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Age-stratified long-term outcomes of perampanel in focal seizure: A multicenter real-world study in South Korea

Bo Kyu Choi [a,b], Hyun-Woo Kim [c,d], Yun Ho Choi [e], Hye-Rim Shin [f], Kyoung Jin Hwang [g], Jee Hyun Kim [h], Jung Bin Kim [i], Hee-Jin Im [j], Won-Joo Kim [a,b,*]

[a] Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, , Republic of Korea
[b] Epilepsy Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea
[c] Hyun Neurology Clinic, Busan, Republic of Korea
[d] Departments of Neurology, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea
[e] Department of Neurology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[f] Department of Neurology, Dankook University Hospital, Cheonan, Republic of Korea
[g] Department of Neurology, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul, Republic of Korea
[h] Department of Neurology, Seoul Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea
[i] Department of Neurology, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea
[j] Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University Medical Center, Hwaseong, Republic of Korea

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ABSTRACT

Objective: Perampanel (PER) is a third-generation antiseizure medication (ASM) increasingly used in clinical practice. However, evidence regarding its long-term effectiveness and safety in elderly patients remains limited, particularly in Asian populations.

Methods: This multicenter, retrospective, longitudinal study included patients with focal seizures treated with PER at eight tertiary hospitals in South Korea between 2016 and 2024. Patients with primarily generalized seizures or insufficient baseline or follow-up data were excluded. Elderly patients were defined as those aged 65 years or older. Treatment retention rate, effectiveness, and adverse events were assessed over a follow-up period of up to three years. Effectiveness at 12 months was defined based on responder status or seizure freedom. Multivariate logistic regression analyses were performed to identify factors associated with effectiveness and adverse events.

Results: A total of 528 patients were included, of whom 108 were elderly. Overall retention rates were 59.1% at 12 months and 23.7% at 36 months. Elderly patients showed generally favorable treatment responses, with higher responder and seizure-free rates compared with non-elderly patients. Psychiatric comorbidity and multifocal epileptogenic zone localization were independently associated with reduced 12-month effectiveness. In contrast, focal slowing on scalp electroencephalography was positively associated with effectiveness and remained significant after age adjustment. Adverse events occurred in 50.8% of patients and were less frequent in the elderly group. Fast titration within two weeks was a strong independent risk factor for moderate to severe adverse events.

Conclusion: In this study, PER demonstrated sustained effectiveness and acceptable tolerability across age groups. Careful titration and consideration of comorbidity and electroencephalographic features may support more individualized PER use, particularly in elderly patients.

1. Introduction

Epilepsy is one of the most common serious neurological disorders and is associated with a substantial disease burden [1]. With global population aging, the epidemiology of epilepsy has changed substantially over recent decades. The incidence of epilepsy shows a bimodal distribution, with a second and more pronounced peak occurring in elderly patients. In many countries, the highest incidence rates of newly

* Corresponding authors: Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Address: 211, Eonju-ro, Gangnam-gu, Seoul, 06273, Republic of Korea.
E-mail address: kzoo@yuhs.ac (W.-J. Kim).

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diagnosed epilepsy are now observed in elderly, largely driven by age-related structural brain diseases such as cerebrovascular disease, neurodegenerative disorders, and brain tumors [2]. Therefore, the clinical use of antiseizure medication (ASM) requires careful evaluation of age-related differences, particularly when treating elderly patients compared with younger populations [3].

In recent years, third-generation ASM have been increasingly used across many countries because of their favorable efficacy and relatively low incidence of adverse effects [4,5]. Among these agents, perampanel (PER) is a highly selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist [6]. It was first introduced in Korea in 2016 and has since been widely prescribed to a large population of patients with epilepsy [7,8]. Its safety and efficacy as adjunctive therapy in patients with refractory epilepsy have been demonstrated in randomized, double-blind, placebo-controlled trials and their open-label extension studies, as well as in multiple real-world multicenter investigations [8–10]. Early clinical trials primarily assessed PER in patients with drug-resistant epilepsy receiving two or more concomitant ASM, reporting modest responder rates in highly refractory populations [11,12]. Subsequent clinical and real-world studies have shown more favorable seizure outcomes in less refractory settings, suggesting that treatment response to PER may vary according to disease severity and patient characteristics [13,14]. Although PER is now widely used across diverse clinical populations, evidence regarding its effectiveness and tolerability in elderly patients remains limited, as most available studies have been based on relatively small sample sizes. Moreover, few multicenter studies in Asia have evaluated long-term outcomes of PER according to age, particularly using extended follow-up periods. Consequently, data directly comparing treatment outcomes between elderly and non-elderly patients treated with PER are still scarce. In this multicenter study, we investigated the three-year longitudinal outcomes of PER, including effectiveness and safety.

