. Univariable analyses were performed for all candidate predictors. Variables with $p < 0.10$ in univariate analysis were considered for entry into a multivariable model, which was then refined via backward stepwise selection. For each variable, hazard ratios (HR), 95% confidence intervals (CI), and p values are reported (level of significance $p < 0.05$).

CI, confidence interval; HR, hazard ratio; OHE, Overt Hepatic Encephalopathy; PCPG, portocaval pressure gradient; qEEG, quantitative electroencephalography; TIPS, Transjugular Intrahepatic Portosystemic Shunt.

* Large SPSS were evaluated post hoc using pre-procedural CT scans.

**Reference: indication for recurrent/refractory ascites.

*** TIPS were defined “under-dilated” when dilated with an angioplasty balloon-catheter with a diameter less than or equal to 7 mm.

Figure legends

Fig.1. Kaplan-Meier curve for time to recurrent OHE after TIPS placement.

OHE, overt hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt.

Fig. 2. Nomogram of qEEG-TIPS model for individualized prediction of post-TIPS recurrent OHE risk at 3 and 6 months.

OHE, overt hepatic encephalopathy; qEEG, quantitative electroencephalography; TIPS, transjugular intrahepatic portosystemic shunt.

Fig. 3. Decision curve analysis demonstrating net benefit of the qEEG-TIPS nomogram across different threshold probabilities.

Dashed red and green lines showed “full intervention” and “no intervention” strategies; solid blue line qEEG-TIPS model application.

qEEG, quantitative electroencephalography; TIPS, transjugular intrahepatic portosystemic shunt.

Fig. 4. Recurrent OHE-free probability stratified according to qEEG-TIPS risk groups (high-risk: score ≥0.48; low-risk: score <0.48).

Differences in recurrent OHE incidence were assessed using log-rank tests.

OHE, overt hepatic encephalopathy; qEEG, quantitative electroencephalography; TIPS, transjugular intrahepatic portosystemic shunt.

Fig. 5. Time-dependent receiver operating characteristic curves of the qEEG-TIPS model at (A) 3 months and (B) 6 months post-TIPS.

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AUC, area under the curve; OHE, overt hepatic encephalopathy; qEEG, quantitative electroencephalography; TIPS, transjugular intrahepatic portosystemic shunt.

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Figures

Fig. 1.

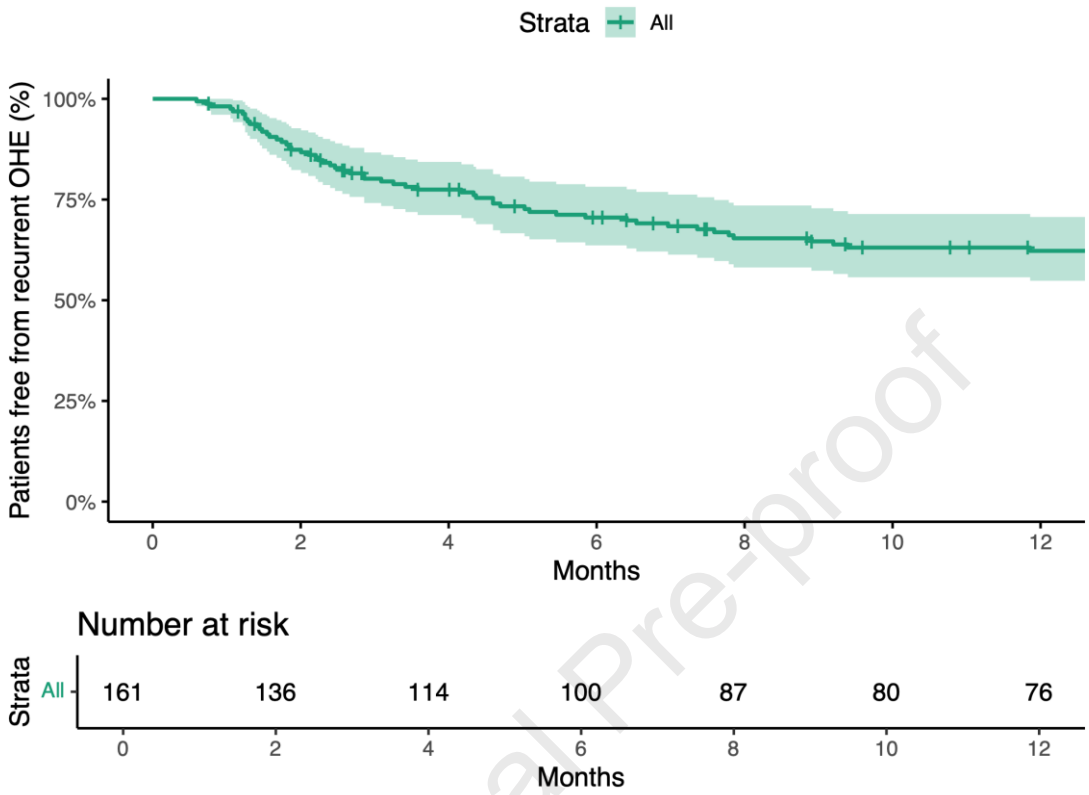

Fig. 2.

