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RESEARCH ARTICLE

# Enlarged perivascular space in the temporal lobe as a prognostic marker in temporal lobe epilepsy with hippocampal sclerosis

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## Abstract

**Objective:** This study was undertaken to investigate the regional burden of enlarged perivascular spaces (EPVSs) in patients with temporal lobe epilepsy with hippocampal sclerosis (TLE-HS) and explore its prognostic relevance.

**Methods:** In this retrospective observational study, EPVSs in the temporal lobe (T-EPVS), centrum semiovale (CS-EPVS), basal ganglia (BG-EPVS), midbrain, and hippocampus were visually rated in 68 treatment-naïve patients with TLE-HS. Regional EPVS burden was dichotomized into high and low degrees (cutoff: >10 for BG-EPVS/T-EPVS; >20 for CS-EPVS). Cox proportional hazards models were used to determine the potential predictors of seizure freedom (SF; no seizure for >1 year) and delayed SF (SF achieved >6 months after initiating antiseizure medication [ASM]). Multivariate logistic regression using stepwise variable selection based on the Akaike information criterion was performed to investigate whether EPVS burden was associated with medical refractoriness (never achieving SF).

**Results:** Of the 68 patients, 20 were classified into the refractory group (29.4%). The high T-EPVS group had an older epilepsy onset (37.3 ± 12.3 vs. 26.5 ± 13.0 years, $p = .005$), higher pretreatment seizure density (median = 12.0, interquartile range [IQR] = 5.0–20.0 vs. 4.0, IQR = 2.0–10.5, $p = .008$), and lower focal to bilateral tonic–clonic seizure prevalence (13.3% vs. 73.6%, $p < .001$) than the low T-EPVS group. High T-EPVS burden (odds ratio [OR] = 10.908, 95% confidence interval [CI] = 1.895–62.789) was an independent predictor of medial refractoriness, along with female sex (OR = 12.906, 95% CI = 2.214–75.220) and ASM treatment duration (OR = .985, 95% CI = .971–.999). The low T-EPVS group had higher probability of achieving delayed SF than the high T-EPVS group ($p_{\text{Log-rank}} = .030$, $p_{\text{Cox regression}} = .038$), whereas the probability of achieving SF was comparable between the two groups ($p_{\text{Log-rank}} = .053$, $p_{\text{Cox regression}} = .146$).

**Significance:** Increased T-EPVS burden may serve as an imaging marker of unfavorable prognosis in patients with TLE-HS, underscoring the potential role of perivascular dysfunction in diminished ASM response.

KEYWORDS
glymphatic function, imaging biomarker, mesial temporal lobe epilepsy, perivascular space, prognosis

## 1 | INTRODUCTION

Temporal lobe epilepsy with hippocampal sclerosis (TLE-HS) is one of the most common and well-characterized epilepsy syndromes.[1] TLE-HS is recognized as medically intractable epilepsy with a poor prognosis compared with that of other types of focal epilepsy.[2–4] On the other hand, drug-resistant TLE-HS is a highly treatable surgical condition with good postoperative outcomes, with seizure remission rates of 60%–80%.[5–7] Therefore, early identification of poor responders to antiseizure medication (ASM) is crucial in facilitating timely consideration of early surgical treatment in nonresponders. However, to date, no reliable predictor for the prognosis of TLE-HS has been established.

Recently, the potential association between impaired glymphatic function and epilepsy has been increasingly recognized.[8–10] Although the exact mechanism remains elusive, glymphatic dysfunction is thought to contribute to glutamate accumulation, oxidative stress, and neuroinflammation, all of which may play a role in abnormal neuronal activity and seizure propagation.[11,12] Perivascular spaces (PVSs), one of the key components of the glymphatic system, are fluid-filled compartments that surround the walls of small penetrating cerebral vessels.[13–15] Although PVSs are primarily recognized for their role as a clearance route for fluid and solutes from the central nervous system,[16] emerging evidence highlights a much broader range of functions beyond clearance. Given the anatomical proximity of endothelial cells, neurons, pericytes, and astrocytes within this space, PVSs serve as a crucial crossroad where neuronal, immune, and vascular mechanisms converge,[17] providing insight into a wide variety of neurological disorders including epilepsy.[12,18–23] Although PVSs are not detected on conventional magnetic resonance imaging (MRI) under physiological conditions, in pathological conditions involving dysfunctional perivascular clearance, interstitial fluid stagnation induces retrograde dilation of PVS to a degree that can be visible on MRI.[15] Therefore, MRI-visible enlarged PVSs (EPVSs) are increasingly recognized as indicators of perivascular dysfunction, or in a broader context, glymphatic dysfunction. In this regard, investigation of EPVSs may provide insight into understanding the pathophysiology and prognosis in TLE-HS.

EPVSs are observed across various brain regions, including the basal ganglia (BG-EPVS), centrum semiovale (CS-EPVS), midbrain, and hippocampus,[13] and their regional burden appears to vary depending on the underlying etiologies.[19,20] Furthermore, a visual rating system for EPVSs located in the temporal lobe (T-EPVS) was recently introduced.[19] Given the anatomical proximity to HS and the key role of the temporal lobe in TLE-HS, T-EPVS may provide insight in understanding the pathophysiology and prognosis in TLE-HS. Therefore, this study aimed to investigate the regional burden of T-EPVS alongside EPVSs in other brain regions in treatment-naïve patients with TLE-HS and to further explore its prognostic relevance.

