

Systemic Infection and Brain Resilience in Patients With Seizures: An Inverse-Model Hypothesis From a Retrospective Cohort Study

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Research Article

Keywords: Systemic infection, seizure, cerebral small vessel disease, chronic brain lesion, brain resilience, neuroinflammation, epileptogenesis, pneumonia, urinary tract infection, bacteremia

Posted Date: April 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9149796/v1>

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Additional Declarations: No competing interests reported.

Abstract

Introduction: Systemic infection and seizures frequently co-occur in patients. Nevertheless, the association between seizures, its triggers and concurrent systemic infectious diseases (CSIDs) other than central nervous system infections remains unclear.

Methods: This retrospective cross-sectional study evaluated 216 inpatients with ongoing seizures at a tertiary center in Taiwan in 2018. Clinical, radiological, and microbiological characteristics were compared between the patients with or without CSIDs.

Results: CSIDs were identified in 72.6% of the patients. Those with CSIDs were older ($p = 0.0020$), and had more dementia ($p = 0.0180$), hippocampal atrophy ($p = 0.0167$), chronic brain injury ($p = 0.0091$), and greater cerebral small vessel disease (CSVD) burden (CT, $p = 0.0373$; MRI, $p = 0.0373$). Interestingly, those with severe CSIDs (septic shock, bacteremia) had lower CSVD burden ($p = 0.0365$, white matter lesion positivity; $p = 0.0190$, deep white matter Fazekas score) than mild CSIDs. Multivariate logistic regression confirmed this inverse relationship (adjusted OR: 10.2, $p = 0.0448$) for deep white matter Fazekas score. Additionally, seizures associated with Gram-positive cocci (GPC) infections occurred in patients with lower burden of chronic brain injury ($p = 0.0099$) and hippocampal atrophy ($p = 0.0391$) compared to Gram-negative bacilli (GNB) infections.

Conclusion: These findings support an “Inverse model” hypothesis where systemic inflammation and diminished brain resilience are linked in seizure manifestation. Consequently, in older adults with chronic brain lesions, seizures may occur even in the setting of mild infections. In contrast, more severe infections tend to be associated with seizures in patients with uncompromised brains. Seizure risk was higher in patients with GPC infections than in those with GNB infections. These results underscore the importance of screening for systemic infections in older patients or those with dementia or higher chronic brain lesion burden who present with seizures, even in the absence of fever.

Key summary points

1. Systemic infections are a frequent and underrecognized contributor to seizure occurrence, particularly in older adults with chronic structural brain lesions. However, the complex interplay between systemic infections and preexisting brain pathology in patients with seizures remains to be elucidated.
2. Among patients with concurrent systemic infectious diseases and seizures, an inverse association was observed between infection severity and brain lesion burden, suggesting that milder infections are associated with seizures in structurally vulnerable brains, whereas more severe infections are typically observed in patients with relatively structurally intact brains.
3. We proposed an “Inverse-Model” hypothesis, in which seizures result from the combined effects of systemic inflammation and diminished brain resilience, especially in older patients or those with cognitive impairment.

4. Within the “Inverse-Model” framework, seizure associated with Gram-positive coccal infections occurred under significantly lower brain lesion burdens than those associated with Gram-negative bacilli, suggesting Gram-positive cocci may pose a higher seizure risk.
5. In patients presenting with seizures who have dementia or a higher burden of chronic brain lesions, a more thorough investigation for systemic infections is warranted.

Introduction

Seizures are a neurological disorder not uncommon among hospitalized patients. Among the various triggers, systemic infections, such as pneumonia, urinary tract infection, cellulitis, or bacteremia, are frequently encountered during seizure evaluation. However, the basic profile and mechanistic influence of these concurrent systemic infectious diseases (CSIDs) on seizure occurrence remain underexplored, especially when central nervous system (CNS) infections are excluded. The literature reports few clinical profiles of patients with CSIDs and seizures [1, 2], and even fewer studies have examined the causal relationships among established seizure-triggering factors. Brain resilience, or the brain’s ability to resist systemic stressors, may provide a framework for interpreting these interactions. Brain resilience may decline because of chronic brain lesions caused by hippocampal atrophy [3], neurosurgical intervention [4] traumatic brain injury (TBI) [5] or cerebral small vessel disease (CSVD) [6, 7]. The present study hypothesized that patients with compromised brain resilience may be at greater risk of experiencing seizures than those with uncompromised brain resilience are.