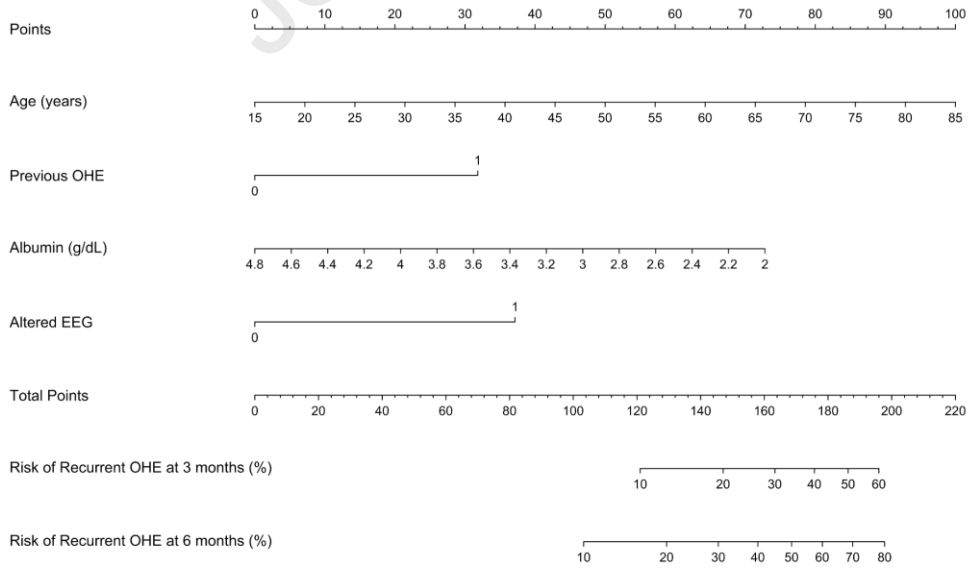

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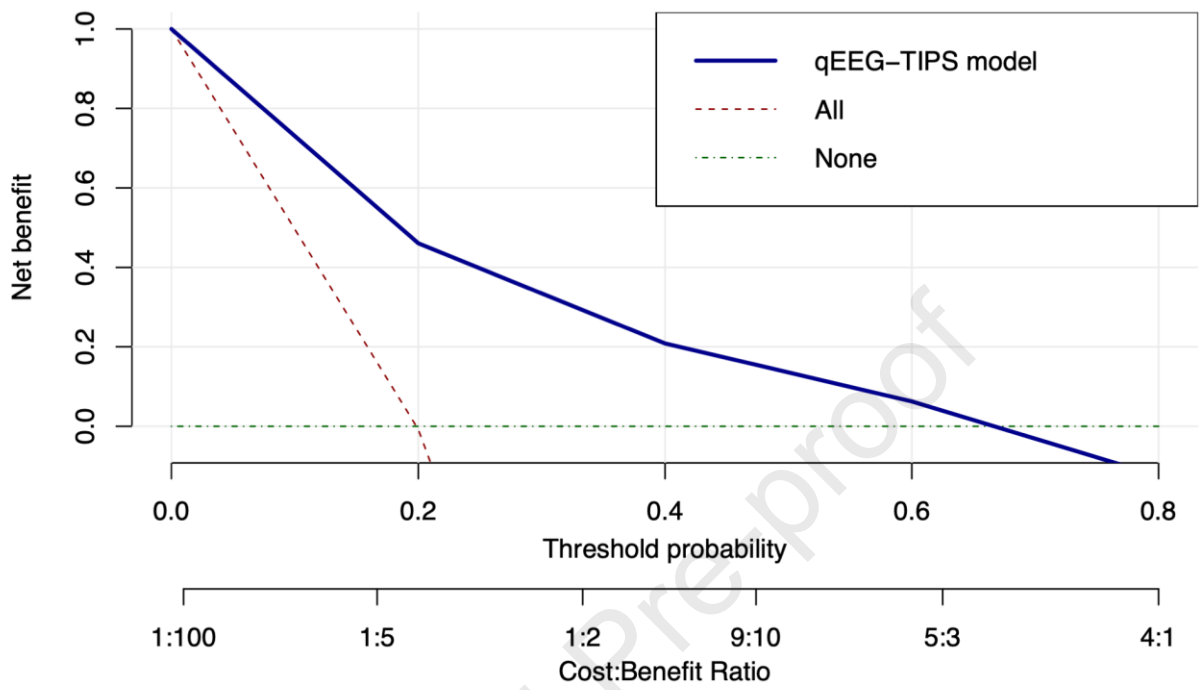
Fig. 3.