**Key points**

- High temporal lobe EPVS burden was identified as a risk factor for medical refractoriness.
- High temporal lobe EPVS burden was associated with a lower likelihood of achieving SF beyond 6 months after ASM initiation.
- High temporal lobe EPVS burden may indicate unfavorable prognosis in patients with TLE-HS.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

In this retrospective observational study, we screened cases recorded in the Yonsei Epilepsy Registry database between August 2006 and December 2023 to identify potential candidates eligible for our study based on the following inclusion criteria: (1) patients with seizure semiology and electroencephalographic (EEG) findings consistent with TLE; (2) MRI findings consistent with TLE-HS (presence of atrophy on T1-weighted images and/or hyperintensity on T2-weighted images in the hippocampus); a neuroradiologist and a neurologist independently evaluated each patient's MRI scan and enrolled them only upon mutual agreement that they had HS; and (3) patients with TLE-HS who had never been treated before their first visit (i.e., treatment-naïve). The exclusion criteria were as follows: (1) follow-up ≤18 months ($n = 14$), (2) poor adherence to ASM ($n = 3$), (3) brain MRI performed ≥1 month after commencing treatment ($n = 3$), (4) poor scan quality owing to motion

artifacts ($n = 1$), and (5) dual pathology except ipsilateral amygdala enlargement ($n = 5$). Notably, patients with HS on MRI related to late onset intracranial infection, autoimmune encephalitis, or new onset refractory status epilepticus were not registered as having TLE in the Yonsei Epilepsy Registry. Finally, 68 treatment-naïve patients with TLE-HS were included in this study. The detailed patient selection process for this study is provided in Figure S1.

## 2.2 | Standard protocol approvals, registrations, and patient consents

The study was approved by the institutional review board of Severance Hospital (IRB No. 4–2023-0688) and was conducted in accordance with all relevant ethical regulations. The requirement for informed consent from patients was waived in this study due to the retrospective study design.

## 2.3 | Data collection

Data on demographic and seizure-related clinical variables, including age at first clinic visit (i.e., age at MRI), age at epilepsy onset, duration of medical treatment (from the initiation of ASM treatment to the last visit or until temporal lobectomy), sex, family history of seizures, history of febrile seizures, history of central nervous system infection before the age of 5 years, presence of aura or focal to bilateral tonic–clonic seizures (FBTCS), pretreatment seizure density (number of seizures in the 3 months before the first visit), abnormalities on initial routine EEG, side of HS on MRI, number of ASMs in the regimen at the last visit, all ASMs taken, and temporal lobectomy, were collected. Patients were defined as having vascular risk factors if they had a history of hypertension, diabetes mellitus, or dyslipidemia or were taking antihypertensive, antidiabetic, or antidyslipidemic drugs at enrollment.

## 2.4 | Assessment of regional EPVSs, lacunes, and white matter hyperintensities

All patients underwent an epilepsy-dedicated, high-resolution MRI including T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (refer to Appendix S1). Two trained neurologists (S.C. and H.K.N.) who were blinded to the clinical information assessed visible EPVSs on T2-weighted images according to the Standards for Reporting Vascular Changes on Neuroimaging criteria.[13] BG-EPVS, CS-EPVS, and T-EPVS were rated as previously described.[19,20,24] Briefly, EPVSs were defined as lesions that appeared round, ovoid, or linear depending on their orientation to the imaging plane, with a diameter of 1–3 mm and a signal intensity similar to that of cerebrospinal fluid. The number of EPVSs in the three regions was counted independently in all relevant slices for the anatomical area in both hemispheres, and the highest number in each region from one hemisphere was used for a 4-point visual rating scale (0 = no EPVS, 1 = 1–10 EPVSs, 2 = 11–20 EPVSs, 3 = 21–40 EPVSs, and 4 = >40 EPVSs). We dichotomized the degree of EPVSs in each location into high and low using the following cutoffs from a previous study: $n = 20$ for CS-EPVS and $n = 10$ for BG-EPVS and T-EPVS (Figure 1). In addition, midbrain and hippocampal EPVSs were rated and dichotomized as "none" or "the presence of one or more visible EPVSs." In case of any discrepancies in the visual rating of EPVS burden, consensus was reached through discussion between the two clinicians.

Two neurologists also assessed other measures related to the burden of small vessel disease, including lacunes and white matter hyperintensities (WMHs). Lacunes were defined as hyperintense lesions 3–15 mm in diameter in the subcortical area with a perilesional halo on FLAIR images. WMHs were defined as hyperintense white matter lesions on FLAIR images and graded separately in the deep subcortical and periventricular regions according to the visual rating scale developed by the Clinical Research Center for Dementia of South Korea group.[25,26]

## 2.5 | Outcome assessment

Seizure freedom (SF) was defined as no seizures, including auras, for >1 year. First, seizure outcomes were classified into four mutually exclusive temporal patterns, as described in previous literature for newly diagnosed epilepsy[27] as follows: (1) patients who achieved early SF (within 6 months of initiation of therapy) and maintained seizure-free status throughout the follow-up period (Pattern A), (2) patients who achieved delayed SF (after 6 months of initiation of therapy) and maintained seizure-free status throughout follow-up (Pattern B), (3) patients exhibiting a fluctuating course with periods of SF interspersed with relapses (Pattern C), and (4) patients who never achieved SF for any complete year (Pattern D). In this study, Pattern D was defined as "medical refractoriness," which differs from other patterns that achieved SF at least once during ASM treatment. Based on the aforementioned definition, patients were classified into the refractory and nonrefractory groups.