Factors linked to infection may also influence seizure susceptibility. Although fever is a well-documented trigger of seizures [8] and febrile infection-related epilepsy syndrome, a rare acute-onset chronic epilepsy syndrome in children [9], its role in adult seizure susceptibility remains unclear. Additionally, pathogens may generally differ in their epileptogenic potential. For example, Gram-positive cocci (GPC), such as *Staphylococcus* and *Streptococcus*, produce superantigens that induce toxic shock syndrome [10], whereas lipopolysaccharides or endotoxins—the principal cell wall components of Gram-negative bacilli (GNB)—are critical to sepsis and systemic inflammation [11].

The present study described the clinical, imaging, and microbiological profiles of patients with seizures and CSIDs, compared patients with and without CSIDs, and analyzed the differences in infection severity, febrile status, and microbiology among patients with CSIDs. The cohort included only patients hospitalized in 2018, with this limited timeframe imposed to mitigate confounding from hospital admission trends linked to COVID-19.

Methods

This retrospective cross-sectional study included patients admitted to National Cheng Kung University Hospital in Tainan, Taiwan, between January 1 and December 31, 2018, for medical treatment who experienced seizures at admission or during hospitalization. Patient data were retrieved using keywords such as (1) “seizure,” “epilepsy,” “convulsion,” and “status epilepticus.” or (2) *International Classification*

of Diseases (ICD)-9 or ICD -10 codes for seizures in nonsurgical wards were employed through electronic medical records to obtain patients (Supplementary Material, Table S1). Initially, 533 patients were identified with profiles matching the keywords or having relevant *ICD* codes. After a comprehensive review of these patients' medical records, 318 patients were excluded due to the following reasons: absence of a documented seizure event during hospitalization, a final diagnosis inconsistent with seizure, insufficient clinical information to distinguish seizures from other non-epileptic movement disorders, or confirmed CNS infection. The final analysis included 216 patient–events (Figure 1).

We collected data on the patients' demographic characteristics, seizure semiology, comorbidities, systemic infection status, and radiological findings. The seizure-specific dataset comprised information on seizure category (acute symptomatic or provoked seizures are defined by the presence of an acute systemic or neurological insult like recent stroke, brain tumor, anoxic brain injury, metabolic imbalance, fever, or ASM withdrawal. In contrast, unprovoked seizures are those occurring in the absence of an identifiable clinical trigger) [12], seizure type (focal preserved or impaired consciousness seizure, focal-to-bilateral tonic-clonic seizure and generalized onset seizure) [13], seizure onset location (before or during emergency room visit or during hospitalization), date and sequence of seizures and CSIDs, and antiseizure medication (ASM) use before and after the hospital visit. The ASMs prescribed were levetiracetam, valproate, carbamazepine, oxcarbazepine, phenytoin, topiramate, vigabatrin, clonazepam, lamotrigine, zonisamide, phenobarbital, perampanel, and clobazam. Infection profiles encompassed information regarding vital signs, arterial blood gas, infection site, and microbiological findings. Brain imaging abnormalities identified through computed tomography (CT) or magnetic resonance imaging (MRI) were recorded, as were seizure-triggering factors such as serum sodium, calcium, magnesium levels, blood glucose levels, and offending antimicrobial agents (Supplementary Material, Table S2).

The definition of CSID emphasizes “concurrent” occurrence of systemic infection and seizure which was defined either (1) when systemic infection was detected at the time of seizure onset or (2) within post-ictal 24 hours for not leaving out atypical presentation of infectious diseases especially in geriatric/frail population [14-16], or (3) when seizures occurred during the ongoing treatment of a documented systemic infection. Evidence of infections was confirmed by clinical signs, antibiotic initiation, and microbiologic workup. Infections developing more than 24 hours post-seizure were excluded. (Figure 2).

To compare comorbidities across groups, we applied the Charlson Comorbidity Index (CCI) and Epilepsy-Specific Comorbidity Index. Comorbidity presence and scores were determined through a comprehensive electronic medical record examination involving consideration of conditions ranging from hypertension and diabetes mellitus to malignancy, either non-metastatic or metastatic, solid or hematologic malignancies categorized by disease status as in remission, stable, or progressive.

Because CNS infection is well established as a cause of seizures, CSIDs were defined as non-CNS infections diagnosed through clinical, laboratory, and imaging findings. They included pneumonia, urinary tract infection, skin or soft-tissue infection (cellulitis, open wound, pressure sore), enteritis/colitis, biliary tract infection, abscess, peritonitis, septic arthritis, bacteremia / septic shock with or without identifiable

primary origin. Included patients were stratified into CSID and non-CSID groups. CSID severity was categorized as mild (characterized by the absence of septic shock or bacteremia) or severe (characterized by the presence of septic shock or bacteremia). Seizure-triggering antimicrobial agents, such as carbapenem (imipenem, ertapenem and meropenem) and cefepime, were identified using electronic medical records and assessments made by neurologists or other physicians.