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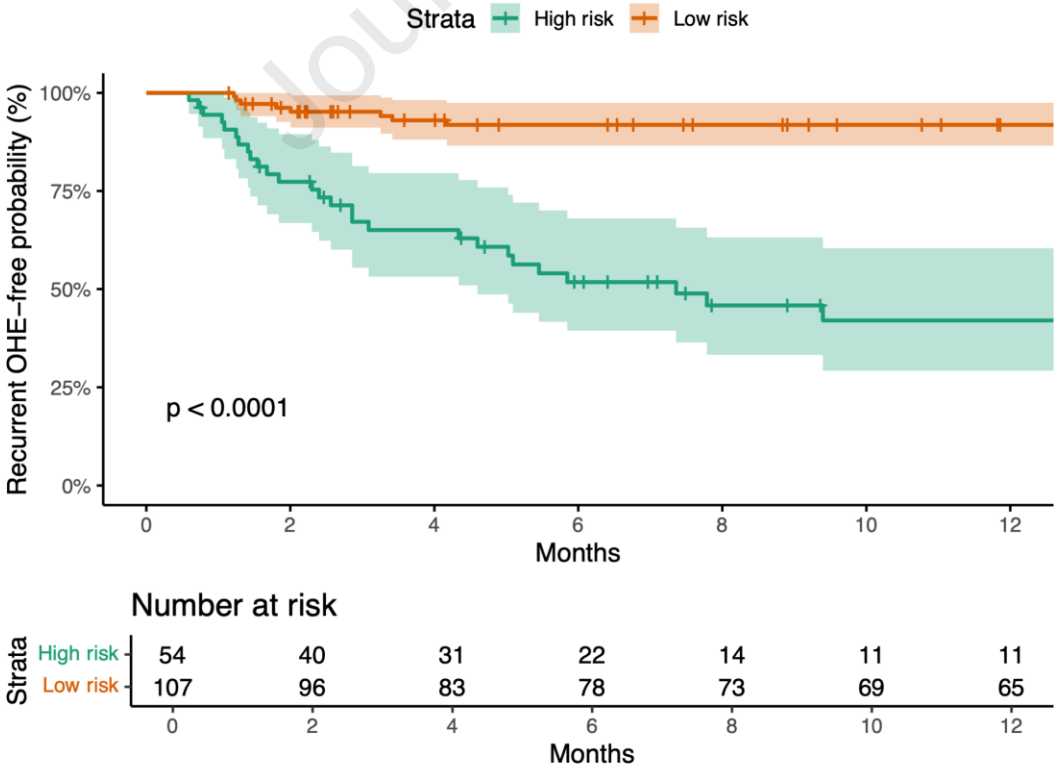

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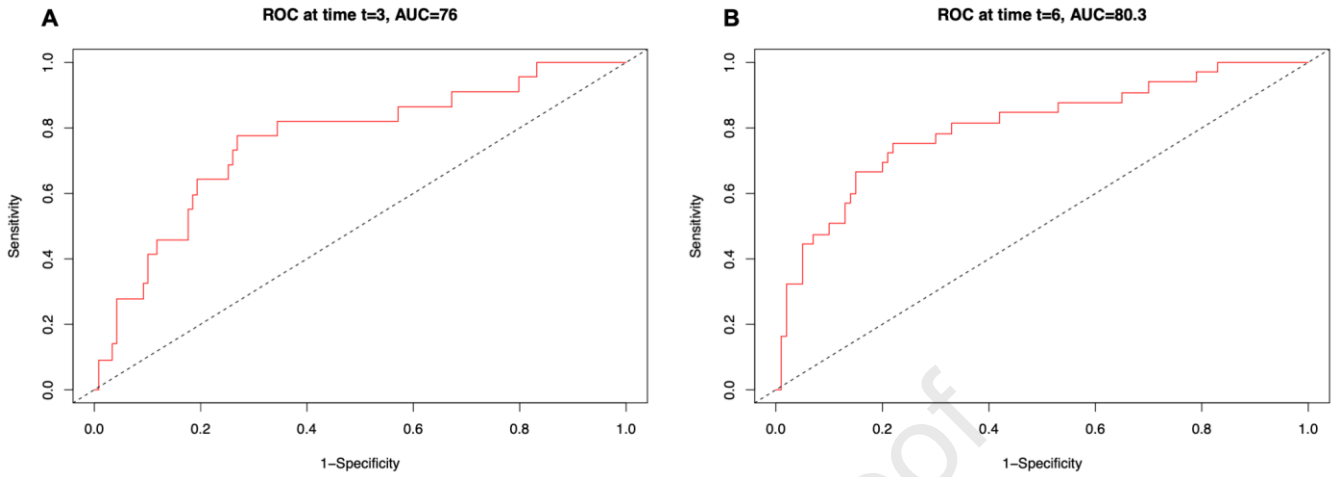
Fig. 5.