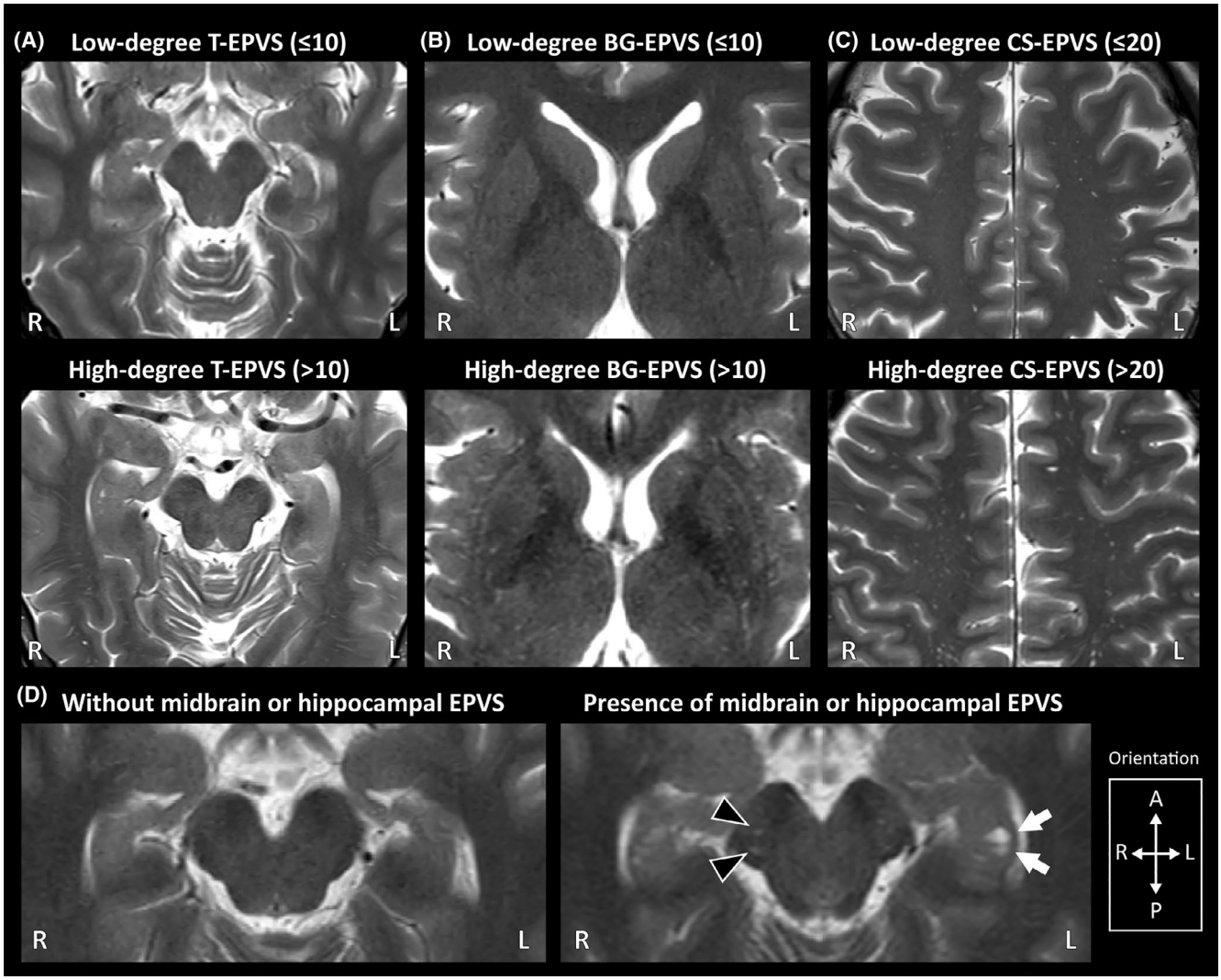


**FIGURE 1** Enlarged perivascular spaces (EPVSs) in each anatomical location. (A–C) Representative T2-weighted images for EPVSs in the (A) temporal lobe (T-EPVS), (B) basal ganglia (BG-EPVS), and (C) centrum semiovale (CS-EPVS) are presented. EPVS burden was defined as high degree by applying the cutoff of 10 for T-EPVS/BG-EPVS and 20 for CS-EPVS. (D) EPVSs located in the midbrain (arrowheads) and hippocampus (arrows) are illustrated. Given the relatively low midbrain/hippocampal EPVS burden in our study population, they were classified as either present or absent. A, anterior; L, left; P, posterior; R, right.

## 2.6 | Statistical analyses

Cohen kappa statistics were used to determine the interrater reliability for assessing EPVSs between the two raters.[28] Continuous variables were compared using Student *t*-test for normally distributed data and Mann–Whitney *U*-test for nonparametric data. Categorical data were compared using Pearson $\chi^2$ or Fisher exact test. In addressing the issue of multiple comparisons, the false discovery rate method was applied using the R package "fdrtool."[29]

Logistic regression analyses were performed to identify potential determinants associated with medical refractoriness in TLE-HS (Model 1). The variables for the multivariate logistic regression model were determined by using the stepwise selection method based on the Akaike information criterion (AIC). In this method, variables were sequentially added or removed, beginning with the null model, and the optimal model with the lowest AIC was adopted.[30] Of note, the total number of ASMs used and the number of patients who underwent temporal lobectomy were not included as covariates in the multivariate model, as they were determined to be a consequence rather than a cause of medical refractoriness. The performance of the model was reported based on the area under the receiver operating characteristic curve (AUROC).

In addition to the logistic regression model, the random forest model utilizing the entire dataset was developed to confirm the robustness of our findings and minimize the risk of overfitting (Model 2). To determine the optimal hyperparameters for the random forest, the grid search algorithm with repeated 10-fold cross-validation was utilized. The grid

search algorithm provides best parameters such as number of trees in the forest, minimum size of terminal nodes, and number of features analyzed at each node to find the best split (for a dataset with $p$ features, square root of $p$ was used in each split). The AUROC statistics for evaluating random forest model performance was calculated based on the percentage votes per class of all trees. Random forest model was performed using the R package "randomForest."[31]

Kaplan–Meier analysis was performed to estimate the probability of achieving SF during ASM treatment for the high and low T-EPVS groups. Time to SF was calculated by subtracting the date of treatment initiation from the date of the start of a seizure-free period of 1 year or more. If the event was not achieved, the time to SF was determined as the duration of the ASM treatment, which was the total follow-up time for nonsurgical patients and the follow-up time to temporal lobectomy for surgical patients. A log-rank test was used to compare probabilities of achieving SF between groups. The proportional hazards assumption was tested using the log–log survival plot and the Grambsch–Therneau test. We used Cox regression models to compare medical refractoriness between the high and low T-EPVS groups while adjusting for age at MRI, sex, and presence of aura. Furthermore, the probability of achieving delayed (>6 months after ASM initiation) SF was examined for the high and low T-EPVS groups. Statistical analyses were performed using Statistical Package for Social Sciences version 27.0 software (SPSS) or the R software package (version 4.4.1, R Foundation for Statistical Computing) for Windows.