We also analyzed the patients' CT and MRI findings. In an image scoring analysis, we considered the evaluation metrics of medial temporal atrophy score [17], modified visual rating scale for CT CSVD score [18], STRIVE (STandards for Reporting and Imaging of Small Vessel Disease) criteria for MRI CSVD [19] score, Fazekas score for white matter hyperintensity (WMHI) [20], and cerebral microbleed (CM) [19], enlarged perivascular space (EPVS) [21], and lacunar stroke [19] scoring criteria. The inclusion criteria and respective scoring rules for each brain imaging item are provided (Supplementary Material, Table S3). Imaging abnormalities were classified into three categories for seizure association analysis: (1) recent brain injury, such as recent stroke, brain tumor, and anoxic brain injury; (2) chronic brain injury, such as old stroke, encephalomalacia, TBI, and surgical brain injury; and (3) developmental anomalies, such as cortical dysplasia, mesial temporal sclerosis, vascular anomaly, and microcephaly.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics (version 24.0, IBM Corp., Armonk, NY). Continuous variables were initially tested for normality using the Shapiro–Wilk test. Variables with normal distributions were presented as means $\pm$ standard deviations (SD) and compared using the independent Student's *t* test. Variables that did not follow a normal distribution were reported as median (interquartile range, IQR) and analyzed using the Mann–Whitney U test. Categorical variables were expressed as counts and percentages, and between-group comparisons were performed using the Chi-square test or Fisher's exact test where appropriate (e.g., when expected counts were <5).

For subgroup analyses (e.g., mild vs. severe CSID, febrile vs. afebrile, GPC vs. GNB), the same principles were applied: Shapiro–Wilk testing for continuous variables, followed by appropriate parametric or non-parametric tests depending on the data distribution. Statistical significance was defined as a two-tailed *p* value < 0.05. No adjustments were made for multiple comparisons, as this was an exploratory study aimed at hypothesis generation.

Where applicable, missing data were noted, and analysis was conducted on available cases without imputation.

Interrater Reliability

Cohen's κ coefficient was used for categorical variables, and intraclass correlation coefficients (ICCs) were used for continuous variables. Two raters (one neurologist, Y.T. Huang and one neuroradiologist, T. R. Chen) scored the images after completing training to do so, and the reliability of their assessments was confirmed by using a random sample comprising 10% of the total imaging studies. The interrater

reliability was acceptable for all neuroimaging biomarkers ($\kappa = 0.773$ for hippocampal atrophy; ICC = 0.857 for lacune number; ICC = 0.835 for CT CSVD score; ICC = 0.750 for Fazekas score, deep WMHI; ICC = 0.866 for Fazekas score, periventricular WMHI; ICC = 0.833 for deep CMs ; ICC = 0.870 for cortical CMs; ICC = 0.727 for basal ganglion EPVS; and ICC = 0.886 for centrum semiovale EPVS).

Results

Among the 216 included patients, 210 (97.2%) of the seizures were classified as acute symptomatic seizures. 157 (72.6%) had CSIDs, and 59 did not. The patients with CSIDs were older (65.9 ± 18.7 years vs. 56.3 ± 20.4 years, $p = 0.0020$), had a higher prevalence of acute symptomatic seizures (100% vs. 89.8%, $p = 0.0003$) and generalized seizures (55.8% vs. 37.1%, $p = 0.0386$), had a lower prevalence of malignancy (26.6% vs. 44.5%, $p = 0.0056$), and were more likely to have dementia (25.3% vs. 9.7%, $p = 0.0180$) relative to those without CSIDs.

Infection-related manifestations, specifically, peri-ictal fever (35.0% vs. 8.5%, $p = 0.0001$), septic shock (15.3% vs. 1.7%, $p = 0.0054$), and acid–base imbalance (respiratory acidosis, alkalosis, or metabolic acidosis, 53.9% vs. 23.7%, $p = 0.0001$) were more frequent in the CSID group. By contrast, recent brain injuries (stroke, brain tumors, and anoxic brain injury) were more common in the non-CSID group (47.5% vs. 27.4%, $p = 0.0051$). Chronic brain injuries, such as old stroke, encephalomalacia, TBI, and surgical brain injury, were more prevalent in the CSID group (50.3% vs. 30.5%, $p = 0.0091$).