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ALT, U/L, (IQR)	23 (15)	23 (15)	22 (16)	0.936
Creatinine, mg/dL (IQR)	0.84 (0.44)	0.81 (0.38)	0.94 (0.51)	0.027
Hemoglobin, g/dl, ± SD	10.5 ± 3.0	10.7 ± 3.4	10.3 ± 2.6	0.192
INR (IQR)	1.36 (0.29)	1.36 (0.25)	1.36 (0.31)	0.594
Serum sodium, mmol/L (IQR)	138 (5)	138 (4)	137 (7)	0.016
Scores:				
Child-Pugh score, n (IQR)	7 (2)	7 (2)	8 (2)	0.014
Child-Pugh class, %				0.031
- A	53 (33)	37 (39)	16 (25)	
- B	90 (56)	53 (55)	37 (57)	
- C	18 (11)	6 (6)	12 (18)	
MELD-Na score (IQR)	13 (6)	12 (6)	14 (7)	0.001
Hemodynamic Assessment				

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	Total cohort (N = 161)	Normal qEEG group (n = 96)	Altered qEEG group (n = 65)	p value
Stent-graft type**, n (%)				0.400
- 8 mm	36 (22)	18 (19)	18 (28)	
- 10 mm	31 (19)	19 (20)	12 (19)	
- VCX	94 (58)	59 (62)	35 (54)	
Under-dilated TIPS***, n (%)	127 (79)	77 (80)	50 (77)	0.695
PCPG before TIPS, mmHg (IQR)	22 (7)	22 (7)	22 (7)	0.913
PCPG after TIPS, mmHg (IQR)	14 (5)	14 (4)	13 (5)	0.619
PCPG relative drop, % ± SD	38 ± 14	37 ± 14	39 ± 14	0.358
Post PCPG <10 mmHg, n (%)	20 (12)	11 (12)	9 (14)	0.808
PCPG drop >50%, n (%)	32 (20)	16 (17)	16 (25)	0.232
qEEG parameters				
qEEG to TIPS time, days (IQR)	1 (6)	1 (6)	1 (6)	0.338
MDF, Hz ± SD	9.6 ± 2.3	11.1 ± 1.6	7.7 ± 1.6	<0.001
- Alpha relative power, (%)	30.9 (25.0)	46.2 (20.0)	22.4 (13.6)	<0.001
- Beta relative power, (%)	15.4 (16.4)	26.0 (19.5)	10.7 (6.5)	<0.001
- Delta relative power, (%)	8.8 (8.6)	7.0 (5.8)	10.9 (11.7)	<0.001
- Theta relative power, (%)	27.2 (33.6)	16.5 (12.4)	49.9 (10.5)	<0.001

For data with a normal distribution, results are reported as mean ± standard deviation; for non-normally distributed data, median with interquartile range in brackets is provided. Comparison between “Normal qEEG” and “Altered qEEG” groups were performed using the t-test or Wilcoxon rank-sum test for continuous variables, depending on distribution, and the chi-squared or Fisher’s exact test for categorical variables.

ALD, alcohol-related liver disease; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; COPD, Chronic Obstructive Pulmonary Disease; CKD, chronic kidney disease; MAFLD, Metabolic Dysfunction-Associated Fatty Liver Disease; MDF, Mean Dominant Frequency; MELD-Na, Model for End-Stage Liver Disease-Sodium; OHE, Overt Hepatic Encephalopathy; PCPG, portocaval pressure gradient; qEEG, quantitative electroencephalography; TIPS, Transjugular Intrahepatic Portosystemic Shunt; VCX, VIATORR® Controlled Expansion.

*Others etiologies included autoimmune hepatitis, hemochromatosis, and cryptogenic cirrhosis.

** Stent-graft type refers to the different TIPS-dedicated stents available during the enrollment period: VIATORR® TIPS stent-grafts (VTS) with 8- or 10-mm nominal diameter, and VIATORR® Controlled Expansion (VCX).

*** TIPS were defined “under-dilated” when dilated with an angioplasty balloon-catheter with a diameter less than or equal to 7 mm.

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Table 2. Univariable and multivariable Cox regression analyses for prediction of post-TIPS recurrent OHE.