2. Methods

2.1. Patient selection

This observational, multicenter, retrospective, longitudinal study included patients recruited from eight tertiary hospitals in South Korea. Because the aim of this study was to compare outcomes between elderly and non-elderly adult patients, only patients aged ≥18 years were included [13]. Data were collected from patients who received PER either as monotherapy or adjunctive therapy were eligible for inclusion, between February 2016 and January 2024. Patients with primary generalized seizures were excluded, and only those with focal seizures were included in the analysis. The diagnosis of focal seizures was established according to the International League Against Epilepsy (ILAE) classification, based on clinical semiology, EEG, and neuroimaging findings. In addition, epilepsy etiology was classified according to the ILAE etiological classification framework into structural, genetic, immune, infectious, metabolic, and unknown categories. Patients without available baseline seizure data or follow-up information after PER initiation were excluded.

Baseline data included demographic variables and clinical characteristics. Epileptogenic zone localization was classified as frontal, parietal, occipital, multifocal, or undetermined based on electroclinical and neuroimaging findings. Elderly patients were defined as those aged 65 years or older at the time of PER initiation. Initial dosing and titration of PER were determined by the treating physician according to clinical judgment and routine practice. In this retrospective study, follow-up visits occurred according to clinical need in routine practice, and effectiveness and safety outcomes were assigned to the nearest predefined follow-up timepoints at 3, 6, 9, 12, 24, and 36 months after PER initiation or at study discontinuation. Each evaluation included: a) date of assessment; b) current PER dose and titration speed; c) number of seizures since the last assessment. This study was approved by the Gangnam Severance Hospital Institutional Review Boards and Committee on Human Research (3–2022–0488), with a waiver of informed consent due to the retrospective design.

2.2. Outcome measurement

Follow-up evaluations were conducted at 3, 6, 9, 12, 24, and 36 months after initiating PER. At each timepoint, the retention rate, 50% responder rate (≥ 50% reduction in seizure frequency), and seizure freedom were assessed. For patients who discontinued PER within 12 months, treatment duration, dose at discontinuation, and reason for discontinuation were additionally documented.

Effectiveness at 12 months was defined based on documented treatment response, including responder rate or seizure freedom [10,15]. When response data at 12 months were available, responders were classified as effective. Patients who discontinued PER before 12 months for reasons other than loss to follow-up or death were classified as non-effective, whereas those lost to follow-up or who died were considered unevaluable. To evaluate factors associated with effectiveness, patient-related clinical variables including age, sex, and duration of epilepsy were analyzed. Medical comorbidities were summarized using the Charlson Comorbidity Index (CCI), while psychiatric comorbidities were dichotomized as present or absent. Concomitant ASM were categorized according to mechanisms as sodium channel blockers, GABA enhancers, calcium channel blockers, synaptic vesicle protein 2A (SV2A) modulators, mixed-mechanism agents. They were also classified regarding metabolism as enzyme-inducing antiseizure medication (EIASM) were included as covariates in the analysis.

2.3. Safety assessment

The safety and tolerability profile was determined by the frequency of treatment discontinuation attributable to adverse events and by the occurrence of PER-related adverse events during follow-up. Adverse events were assessed throughout the entire follow-up period, including their type, PER dose at onset, severity, causality, and outcome.

2.4. Statistical analysis

All statistical analyses were performed using R software (version 4.1.1). Retention rates were estimated using Kaplan–Meier survival analysis, and group differences were assessed using the log-rank test. Comparisons of categorical variables between elderly and non-elderly patients were performed using the chi-square test or Fisher's exact test, as appropriate. Factors associated with treatment effectiveness at 12 months were evaluated using univariate and multivariate logistic regression analyses, with results reported as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Interaction terms between age group and selected clinical variables were included to assess potential effect modification by age. Multivariate logistic regression analyses were also performed to identify factors associated with the occurrence of adverse events, moderate to severe adverse events, and adverse event prognosis among affected patients. Forest plots were used to visualize the results of multivariate analyses. All tests were two-sided, and a P value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Between February 2016 and January 2024, 528 patients with focal seizures were included from eight tertiary hospitals in South Korea. Of these, 108 were classified as elderly (≥65 years), and 420 were non-elderly (<65 years) (Table 1). The mean age of all patients was 48.0 ± 17.2 years, and 237 of them were female. The mean duration of epilepsy

Table 1
Baseline clinical characteristics of patients with focal epilepsy receiving perampanel (PER) according to age group.