## 3 | RESULTS

### 3.1 | Interrater reliability of EPVS

The kappa values for interrater reliability in EPVS grading were .861, .865, .879, .911, and .854 for the BG, CS, temporal lobe, midbrain, and hippocampus, respectively.

### 3.2 | Demographic, clinical, and imaging characteristics of the study population

The demographic, clinical, and imaging characteristics of the 68 treatment-naïve patients with TLE-HS are summarized in Table 1. Our study population included 32 men and 36 women, with a median duration of ASM treatment of 71.5 months (interquartile range [IQR] =41.3–139.3). In 36 patients (52.9%), the number of T-EPVSs was lower in the temporal lobe with HS than in the contralateral temporal lobe. Of the 68 patients, seven (10.3%) underwent a temporal lobectomy, three of whom underwent surgery before 18 months of ASM treatment owing to persistent seizures despite >1 year of medication.

### 3.3 | Comparison of medically refractory and nonrefractory groups

Of the 68 treatment-naïve patients with TLE-HS, 20 were classified into the refractory group (29.4%) and 48 into the nonrefractory group (70.6%; Table 1). Patients in the refractory group had a shorter duration of ASM treatment (median = 38.0 months, IQR = 21.0–102.8) than those in the nonrefractory group (median = 82.5 months, IQR = 60.3–156.3, $p = .002$). The refractory group had a higher proportion of women (85.0% [17/20] vs. 39.6% [19/48], $p = .001$) and were more likely to have auras (85.0% [17/20] vs. 54.2% [26/48], $p = .016$) than the nonrefractory group. The refractory group also had a higher proportion of patients with high T-EPVS burden (40.0% [8/20]) than the nonrefractory group (14.6% [7/48], $p = .029$). No significant differences were found in the presence of lacunes, WMH burden, and EPVS burden in the other regions, including BG, CS, midbrain, and hippocampus, between the two groups. The total number of ASMs used (median = 4.5, IQR = 3.3–6.8 vs. median = 2.0, IQR = 1.0–4.0, $p < .001$) and the number of patients who underwent temporal lobectomy (30.0% [6/20] vs. 2.1% [1/48], $p = .002$) were higher in the refractory group than in the nonrefractory group (refer to Table S1 for further details).

### 3.4 | Comparison of high and low T-EPVS groups

Of the 68 treatment-naïve patients with TLE-HS, 15 were included in the high T-EPVS group (22.1%) and 53 in the low T-EPVS group (77.9%; Table 2). Patients with high T-EPVS burden were older at epilepsy onset (37.3 ± 12.3 vs. 26.5 ± 13.0 years, $p = .006$) and at the point of MRI acquisition (44.7 ± 11.6 vs. 34.7 ± 12.4 years, $p = .007$) and had higher pretreatment seizure density (median = 12.0, IQR = 5.0–20.0 vs. median = 4.0, IQR = 2.0–10.5, $p = .008$) than those with low T-EPVS burden. Significantly fewer patients with FBTCS were observed in the high T-EPVS group (13.3% [2/15]) than in the low T-EPVS group (73.6% [39/53], $p < .001$). Detailed findings are summarized in Table S2.

### 3.5 | Potential determinants of medical refractoriness

The multivariate logistic regression model based on the stepwise AIC method (Model 1) identified a high

**TABLE 1** Demographic, clinical, and imaging characteristics of the study population.

| Characteristic | Total, $N=68$ | Refractory, $n=20$ | Nonrefractory, $n=48$ | $p$ | $q$ |
|---|---|---|---|---|---|
| Demographic and clinical factors | | | | | |
| Age at MRI at first visit, years | 36.9 ± 12.9 | 35.5 ± 11.1 | 37.5 ± 13.6 | .553 | .629 |
| Age at seizure onset, years | 28.9 ± 13.5 | 27.4 ± 12.5 | 29.6 ± 14.0 | .552 | .629 |
| Sex, female, *n* (%) | 36 (52.9) | 17 (85.0) | 19 (39.6) | .001[a] | .009[b] |
| Presence of aura, *n* (%) | 43 (63.2) | 17 (85.0) | 26 (54.2) | .016[a] | .076 |
| Presence of FBTCS, *n* (%) | 41 (60.3) | 9 (45.0) | 32 (66.7) | .096 | .227 |
| Pretreatment seizure density, events/3 months | 6.0 (2.3–14.0) | 9.0 (4.3–16.0) | 4.0 (2.0–14.0) | .088[c] | .213 |
| Abnormalities on initial EEG, *n* (%) | 53 (77.9) | 16 (80.0) | 37 (77.1) | >.999[d] | .754 |
| ASM treatment duration, months | 71.5 (41.3–139.3) | 38.0 (21.0–102.8) | 82.5 (60.3–156.3) | .002[a,c] | .014[b] |
| Imaging factors, *n* (%) | | | | | |
| Side of HS on MRI | | | | | |
| Right | 29 (42.6) | 9 (45.0) | 20 (41.7) | .582[d] | .641 |
| Left | 35 (51.5) | 11 (55.0) | 24 (50.0) | | |
| Bilateral | 4 (5.9) | 0 (.0) | 4 (8.3) | | |
| Presence of lacunes | 5 (7.4) | 2 (10.0) | 3 (6.3) | .627[d] | .658 |
| WMH burden, *n* (%) | | | | | |
| WMH grade ≥ 2 | 1 (1.5) | 0 (.0) | 1 (2.1) | >.999[d] | .754 |
| DWMH grade ≥ 2 | 1 (1.5) | 0 (.0) | 1 (2.1) | >.999[d] | .754 |
| PWMH grade ≥ 2 | 4 (5.9) | 0 (.0) | 4 (8.3) | .312[d] | .489 |
| EPVS burden | | | | | |
| High-degree BG-EPVS | 17 (25.0) | 6 (30.0) | 11 (22.9) | .539 | .623 |
| High-degree CS-EPVS | 28 (41.2) | 10 (50.0) | 18 (37.5) | .340 | .510 |
| High-degree T-EPVS | 15 (22.1) | 8 (40.0) | 7 (14.6) | .029[a,d] | .104 |
| Presence of midbrain EPVS | 47 (69.1) | 14 (70.0) | 33 (68.8) | .919 | .738 |
| Presence of hippocampal EPVS | 38 (55.9) | 8 (40.0) | 30 (62.5) | .089 | .214 |
| EPVS laterality | | | | | |
| Higher T-EPVS on HS side | 23 (33.8) | 7 (35.0) | 16 (33.3) | .421 | .564 |
| Lower T-EPVS on HS side | 36 (52.9) | 12 (60.0) | 24 (50.0) | | |
| Equal T-EPVS degree or bilateral HS | 9 (13.2) | 1 (5.0) | 8 (16.7) | | |