	Univariable analysis			Multivariable analysis		
Characteristic	HR	95% CI	P value	HR	95% CI	P value
Age, y	1.05	1.02-1.09	0.002	1.04	1.01-1.08	0.026
Albumin, g/dl	0.42	0.24-0.75	0.003	0.47	0.26-0.86	0.015
Altered qEEG	4.37	2.10-9.12	<0.001	2.92	1.35-6.29	0.006
Ammonia, µmol/L	1.01	1.00-1.02	0.043	-	-	-
Creatinine, mg/dL	1.14	0.58-2.23	0.7	-	-	-
INR	1.52	0.40-5.84	0.5	-	-	-
Male sex	0.94	0.46-1.92	0.9	-	-	-
PCPG drop > 50%	0.71	0.33-1.51	0.4	-	-	-
PCPG post-TIPS <10 mmHg	0.91	0.32-2.59	0.9	-	-	-
Prior episodes of OHE	3.11	1.52-6.35	0.002	2.50	1.19-5.25	0.015
Serum sodium, mmol/L	0.98	0.90-1.06	0.5	-	-	-
Large SPSS*	0.90	0.41-1.98	0.8	-	-	-
TIPS indication**	0.43	0.22-0.85	0.015	-	-	-
TIPS under-dilated***	0.51	0.25-1.02	0.059	-	-	-
Total Bilirubin, mg/dL	1.16	0.87-1.53	0.3	-	-	-

Cox proportional hazards regression was used to explore associations between baseline variables and the risk of recurrent OHE after TIPS. Univariable analyses were performed for all candidate predictors. Variables with $p < 0.10$ in univariate analysis were considered for entry into a multivariable model, which was then refined via backward stepwise selection. For each variable, hazard ratios (HR), 95% confidence intervals (CI), and p values are reported (level of significance $p < 0.05$).

CI, confidence interval; HR, hazard ratio; OHE, Overt Hepatic Encephalopathy; PCPG, portocaval pressure gradient; qEEG, quantitative electroencephalography; TIPS, Transjugular Intrahepatic Portosystemic Shunt.

* Large SPSS were evaluated post hoc using pre-procedural CT scans.

**Reference: indication for recurrent/refractory ascites.

*** TIPS were defined “under-dilated” when dilated with an angioplasty balloon-catheter with a diameter less than or equal to 7 mm.

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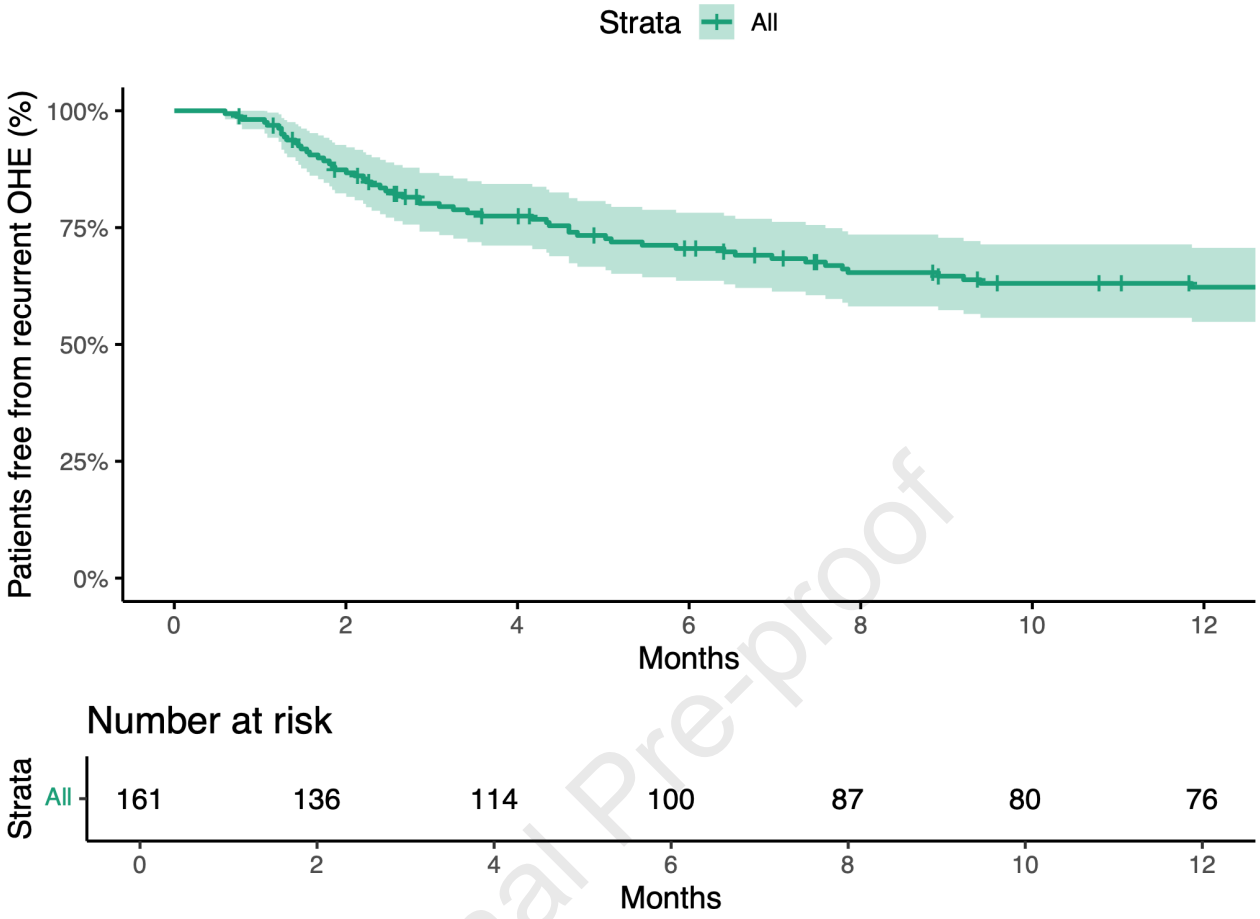