Clinical characteristics	Whole population (n = 528)	Non-elderly (age < 65 years) (n = 420)	Elderly (age ≥ 65 years) (n = 108)	P-value *
Age (mean)	48.0 ± 17.2	41.8 ± 13.0	72.2 ± 6.8	-
Female (sex)	237 (44.9%)	194 (46.2%)	43 (39.8%)	0.280
Epilepsy duration	15.5 ± 13.4	16.1 ± 12.9	12.9 ± 15.1	0.042
Etiology				0.045
Structural	224 (42.4%)	166 (39.5%)	58 (53.7%)	
Genetic	12 (2.3%)	12 (2.9%)	0 (0.0%)	
Immune	17 (3.2%)	13 (3.1%)	4 (3.7%)	
Infectious	50 (9.5%)	43 (10.2%)	7 (6.5%)	
Metabolic	9 (1.7%)	6 (1.4%)	3 (2.8%)	
Unknown	216 (40.9%)	180 (42.9%)	36 (33.3%)	
Brain MRI with relevant lesion	233 (44.1%)	178 (42.4%)	55 (50.9%)	0.254
Electroencephalography findings				
Focal epileptiform discharges	265 (50.2%)	212 (50.5%)	53 (49.1%)	0.879
Focal slowing	102 (19.3%)	80 (19.0%)	22 (20.4%)	0.862
Generalized slowing	76 (14.4%)	53 (12.6%)	23 (21.3%)	0.033
Epileptogenic zone				0.030
Frontal	97 (18.4%)	75 (17.9%)	22 (20.4%)	
Temporal	171 (32.4%)	145 (34.5%)	26 (24.1%)	
Parietal	18 (3.4%)	17 (4.0%)	1 (0.9%)	
Occipital	13 (2.5%)	12 (2.9%)	1 (0.9%)	
Multifocal	141 (26.7%)	101 (24.0%)	40 (37.0%)	
Undetermined	88 (16.7%)	70 (16.7%)	18 (16.7%)	
Seizure frequency previous 3months	10.2 ± 30.2	11.9 ± 33.4	3.9 ± 8.3	<0.001
Mode of PER administration				
Early add-on	447 (85.0%)	362 (86.4%)	85 (79.4%)	
Monotherapy	79 (15.0%)	57 (13.6%)	22 (20.6%)	
Fast titration < 2wks	236 (55.7%)	197 (46.9%)	39 (36.1%)	0.057
Medical comorbidities				
Hypertension	69 (13.1%)	32 (7.6%)	37 (34.3%)	<0.001
Diabetes mellitus	44 (8.3%)	21 (5.0%)	23 (21.3%)	<0.001
Dyslipidemia	21 (4.0%)	14 (3.3%)	7 (6.5%)	0.224
Atrial fibrillation	11 (2.1%)	2 (0.5%)	9 (8.3%)	<0.001
Congestive heart failure	8 (1.5%)	4 (1.0%)	4 (3.7%)	0.100
Valvular heart disease	4 (0.8%)	3 (0.7%)	1 (0.9%)	1.000
Ischemic heart disease	11 (2.1%)	1 (0.2%)	10 (9.3%)	<0.001
Chronic obstructive pulmonary disease	11 (2.1%)	0 (0.0%)	11 (10.2%)	<0.001
Chronic kidney disease	18 (3.4%)	11 (2.6%)	7 (6.5%)	0.094
Connective tissue disorder	7 (1.3%)	5 (1.2%)	2 (1.9%)	0.949
Liver disease	27 (5.1%)	19 (4.5%)	8 (7.4%)	0.333
Thyroid disease	21 (4.0%)	17 (4.0%)	4 (3.7%)	1.000
Cancer	23 (4.3%)	10 (2.4%)	13 (12.0%)	0.005
Neurologic history				
Brain tumor	25 (4.7%)	22 (5.2%)	3 (2.8%)	0.412
Central nervous system infection	43 (8.1%)	37 (8.8%)	6 (5.6%)	0.365
Cerebral hemorrhage	51 (9.7%)	29 (6.9%)	22 (20.4%)	<0.001
Cerebral infarction	26 (4.9%)	10 (2.4%)	16 (14.8%)	<0.001
Traumatic brain injury	19 (3.6%)	14 (3.3%)	5 (4.6%)	0.722
Febrile convulsion	5 (0.9%)	5 (1.2%)	0 (0.0%)	0.560
Perinatal insult	15 (2.8%)	12 (2.9%)	3 (2.8%)	1.000
Hypoxic brain injury	6 (1.1%)	2 (0.5%)	4 (3.7%)	0.021
Dementia	20 (3.8%)	6 (1.4%)	14 (13.0%)	<0.001
Parkinson's disease	3 (0.6%)	2 (0.5%)	1 (0.9%)	1.000
Psychiatric comorbidities				
Anxiety disorder	9 (1.7%)	6 (1.4%)	3 (2.8%)	0.583
Panic disorder	4 (0.8%)	4 (1.0%)	0 (0.0%)	0.692
Bipolar disorder	11 (2.1%)	10 (2.4%)	1 (0.9%)	0.571
Depressive disorder	35 (6.6%)	31 (7.4%)	4 (3.7%)	0.249
Mental retardation	54 (10.2%)	53 (12.6%)	1 (0.9%)	0.001
Autism	3 (0.6%)	3 (0.7%)	0 (0.0%)	0.870
Schizophrenia	10 (1.9%)	8 (1.9%)	2 (1.9%)	1.000
Co ASM count previous	2.5 ± 1.5	2.5 ± 1.5	2.4 ± 1.6	0.563
Concomitant ASMs at baseline				
Levetiracetam	274 (51.9%)	219 (52.1%)	55 (50.9%)	0.906
Valproic acid	207 (39.2%)	157 (37.4%)	50 (46.3%)	0.114
Lamotrigine	134 (25.4%)	116 (27.6%)	18 (16.7%)	0.027
Topiramate	123 (23.3%)	101 (24.0%)	22 (20.4%)	0.497
Lacosamide	96 (18.2%)	72 (17.1%)	24 (22.2%)	0.280
Oxcarbazepine	89 (16.9%)	75 (17.9%)	14 (13.0%)	0.286
Phenytoin	65 (12.3%)	46 (11.0%)	19 (17.6%)	0.087
Carbamazepine	62 (11.7%)	54 (12.9%)	8 (7.4%)	0.161
Clobazam	49 (9.3%)	42 (10.0%)	7 (6.5%)	0.348
Zonisamide	45 (8.5%)	41 (9.8%)	4 (3.7%)	0.069
Clonazepam	32 (6.1%)	24 (5.7%)	8 (7.4%)	0.666
Phenobarbital	27 (5.1%)	21 (5.0%)	6 (5.6%)	1.000
Pregabalin	22 (4.2%)	17 (4.0%)	5 (4.6%)	1.000
Vigabatrin	8 (1.5%)	8 (1.9%)	0 (0.0%)	0.316