*Note*: Normally distributed continuous variables are presented as mean ± SD and compared using *t*-test.

Abbreviations: ASM, antiseizure medication; BG, basal ganglia; CS, centrum semiovale; DWMH, deep WMH; EEG, electroencephalogram; EPVS, enlarged perivascular space; FBTCS, focal to bilateral tonic–clonic seizure; HS, hippocampal sclerosis; MRI, magnetic resonance imaging; PWMH, periventricular WMH; T, temporal lobe; WMH, white matter hyperintensity.

[a] $p < .05$.

[b] $q$ (false discovery rate-corrected $p$) $< .05$.

[c] Continuous variables with nonparametric distribution are presented as median (Q1–Q3) and compared using the Mann–Whitney *U*-test.

[d] Fisher exact test was used. Otherwise, $\chi^2$ test was used for comparing categorical variables.

T-EPVS burden (odds ratio [OR] = 10.908, 95% confidence interval [CI] = 1.895–62.789, $p = .007$) as an independent predictor of medical refractoriness in treatment-naïve patients with TLE-HS, along with female sex (OR = 12.906, 95% CI = 2.214–75.220, $p = .004$) and ASM treatment duration (OR = .985, 95% CI = .971–.999, $p = .043$; Table 3). The AUROC for Model 1 was .874 (95% CI = .783–.965).

## 3.6 | Random forest model

Ranked importance of the variables predicting medical refractoriness in patients with TLE-HS is presented in Figure 2A. In terms of the mean decrease in Gini index, the top five variables associated with medical refractoriness were ASM treatment duration, pretreatment seizure density, age at MRI, female sex, and high T-EPVS burden.

**TABLE 2** Demographic, clinical, and imaging characteristics of the high and low T-EPVS groups.

| Characteristics | Total, $N=68$ | High T-EPVS, $n=15$ | Low T-EPVS, $n=53$ | $p$ | $q$ |
|---|---|---|---|---|---|
| Demographic and clinical factors | | | | | |
| Age at MRI at first visit, years | 36.9 ± 12.9 | 44.7 ± 11.6 | 34.7 ± 12.4 | .007[a] | .016[b] |
| Age at seizure onset, years | 28.9 ± 13.5 | 37.3 ± 12.3 | 26.5 ± 13.0 | .006[a] | .015[b] |
| Sex, female, *n* (%) | 36 (52.9) | 7 (46.7) | 29 (54.7) | .581 | .388 |
| Presence of aura, *n* (%) | 43 (63.2) | 12 (80.0) | 31 (58.5) | .127 | .122 |
| Presence of FBTCS, *n* (%) | 41 (60.3) | 2 (13.3) | 39 (73.6) | <.001[a] | <.001[b] |
| Pretreatment seizure density, events/3 months | 6.0 (2.3–14.0) | 12.0 (5.0–20.0) | 4.0 (2.0–10.5) | .008[a,c] | .017[b] |
| Abnormalities on initial EEG, *n* (%) | 53 (77.9) | 13 (86.7) | 40 (75.5) | .492[d] | .349 |
| ASM treatment duration, months | 71.5 (41.3–139.3) | 87.0 (40.0–129.0) | 70.0 (42.0–141.5) | .767[c] | .456 |
| Vascular risk factor, *n* (%) | | | | | |
| Hypertension | 8 (11.8) | 4 (26.7) | 4 (7.5) | .065[d] | .069 |
| Diabetes mellitus | 2 (2.9) | 1 (6.7) | 1 (1.9) | .395[d] | .301 |
| Dyslipidemia | 5 (7.4) | 3 (20.0) | 2 (3.8) | .067[d] | .070 |
| Imaging factors, *n* (%) | | | | | |
| Side of HS on MRI | | | | | |
| Right | 29 (42.6) | 8 (53.3) | 21 (39.6) | .571[d] | .384 |
| Left | 35 (51.5) | 7 (46.7) | 28 (52.8) | | |
| Bilateral | 4 (5.9) | 0 (.0) | 4 (7.5) | | |
| Presence of lacunes | 5 (7.4) | 3 (20.0) | 2 (3.8) | .067[d] | .070 |
| WMH burden | | | | | |
| WMH grade ≥ 2 | 1 (1.5) | 0 (.0) | 1 (1.9) | >.999[d] | .522 |
| DWMH grade ≥ 2 | 1 (1.5) | 0 (.0) | 1 (1.9) | >.999[d] | .522 |
| PWMH grade ≥ 2 | 4 (5.9) | 3 (20.0) | 1 (1.9) | .031[a,d] | .046[b] |

*Note*: Normally distributed continuous variables are presented as mean ± SD and compared using *t*-test.