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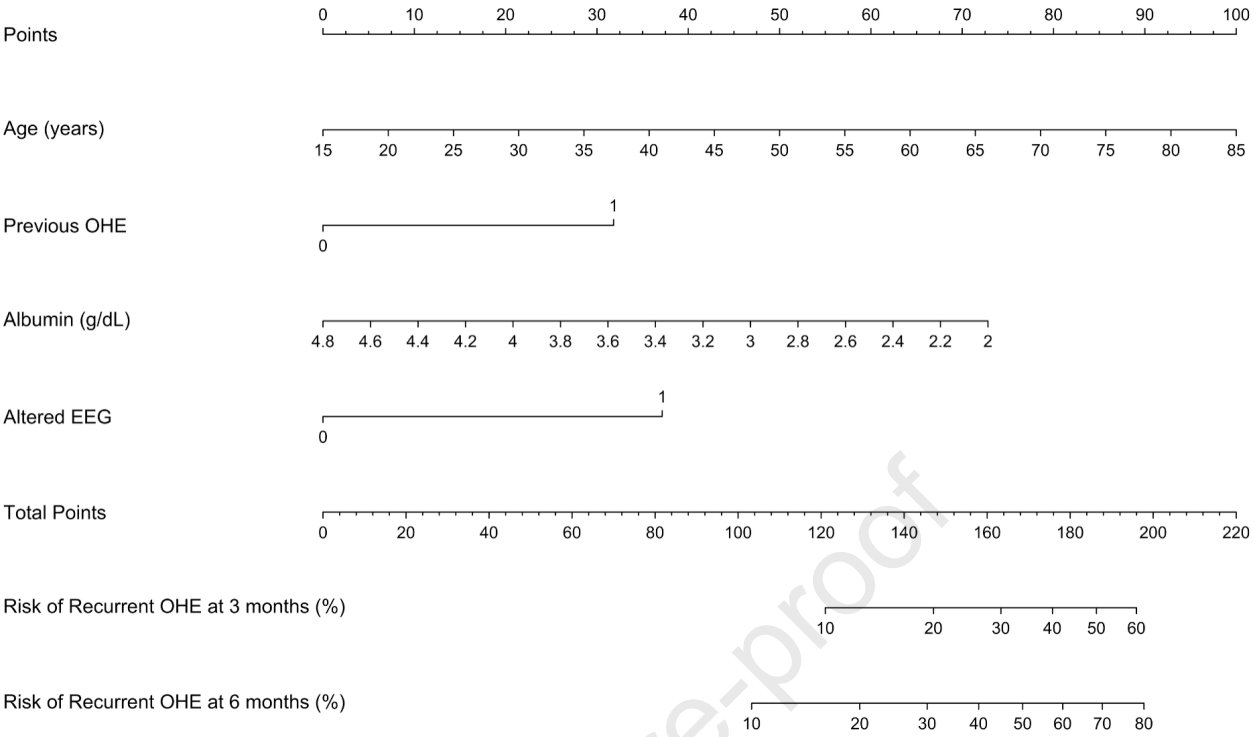