ASM: antiseizure medication.
* Independent t-test was used to compare continuous variables and Chi-square test was used to compare categorical variables.

was 15.5 ± 13.4 years, and the non-elderly group had a longer duration of epilepsy compared to the elderly group. The mean number of seizures in the 3 months prior to PER administration was 3.9 ± 8.3 in the elderly group and 11.9 ± 33.4 in the non-elderly group, showing a significant difference. Structural etiologies were more frequent in the elderly group, and elderly patients also had a higher prevalence of cerebrovascular history, including cerebral infarction and cerebral hemorrhage, than non-elderly patients. The most commonly co-prescribed drugs included levetiracetam (51.9%), valproate (39.2%), lamotrigine (25.4%), and topiramate (23.3%). Overall, 85.0% of patients received PER as adjunctive therapy, while 15.0% received PER as monotherapy. Fast titration within 2 weeks was performed in 55.7% of patients at the time of administration. The distribution of treatment effectiveness and adverse events across ILAE etiological categories was additionally explored descriptively, and the results are presented in Supplementary Table 1.

3.2. Outcomes

The retention rate in the overall population was 59.1% at 12 months,

decreasing to 33.7% at 24 months and 23.7% at 36 months (Fig. 1A). Retention rates were consistently lower in the elderly group than in the non-elderly group throughout the follow-up period (Fig. 1B). Among 208 patients who discontinued PER within 12 months, adverse events were the leading cause of discontinuation (116 patients, 55.8%), followed by loss to follow-up (65 patients, 31.3%). Less frequent causes included death (14 patients, 6.7%) and seizure aggravation (13 patients, 6.3%) (Fig. 1C). Notably, loss to follow-up accounted for nearly one-third of early discontinuations, precluding confirmation of medication retention status. In the elderly group, loss to follow-up accounted for the largest proportion of treatment discontinuation (27 of 62 patients, 43.5%), whereas in the non-elderly group, adverse events were the most frequent proportional cause of discontinuation (91 of 146 patients, 62.3%) (Fig. 1C). In the overall patient population, the 50% responder rates to PER were 74.0% at 12 months, 63.7% at 24 months, and 61.9% at 36 months (Fig. 1D). When stratified by age, the elderly group demonstrated a more favorable treatment response, with 50% responder rates exceeding 80% up to 24 months and seizure-free rates greater than 60% across all follow-up periods (Fig. 1E, F).

In this study, to account for the impact of loss to follow-up on retention rates, treatment effectiveness at 12 months was defined, and factors associated with treatment effectiveness were analyzed. Among the 528 patients included in the cohort, 431 had evaluable 12-month treatment effectiveness outcomes and were included in the logistic regression analysis. Of these, 231 were classified as effective and 200 as non-effective. Ninety-seven patients were excluded from the primary analysis because 12-month effectiveness could not be evaluated, including 65 patients lost to follow-up, 14 who died before 12 months, and 18 with missing outcome data. Multivariate logistic regression analysis demonstrated that, in the overall population, the presence of psychiatric comorbidities was independently associated with a lower likelihood of treatment effectiveness at 12 months (OR, 0.33; 95% CI, 0.17–0.65; $P = 0.001$), as was multifocal epileptogenic zone localization (OR, 0.36; 95% CI, 0.16–0.79; $P = 0.011$). In contrast, focal slowing on EEG was associated with a higher likelihood of treatment effectiveness (OR, 2.84; 95% CI, 1.29–6.26; $P = 0.010$). In addition, a higher PER dose at 12 months, treated as a continuous variable, was independently associated with increased treatment effectiveness (OR, 1.16 per 1-mg increase; 95% CI, 1.01–1.34; $P = 0.040$). Patients with an undetermined epileptogenic zone also showed a significantly higher likelihood of treatment effectiveness compared with the reference group (OR, 5.26; 95% CI, 1.64–16.90; $P = 0.005$) (Fig. 2). When interaction terms between age group and clinical variables were included in the model, no significant effect modification by age group was observed, except for monotherapy (OR, 341.54; 95% CI, 1.43–81,720.49; $P = 0.037$) in Supplementary Table 2. To evaluate the potential impact of missing outcome data, a sensitivity analysis was performed in which patients without evaluable 12-month effectiveness outcomes were classified as non-effective and included in the analysis ($n = 528$). The results of this analysis were largely consistent with those of the primary model. Psychiatric comorbidity, multifocal epileptogenic zone, focal slowing on EEG, and PER dose at 12 months remained significantly associated with treatment effectiveness (Supplementary Table 3).