Abbreviations: ASM, antiseizure medication; DWMH, deep WMH; EEG, electroencephalogram; FBTCS, focal to bilateral tonic–clonic seizure; HS, hippocampal sclerosis; MRI, magnetic resonance imaging; PWMH, periventricular WMH; T-EPVS, enlarged perivascular space in the temporal lobe; WMH, white matter hyperintensity.

[a] $p < .05$.

[b] $q$ (false discovery rate-corrected $p$) $< .05$.

[c] Continuous variables with nonparametric distribution are presented as median (Q1–Q3) and compared using the Mann–Whitney *U*-test.

[d] Fisher exact test was used. Otherwise, $\chi^2$ test was used for comparing categorical variables.

**TABLE 3** Multivariate logistic regression model for predicting medical refractoriness.

| Variables | Adjusted OR | 95% CI | | $p$ |
|---|---|---|---|---|
| | | Lower | Upper | |
| High T-EPVS | 10.908 | 1.895 | 62.789 | .007 |
| Female sex | 12.906 | 2.214 | 75.220 | .004 |
| ASM treatment duration, months | .985 | .971 | .999 | .043 |

*Note*: Performance: area under the receiver operating characteristic curve = .874 (95% CI = .783–.965). Hosmer–Lemeshow goodness-of-fit: $\chi^2 = 10.298$, $p = .245$.

Abbreviations: ASM, antiseizure medication; CI, confidence interval; OR, odds ratio; T-EPVS, enlarged perivascular space in the temporal lobe.

The AUROC for random forest classification was .813 (95% CI = .693–.932; Figure 2B).

## 3.7 | Cumulative probability of achieving SF according to T-EPVS burden

The time to the start of a seizure-free period of 1 year or more was analyzed using the Kaplan–Meier method for the high and low T-EPVS groups. Seven patients in the high T-EPVS group (46.7%) and 41 in the low T-EPVS group (77.4%) achieved SF with ASM treatment during follow-up. A log-rank test ($p = .053$) and Cox regression model (hazard ratio [HR] = .523, 95% CI = .218–1.253,

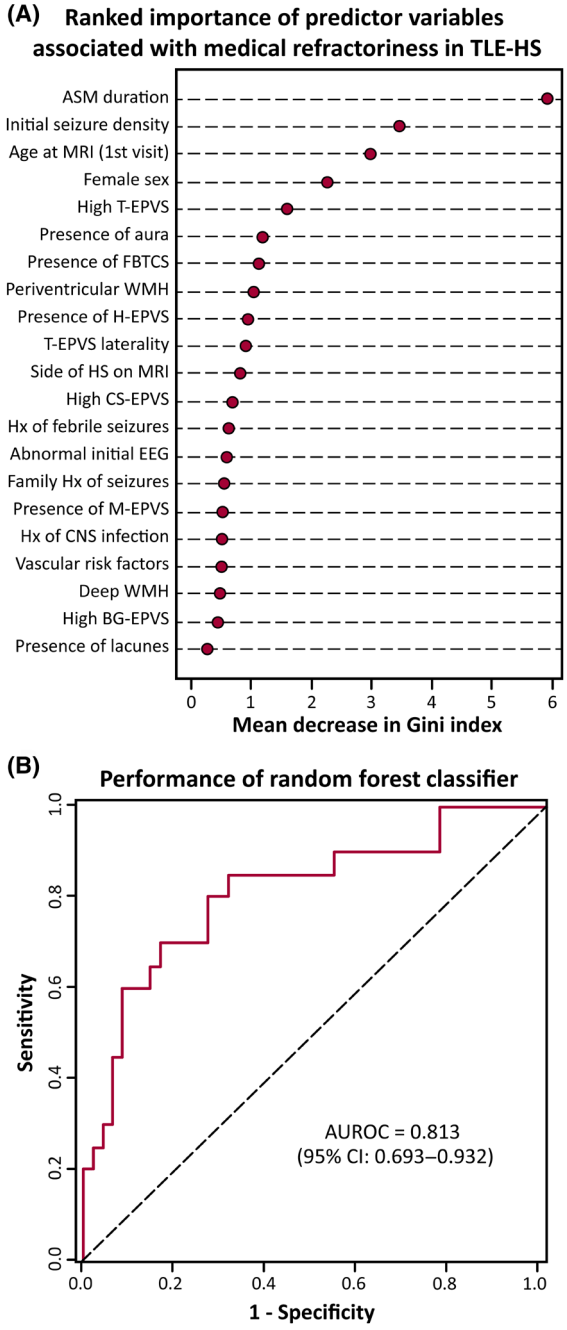


**FIGURE 2** Random forest classification. (A) Ranked importance of the predictor variables associated with medical refractoriness in temporal lobe epilepsy with hippocampal sclerosis (TLE-HS) using random forest model. Notably, high enlarged perivascular space (EPVS) in the temporal lobe (T-EPVS) burden ranked among the top five variables of importance in this analysis. (B) Model performance (area under the receiver operating characteristic curve [AUROC] statistics calculated based on the percentage votes per class of all trees) was .813 (95% confidence interval [CI] = .693–.932). ASM, antiseizure medication; BG-EPVS, basal ganglia EPVS; CNS, central nervous system; CS-EPVS, centrum semiovale EPVS; EEG, electroencephalogram; FBTCS, focal to bilateral tonic–clonic seizures; H-EPVS, hippocampal EPVS; Hx, history; M-EPVS, midbrain EPVS; MRI, magnetic resonance imaging; WMH, white matter hyperintensities.

$p = .146$) revealed that the probability of achieving SF was comparable between the two groups (Figure 3A). To determine the probability of achieving delayed SF, an additional analysis was performed restricting time points beyond 6 months after treatment initiation. A log-rank test ($p = .030$) and Cox regression model (HR = .251, 95% CI = .068–.925, $p = .038$) revealed that the low T-EPVS group had a higher probability of achieving delayed SF than the high T-EPVS group (Figure 3B).