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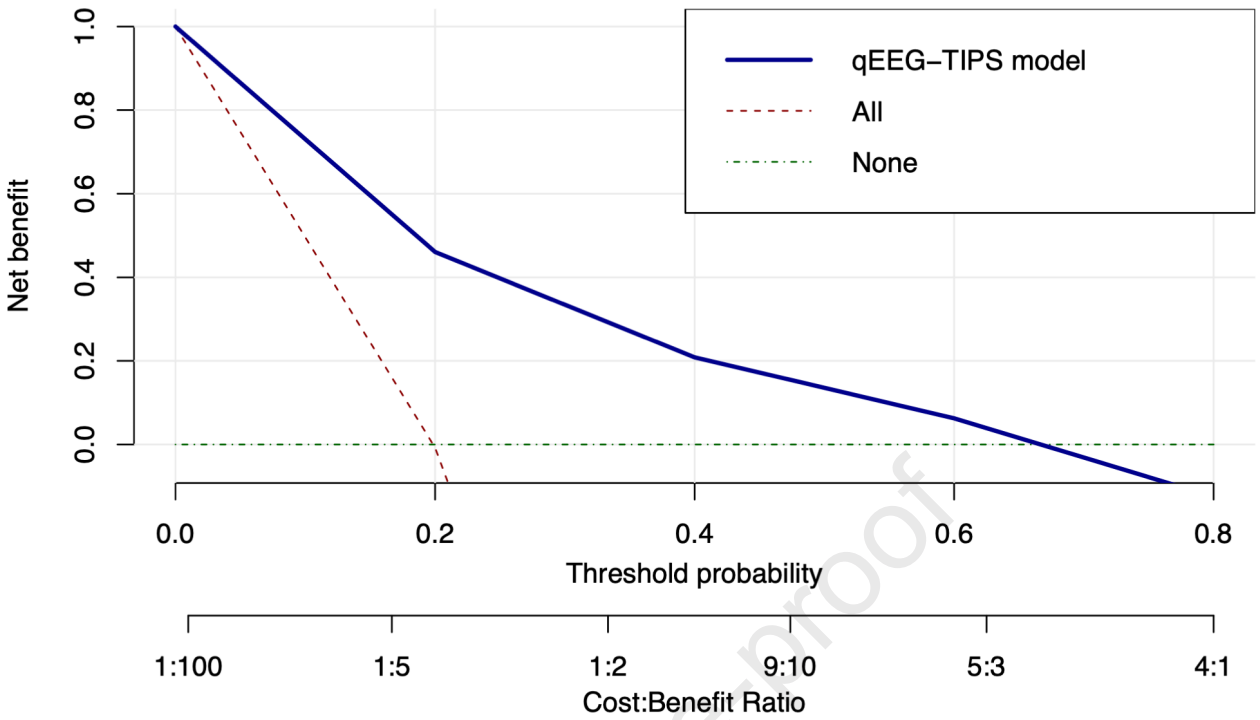

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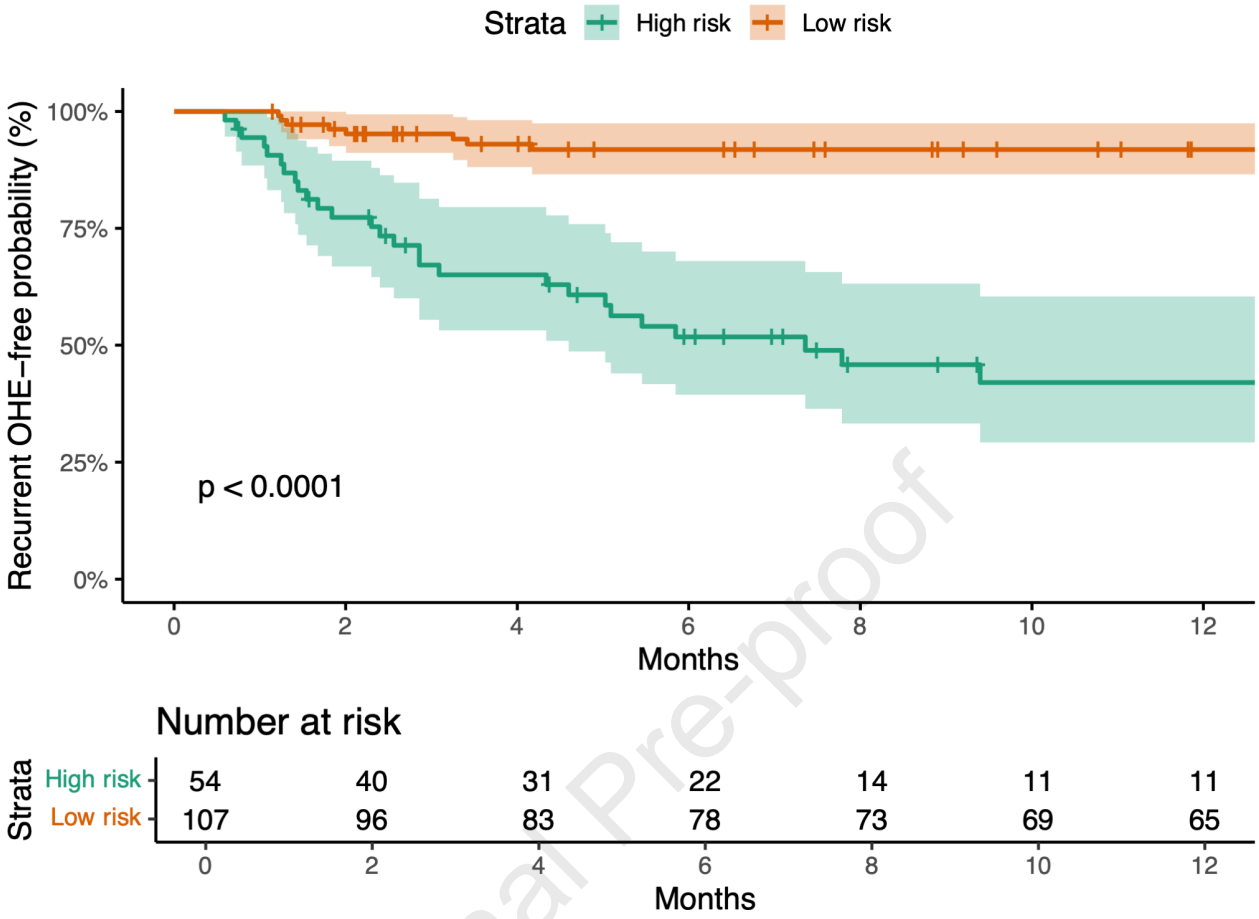