3.3. Adverse events

Adverse events were reported in 50.8% ($n = 268$) of all patients treated with PER. In contrast to previous reports, the incidence of adverse events was lower in the elderly group (39.8%). Among the overall cohort, moderate to severe adverse events occurred in 189 patients; 33 patients in the elderly group (30.5%) and 156 patients in the non-elderly group, indicating a lower frequency in elderly patients. No significant differences were observed in the types of adverse events according to age group (Supplementary Table 4). Furthermore, the distribution of adverse event types did not differ significantly according to treatment strategy (Supplementary Table 5). Moreover, dose-specific analyses revealed no significant differences in adverse event risks between elderly and non-elderly patients across all dose levels (Supplementary Table 6).

To identify factors associated with the occurrence of adverse events, multivariate logistic regression analyses were performed. Using temporal epileptogenic zone localization as the reference, patients with an undetermined epileptogenic zone showed a significantly reduced likelihood of adverse events (OR, 0.15; 95% CI, 0.06–0.38; $P < 0.001$). Among electroencephalographic features, focal epileptiform discharges on routine EEG were associated with a lower risk of adverse events (OR,

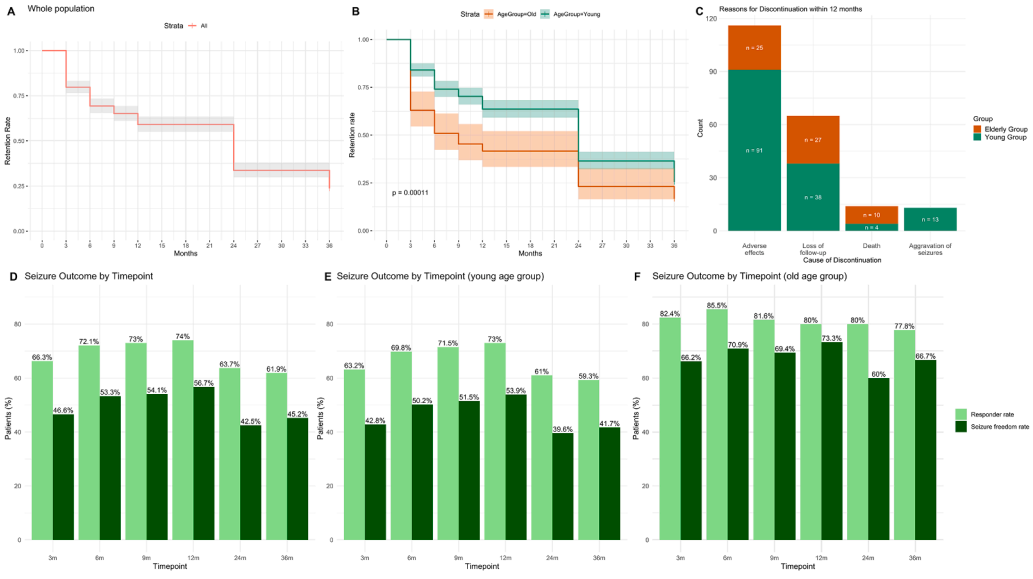

Fig. 1. Retention and seizure outcomes of PER treatment according to age group. (A) Kaplan–Meier estimates of PER retention in the overall study population. (B) Kaplan–Meier curves comparing PER retention between elderly (≥65 years) and non-elderly (<65 years) patients; shaded areas indicate 95% confidence intervals, and the P value was calculated using the log-rank test. (C) Reasons for treatment discontinuation within 12 months, stratified by age group. (D) Seizure outcomes over time in the overall population, categorized as ≥50% seizure reduction (responder), seizure freedom, (E) Seizure outcomes over time in the non-elderly group. (F) Seizure outcomes over time in the elderly group.