## 4 | DISCUSSION

The present study investigated the burden of regional EPVSs in treatment-naïve patients with TLE-HS, offering three major findings: (1) patients with TLE-HS and high T-EPVS burden were likely to present with older age at seizure onset, lower prevalence of FBTCS, and higher pretreatment seizure density; (2) high T-EPVS burden was identified as an independent predictor of medical refractoriness and was associated with a lower likelihood of achieving delayed SF in patients with TLE-HS than in those with low T-EPVS burden, suggesting the importance of perivascular dysfunction in the suboptimal response to ASM; and (3) whereas T-EPVS burden was significantly associated with prognosis in TLE-HS, EPVS burden in other regions showed no such association, underscoring the importance of assessing regional EPVS burden based on anatomical location rather than overall EPVS burden in this diagnostic entity. The main strength of this study was the inclusion of treatment-naïve patients only, which allowed us to explore the relationship between baseline EPVS burden and the clinical course of TLE-HS without the potential confounding influence of previous exposure to ASM. To our knowledge, this study is the first to demonstrate the prognostic implication of T-EPVS in TLE-HS, providing insights into the potential utility of this imaging marker in risk stratification and treatment planning.

Identification of medically refractory patients with TLE-HS has important clinical implications, as prompt recognition of refractoriness may allow for intensive ASM treatment or early surgical intervention, thereby reducing comorbid cognitive and psychosocial dysfunction and mortality.[32,33] Based on our findings, high T-EPVS burden appears to serve as a useful imaging marker associated with poor long-term outcomes. Patients with TLE-HS and high T-EPVS burden had a lower likelihood of achieving SF beyond 6 months after the initiation of ASM (Figure 3B). Consistent with the results of previous literature demonstrating that delayed achievement of SF is an important predictor of long-term outcomes in epilepsy,[34,35] the high T-EPVS group was significantly

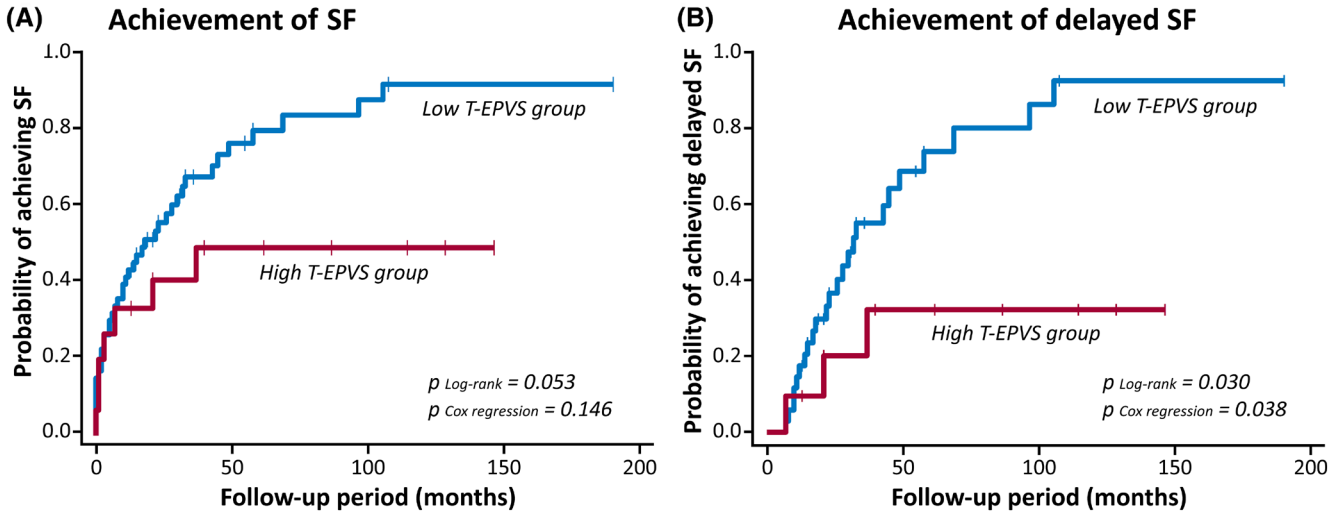


**FIGURE 3** Cumulative probability of achieving seizure freedom (SF) or delayed SF. Kaplan–Meier curve showing the cumulative probability of achieving SF (>1 year) or delayed SF (achievement of SF >6 months after initiation of antiseizure medication). (A) Patients with temporal lobe epilepsy with hippocampal sclerosis who had high and low degree of enlarged perivascular spaces in the temporal lobe (T-EPVS) revealed a comparable probability of achieving SF for at least 1 year ($p_{\text{Log-rank}} = .053$, $p_{\text{Cox regression}} = .146$). (B) The high T-EPVS group showed a significantly lower probability of achieving delayed SF compared to the low T-EPVS group ($p_{\text{Log-rank}} = .030$, $p_{\text{Cox regression}} = .038$).

associated with medical refractoriness (Table 3 and Figure 2A). These findings align with the results of a previous study indicating that patients with focal epilepsy having a lower diffusion tensor image analysis along the perivascular space (DTI-ALPS) index are associated with poor ASM response,[36] highlighting the potential role of glymphatic dysfunction in TLE-HS prognosis. Notably, T-EPVS burden did not remain a significant predictor in the Cox regression model for achieving SF (Figure 3A), despite its significant association with delayed SF and medical refractoriness. These conflicting results may be explained by the pronounced influence of a favorable initial response to ASM, a key determinant of long-term prognosis, potentially masking the effect of T-EPVS in the model. Further studies employing a larger sample size are required to clarify the implications.