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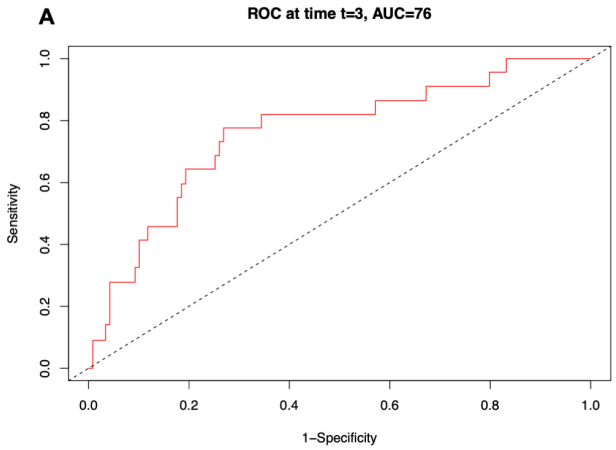

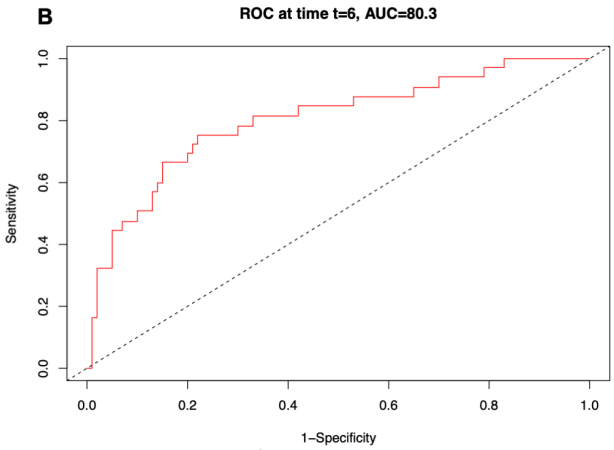

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Figure legends

Fig.1. Kaplan-Meier curve for time to recurrent OHE after TIPS placement.

OHE, overt hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt.

Fig. 2. Nomogram of qEEG-TIPS model for individualized prediction of post-TIPS recurrent OHE risk at 3 and 6 months.

OHE, overt hepatic encephalopathy; qEEG, quantitative electroencephalography; TIPS, transjugular intrahepatic portosystemic shunt.

Fig. 3. Decision curve analysis demonstrating net benefit of the qEEG-TIPS nomogram across different threshold probabilities.

Dashed red and green lines showed “full intervention” and “no intervention” strategies; solid blue line qEEG-TIPS model application.

qEEG, quantitative electroencephalography; TIPS, transjugular intrahepatic portosystemic shunt.

Fig. 4. Recurrent OHE-free probability stratified according to qEEG-TIPS risk groups (high-risk: score ≥0.48; low-risk: score <0.48).

Differences in recurrent OHE incidence were assessed using log-rank tests.

OHE, overt hepatic encephalopathy; qEEG, quantitative electroencephalography; TIPS, transjugular intrahepatic portosystemic shunt.

Fig. 5. Time-dependent receiver operating characteristic curves of the qEEG-TIPS model at (A) 3 months and (B) 6 months post-TIPS.

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AUC, area under the curve; OHE, overt hepatic encephalopathy; qEEG, quantitative electroencephalography; TIPS, transjugular intrahepatic portosystemic shunt.

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- A qEEG-based score predicts recurrent OHE after elective TIPS.
- Age, albumin, prior OHE and qEEG independently predict post-TIPS OHE.
- The qEEG-TIPS score showed good discrimination and internal validation.
- High negative predictive value identifies patients at low OHE risk.
- qEEG provides objective neurophysiological risk stratification before TIPS.

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