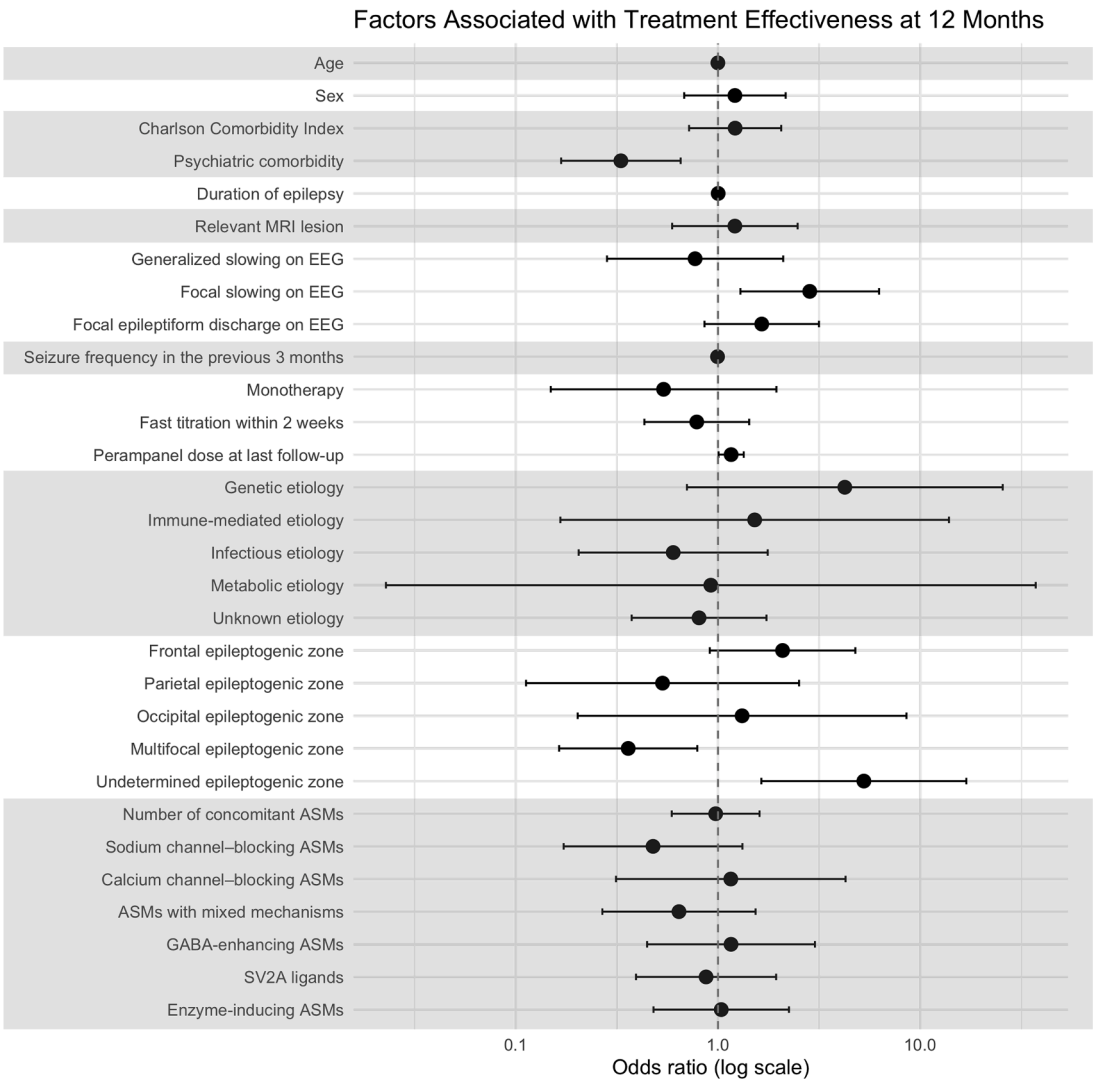

Fig. 2. Factors associated with treatment effectiveness at 12 months identified by multivariate logistic regression analysis. ASM, antiseizure medication; EEG, electroencephalography; MRI, magnetic resonance imaging.

0.40; 95% CI, 0.22–0.72; $P = 0.002$), although this finding should be interpreted cautiously. Other clinical variables, including age, seizure frequency, titration speed, treatment strategy, and concomitant ASM, were not significantly associated with the occurrence of adverse events (Fig. 3A). When the analysis was restricted to moderate to severe adverse events, fast titration within two weeks was identified as a strong independent risk factor (OR, 19.94; 95% CI, 5.71–69.68; $P < 0.001$). A higher CCI score was associated with an increased risk of moderate to severe adverse events (OR, 3.26; 95% CI, 1.01–10.52; $P = 0.049$). No other demographic, electroencephalographic, or treatment-related