Despite the growing interest in the contribution of dysfunctional glymphatic system to epileptogenesis and compromised ASM response, the exact mechanism underlying these processes remains elusive. Hypothetically, seizures have been suggested to disrupt blood–brain barrier (BBB) integrity, leading to accumulation of perivascular immune cells and cytokines, which compromise glymphatic function and suppress cytokine clearance from the brain.[12,37,38] This results in sustained inflammation and the persistent accumulation of cytokines, further increasing seizure activity and exacerbating BBB disruption, thereby reinforcing a vicious cycle of glymphatic dysfunction, neuroinflammation, and seizures.[12,39,40] This hypothesis is supported by studies demonstrating that patients with epilepsy, including TLE-HS, tend to show significantly lower DTI-ALPS indices than healthy controls.[9,36,41] Furthermore, they also suggest that patients with focal epilepsy who have impaired glymphatic function tend to exhibit inadequate ASM response.[36]

Notably, unlike T-EPVS, EPVSs located elsewhere (BG-EPVS, CS-EPVS, EPVS in the midbrain and hippocampus) did not reveal any significant association with the prognosis of the patients with TLE-HS (Figure 2A). This may be explained by the anatomical proximity of the temporal lobe to HS. In support of this speculation, patients with high T-EPVS burden exhibited higher pretreatment seizure density, which may predispose to PVS alterations in the temporal lobe rather than in more distant regions. Nonetheless, this prompts further questions, such as why hippocampal EPVS, which is anatomically closer to the HS, failed to exhibit a stronger association, or why the laterality of T-EPVS burden does not correlate with the more affected side of HS. Alternatively, the significant association between T-EPVS burden and TLE-HS prognosis may be attributable to the lower susceptibility of T-EPVS to vascular risk factors than that of BG-EPVS or CS-EPVS, making T-EPVS a better marker of glymphatic dysfunction.[19,20] Although our data cannot fully explain this association, our findings stress the importance of evaluating EPVS burden based on anatomical regions rather than as a global burden, as its etiological relevance varies by location.

Unlike healthy controls or patients with neurodegenerative disorders in whom EPVSs tend to exhibit symmetric distribution,[19,20,42] a substantial number of studies in the field of epilepsy, particularly involving cases of focal

epilepsy, poststroke epilepsy, or posttraumatic epilepsy, have reported asymmetric EPVS distribution.[12,21–23] Regarding the relationship between the side of the increased EPVS burden and the site of seizure, however, inconsistent findings have been reported across studies and disease entities. For instance, some reported that the asymmetry was primarily attributed to a reduction in EPVSs in the suspected seizure onset zone and the lesion-affected side,[21–23] whereas other studies suggested that the glymphatic impairment tends to be more prominent ipsilateral to the seizure onset zone than in the contralateral hemisphere.[10,43] In our study population, the laterality of T-EPVS burden, whether assessed by count or grade, was not significantly associated with the affected side of the HS, which is consistent with a recent study that found no significant interhemispheric differences in a group of TLE patients.[44] The discrepancies may be explained in several ways. First, differences in the study design and methodologies employed to assess the EPVS burden may have affected the results. Compared to previous studies using quantitative measurement of EPVS burden via dedicated software or DTI-ALPS indices, we assessed EPVS burden based on a validated visual rating scale and manual count of EPVSs, which may not be sensitive enough to capture the association of laterality of EPVS burden and its correlation with the side of the epileptogenic region. Second, the laterality of EPVS burden, as observed in our study, may not be relevant to the seizure onset zone in treatment-naïve patients with TLE-HS. Lastly, our findings may be attributable to the cross-sectional design of the study, which is inherently limited in capturing the dynamic changes in EPVS burden over time. Supporting this perspective, a previous study has reported that EPVS burden in epilepsy may vary at different time points, indicating that associations observed at one time point may not necessarily persist over time.[23] Future longitudinal studies utilizing automatic and quantitative methods to measure EPVS burden are needed to clarify the relationship between EPVS laterality and the seizure onset zone.

This study has several limitations. First, it is limited by its retrospective design and small sample size. Second, given that TLE-HS typically develops during childhood or adolescence,[1,45] the age at epilepsy onset in our study population ($28.9 \pm 13.5$ years) appears to be older than the established age, which may limit the generalizability of our findings. Third, the follow-up period of at least 18 months may be insufficient to determine treatment outcomes. Fourth, the definition of medical refractoriness used in this study may have been excessively rigorous and narrow. The response to ASM is a dynamic process that may involve a transition from a seizure-free state to an uncontrolled state or vice versa. Recent findings suggest that a considerable proportion of patients with TLE-HS tend to exhibit a fluctuating clinical course,[46] with some suggesting that drug response during periods of fluctuation need to be classified as "undefined."[47] Consequently, we adopted the strict definition of medical refractoriness as never having been seizure-free for >1 year in our analysis. Lastly, EPVS burden was assessed using a visual rating scale, as no automated quantification method exists for T-EPVS to date. Furthermore, given that the cutoff of 10 for T-EPVS was adopted from studies on neurodegenerative disorders, there is no guarantee that it represents the optimal threshold for TLE-HS.

## 5 | CONCLUSIONS

The present study demonstrated that increased T-EPVS burden served as an imaging marker predictive for unfavorable prognosis in drug-naïve TLE-HS, highlighting the potential role of perivascular dysfunction in suboptimal response to ASM.

### AUTHOR CONTRIBUTIONS

Conception and design of the study: Soomi Cho, Han Kyu Na, and Kyung Min Kim. Acquisition of data: Soomi Cho and Han Kyu Na. Analysis and interpretation of data: All authors. Drafting of the manuscript: Soomi Cho, Han Kyu Na, and Kyung Min Kim. Critical revision of the manuscript for important intellectual content: All authors.

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None.

### CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

### DATA AVAILABILITY STATEMENT

Data may be shared (anonymized) by the corresponding author at the request of any qualified investigator for the replication of procedures and results.

### ETHICS STATEMENT

The study was approved by the Institutional Review Board of Severance Hospital (IRB No. 4–2023-0688) and was conducted in accordance with all relevant ethical regulations. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

### PATIENT CONSENT STATEMENT

The requirement for informed consent from patients was waived in this study due to the retrospective study design.

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## SUPPORTING INFORMATION

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