Radiological comparisons revealed that the patients with CSIDs were more likely to exhibit hippocampal atrophy (62.3% vs. 44.1%, $p = 0.0167$), have higher CT CSVD scores (1.30 ± 1.16 vs. 0.84 ± 1.11 , $p = 0.0097$), and have higher MRI CSVD scores (1.18 ± 1.22 vs. 0.74 ± 1.11 , $p = 0.0373$) than those without CSIDs were. The MRI-specific features that differed significantly between the groups were deep WMHI (1.22 ± 1.07 vs. 0.81 ± 0.99 , $p = 0.0265$), periventricular WMHI (1.63 ± 1.14 vs. 1.09 ± 1.16 , $p = 0.0093$), and basal ganglion EPVS (1.07 ± 0.84 vs. 0.77 ± 0.76 , $p = 0.0310$). No significant differences were observed between the groups in survival rates and ASM prescriptions (Table 1).

To investigate the observed pattern of more frequent recent brain injury in the non-CSID group and more frequent chronic brain injury in the CSID group, we stratified the patients with CSIDs into mild (characterized by the absence of septic shock or bacteremia) and severe (characterized by the presence of septic shock or bacteremia) subgroups. This classification enabled us to assess whether infection severity was correlated, positively or negatively, with the extent of neuroimaging abnormalities. The conventional perspective regarding CSIDs and seizures suggests that patients with frailty experience more severe infections and more extensive brain pathology, whereas more robust patients have milder infections and exhibit fewer imaging abnormalities. However, the present study proposed an alternative perspective: In patients with more resilient brains and fewer structural abnormalities, seizures tended to be associated with more severe systemic inflammation; conversely, in those with more vulnerable brains, seizures were observed even in the presence of mild infections. This inverse association suggests

that cumulated brain pathologies weaken brain resilience and predispose individuals to seizures (Figure 3).

Among the patients with CSIDs, those with severe infections (septic shock or bacteremia, $n = 49$) had higher CCI values (7.5 ± 3.6 vs. 6.3 ± 3.2 , $p = 0.0398$) and a higher prevalence of heart failure or pulmonary hypertension (53.1% vs. 30.6%, $p = 0.0070$). Additionally, these patients had a lower burden of deep WMHI than the mild CSID group did (0.85 ± 0.78 vs. 1.34 ± 1.13 , $p = 0.0190$), as well as less WMHI overall (19.2% vs. 42.3%, $p = 0.0365$) (Table 2), indicating an inverse association between infection severity and chronic brain lesion burden. To adjust for potential confounding effects from multiple variables showing significance in univariate analysis, variables from Table 2 with $p < 0.1$ —including CCI, ESCI, HF/pulmonary HTN, recent fever, respiratory alkalosis burden, WMHI positivity, and Fazekas score-Deep—were entered into a multivariable logistic regression model. The analysis revealed that only recent fever (adjusted OR: 0.25, $p = 0.0143$) and severe Fazekas score-Deep scoring 2-3 (adjusted OR: 10.2, $p = 0.0448$) remained independently associated with mild CSID (Table 3). These findings reinforce that among seizure patients with comorbid infections, more severe chronic brain changes are associated with milder infection severity, and vice-versa.

To explore the association between CSIDs and seizure occurrence noted in the radiological findings, we investigated the underlying factors contributing to the seizures experienced by the patients with CSIDs to find the driving factors behind. We speculate that infection may precipitate seizures through either host immune response or pathogen-derived antigens or toxins, and fevers reflect a host immune response. And Gram stain classification can be employed as an objective and practical approach to evaluating the ictogenic potential of different pathogen classes.

As an expression of host immune, in febrile status analysis, mild CSID patients were divided into afebrile ($N = 76$) and febrile ($N = 32$) subgroups. The patients with severe CSIDs were excluded to avoid confounding effects from septic shock and bacteremia.

The patients with fever had lower rates of heart failure and pulmonary hypertension (15.6% vs. 36.8%, $p = 0.0288$) and reduced major electrolyte or glucose imbalance (18.8% vs. 38.2%, $p = 0.0491$) than those without fever did. However, no significant differences in neuroimaging markers were observed (Table 4), suggesting that fever had a neutral effect when mediated by radiological abnormality burden on seizure risk in this adult cohort. But still, an analogous inverse relationship existed between febrile status and major electrolyte / glucose imbalance severity.

We further compared the subgroups of patients with CSIDs with positive cultures for GPC and GNB. The GNB subgroup had a significantly higher incidence of urinary tract infections (49.1% vs. 22.2%, $p = 0.0465$) and lower extreme blood urea nitrogen/creatinine ratios (15.1% vs. 50.0%, $p = 0.0080$) than the GPC subgroup did. The patients with GPC infections exhibited a lower burden of chronic brain injury (33.3% vs. 67.9%, $p = 0.0099$) and less hippocampal atrophy (38.9% vs. 66.7%, $p = 0.0391$) than did those with GNB infections (Table 5). These findings suggest that seizures linked to GPCs may occur even in

the absence of extensive preexisting brain pathology, which supports the present study's "Inverse model" of systemic inflammation and seizure susceptibility.