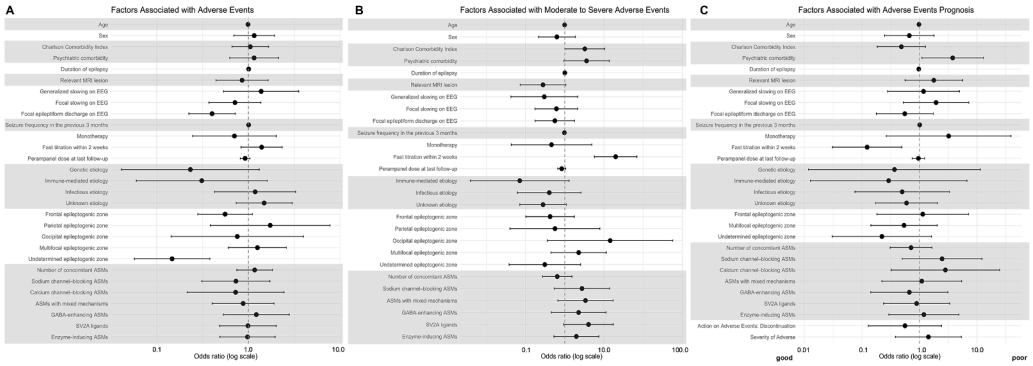

Fig. 3. Multivariate logistic regression analyses of adverse event outcomes. Forest plots show adjusted odds ratios and 95% confidence intervals for (A) any adverse events, (B) moderate to severe adverse events, and (C) adverse event prognosis. ASM, antiseizure medication; EEG, electroencephalography; MRI, magnetic resonance imaging.

variables showed a significant association with moderate to severe adverse events (Fig. 3B). In a subsequent analysis examining factors associated with adverse event prognosis, multivariate logistic regression was performed comparing patients with poor versus favorable adverse event outcomes. Psychiatric comorbidity was independently associated with a poorer adverse event prognosis (OR, 3.79; 95% CI, 1.11–12.95; $P = 0.034$). In contrast, fast titration within two weeks was associated with a significantly reduced probability of poor adverse event prognosis (OR, 0.12; 95% CI, 0.03–0.49; $P = 0.003$), suggesting a more favorable resolution of adverse events despite their occurrence (Fig. 3C).

4. Discussion

This multicenter, real-world study provides age-stratified evidence on the effectiveness and safety of PER in South Korea. PER was associated with sustained effectiveness and acceptable tolerability in elderly patients. Compared with non-elderly patients, elderly individuals tended to experience lower rates and severity of adverse events and showed generally favorable treatment responses. These findings provide further clinical information on PER outcomes across age groups, especially in Asian populations.

In our cohort, elderly patients had a higher frequency of structural etiologies and cerebrovascular history, including cerebral infarction and cerebral hemorrhage. This is clinically relevant because cerebrovascular disease is one of the most common causes of late-onset epilepsy in older adults [16,17]. In elderly patients presenting with late-onset seizures, cerebral amyloid angiopathy should also be considered as a potential underlying etiology [18].

The more favorable treatment response observed in elderly patients in our cohort should be interpreted in the context of several clinical and methodological considerations. At the same time, the responder rates observed in our elderly cohort, particularly during long-term follow-up, were higher than those reported in some previous real-world studies of PER and should therefore be interpreted cautiously [10,13]. Our findings are, however, not entirely inconsistent with prior elderly-focused real-world evidence. Inoue et al. reported higher 50% responder rates in patients aged ≥65 years than in younger adults across focal seizure types, including focal impaired awareness seizures and focal to bilateral tonic-clonic seizures, and Pascarella et al. also described a 12-month responder rate of 89.7% in elderly patients treated with PER in routine clinical practice [9,19]. In this cohort, elderly patients had a lower baseline seizure frequency, which has been consistently associated with better treatment outcomes [6,20]. In addition, because this was a long-term observational study, attrition of non-responders over time may have partly contributed to the relatively high responder rates observed at later follow-up points [21]. Medication adherence may be higher in older patients due to more structured daily routines and closer medical supervision [22,23]. Furthermore, a degree of selection bias cannot be excluded, as clinicians may prescribe PER more cautiously in elderly patients, favoring lower starting doses, slower titration, and more careful patient selection, which could contribute to improved treatment response in this group [24].

In the multivariate analysis, psychiatric comorbidity was independently associated with a lower likelihood of treatment effectiveness of PER at 12 months. This finding is consistent with prior studies showing that psychiatric burden can adversely affect epilepsy outcomes through mechanisms such as reduced medication adherence and altered symptom perception [25]. These results highlight the importance of screening for and actively managing psychiatric comorbidities when initiating PER therapy. This consideration is particularly relevant given that PER has been associated with psychiatric adverse events, supporting the need for careful monitoring in patients with pre-existing psychiatric conditions [26]. Patients with focal slowing on routine EEG were more likely to demonstrate favorable treatment effectiveness at 12 months following PER initiation. This association remained significant after adjustment for age and was the only factor to retain statistical significance in the adjusted analysis, suggesting a potential prognostic role of EEG biomarker. From a clinical perspective, this finding indicates that routine EEG features may provide supplementary information when considering PER treatment, although the underlying mechanisms and causal relationships require further investigation [27]. In addition, epileptogenic zone localization also showed a significant correlation with treatment effectiveness. Multifocal epileptogenic zone localization was independently associated with reduced effectiveness at 12 months, consistent with prior evidence that multifocal seizures reflect greater network complexity and a higher degree of pharmaco-resistance [28]. In contrast, patients with an undetermined epileptogenic zone demonstrated a higher likelihood of treatment effectiveness. In real-world settings, this classification likely reflects diagnostic heterogeneity rather than a uniform biological phenotype. In some patients, limited or inconclusive diagnostic evaluations may have contributed to the absence of a clearly defined epileptogenic zone.

In this study, the overall incidence of adverse events was lower in elderly patients than in non-elderly patients, a finding that differs from the conventional concern that older age is associated with poorer tolerability of ASM [9]. The absence of age-related differences was consistent across all dose levels and across both overall and specific adverse events, supporting the tolerability of dose escalation in elderly patients. These observations may reflect differences in clinical ASM-prescribing practices, as PER is often initiated more cautiously in elderly patients, with slower titration, lower target doses, and closer clinical monitoring [2]. Clinicians may adopt a lower threshold for dose adjustment or discontinuation in this population, allowing earlier intervention when adverse events emerge and potentially preventing progression to more severe or persistent symptoms [2]. These findings should not be interpreted as indicating that PER is intrinsically safer in elderly patients, but rather suggest that, under careful clinical management, it can be used without an excessive adverse event burden. Consistent with prior literature, fast titration within two weeks was identified as a strong independent risk factor for moderate to severe adverse events [29]. This finding aligns with the pharmacological properties of PER as a noncompetitive AMPA receptor antagonist, whereby rapid dose escalation may increase susceptibility to central nervous system–related adverse effects [26]. From a clinical perspective, this underscores the importance of gradual titration as a modifiable and actionable factor to improve tolerability, particularly in patients with advanced age or multiple comorbidities. In analyses focusing on adverse event prognosis among affected patients, psychiatric comorbidity was independently associated with poorer outcomes, suggesting that psychiatric factors may influence not only the occurrence of adverse events but also their persistence and recovery [26]. Psychiatric comorbidity may heighten symptom perception or complicate symptom resolution once adverse events develop [30]. Interestingly, fast titration was associated with a lower likelihood of poor adverse event prognosis. This seemingly paradoxical finding likely reflects differences in clinical response after adverse event onset rather than a protective effect of rapid titration itself. Adverse events emerging early during fast titration may prompt more immediate dose reduction or treatment discontinuation, leading to quicker symptom resolution. Taken together, these results highlight the importance of distinguishing between factors that increase the risk of adverse event occurrence and those that influence adverse event recovery, and they emphasize the need for individualized titration strategies and proactive management of psychiatric comorbidities in clinical practice.

4.1. Limitations

The present study has some limitations. First, the retrospective observational design limits causal inference and introduces the possibility of unmeasured confounding. Second, a substantial proportion of patients were lost to follow-up, which may have influenced retention and effectiveness estimates despite our efforts to account for this in the

analysis. In particular, because long-term effectiveness outcomes were assessed among patients who remained evaluable, attrition over time may have introduced informative censoring and contributed to relatively favorable responder and seizure-free rates at later follow-up points. Third, adverse event reporting was based on clinical documentation and patient reports, and therefore subject to reporting bias and variability in symptom perception. Fourth, the definition of elderly patients as those aged 65 years or older may not fully capture the heterogeneity of aging-related physiological changes. Fifth, because baseline seizure frequency was lower in the elderly group, the relatively favorable effectiveness outcomes observed in that group should be interpreted cautiously. Sixth, because this multicenter cohort consisted exclusively of Asian patients from South Korea, the generalizability of our findings to non-Asian or more ethnically diverse populations may be limited. Finally, confounding by indication cannot be excluded, as prescribing patterns, titration speed, and monitoring intensity may have differed according to patient characteristics.

5. Conclusion

In this multicenter cohort study with extended follow-up, PER showed sustained effectiveness and an acceptable safety profile across age groups. In elderly patients, outcomes appeared comparable to those observed in non-elderly patients. Slow titration was identified as an important modifiable factor associated with tolerability, while routine EEG findings and psychiatric comorbidity may be relevant in interpreting treatment response and adverse events. Although causal inferences are limited by the study design, these findings provide additional real-world evidence supporting the cautious use of PER in elderly patients. Further prospective studies are warranted to better define optimal initiation strategies and long-term outcomes.

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None

Ethics

This study was approved by the Yonsei University Health System, Institutional Review Board (3–2022–0488). Due to the retrospective nature and use of de-identified data, this study was approved with waiver of the requirement to obtain informed consent by the Yonsei University Health System, Institutional Review Board (3–2022–0488). The study was performed in accordance with approved guidelines and regulations for medical research expressed in the Declaration of Helsinki.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2026.03.013.

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