Discussion

The present study identified a high prevalence of CSIDs among the patients hospitalized with ongoing seizures. This finding indicates that CSIDs may be an independent seizure-precipitating factor rather than a coincidental comorbidity or sequela of seizures, particularly in individuals with reduced brain resilience due to chronic structural abnormalities.

To enhance the accuracy of identifying patients with infectious diseases preceding seizures, this study included not only those who showed infectious signs and symptoms at the time of seizure presentation, but also those who developed such features within the first 24 hours postictally. This approach reflects real-world clinical practice, where infectious disease-related signs and symptoms (e.g., fever) often fluctuate and may not perfectly coincide precisely with seizure onset [16]. Some concurrent infectious diseases were noticed shortly after seizure management. Thus, this extended time period is especially crucial for elderly patients, in which population infectious signs and symptoms are often blunted or initially unnoticed [14, 15]. As for the selection of 24-hour window, rather than a narrower (e.g., 12 hours) or broader (e.g., 48-hour) timeframe, it was based on the pathophysiology of postictal complications. Aspiration-related pneumonia, a common sequela following seizures typically manifests with symptoms including cough, fever, purulent sputum, and dyspnea over several days or weeks rather than within hours [22, 23], which were resulted from seizures and poor consciousness in this study setting. This time window was aimed to minimize the potential confounding influence of seizure-induced infections.

The patients with CSIDs were older and more frequently had received a diagnosis of dementia, consistent with epidemiological patterns linking aging to increased susceptibility to infection [24], increased prevalence of dementia [25], and increased seizure risk in individuals with neurodegenerative conditions [26]. Although non-CNS systemic infections and dementia are not direct epileptogenic factors, both may reduce seizure thresholds by modulating systemic inflammation and disrupting neural homeostasis [26, 27].

In the patients with CSIDs in the present study, infection-related features such as peri-ictal fever and acid–base imbalance occurred frequently, indicating an ongoing systemic inflammatory response. These patients also presented with fewer recent but more chronic brain injuries and exhibited higher burdens of CSVD and hippocampal atrophy, which are radiological markers associated with diminished brain resilience [3, 6, 7]. By contrast, the patients without CSIDs were more likely to present with seizure triggers such as acute stroke [28] and brain tumors [29].

To evaluate the temporal and causal relationships between infection and seizures, we stratified the patients with CSIDs into mild and severe subgroups. Although the conventional understanding of seizures and CSIDs suggests that more severe systemic illness coincides with more extensive brain pathology, our patients with severe CSIDs (septic shock or bacteremia) had significantly lower CSVD

burdens than did those with milder infections. This inverse association suggests that more severe systemic inflammation is associated with seizure occurrence in patients with intact brains, whereas even minor systemic disturbances may be associated with seizure occurrence in patients with substantial brain pathology. These results support the proposed "Inverse-Model" hypothesis, in which seizures result from the combined effects of systemic inflammatory stress and preexisting brain vulnerability, especially in elderly or patients comorbid with dementia [7, 10, 11, 30-33].

In comparisons of the incidence of comorbidities between the groups, heart failure and pulmonary hypertension occurred more frequently in the severe CSID group than in the mild CSID group. The mechanism by which heart failure induces seizures may involve circulatory anoxia [34] or seizure-induced asystole presenting as syncope, which is often indistinguishable from seizures with impaired awareness [35]. Although heart failure contributes to CSVD, it typically results in cerebral cortical microinfarcts [36], which differ from deep white matter lesions in this study. Additionally, the severe CSID group exhibited a lower CSVD burden than the non-CSVD group did. This finding may be attributable to the lack of an association between pulmonary hypertension and seizures and CSVD: Pulmonary hypertension has only been linked to seizures in isolated case reports [37, 38], and research has documented no association between pulmonary hypertension and CSVD [39]. Therefore, although heart failure and pulmonary hypertension were more prevalent in the severe CSID group in the current study, these conditions are unlikely to confound the observed inverse association between infection severity and chronic brain lesion burden.

Notably, the patients with CSIDs linked to GPC exhibited significantly lower chronic brain lesion burden than those with CSIDs linked to GNB did. The literature in this field has primarily addressed Staphylococcal or Streptococcal toxic shock syndrome, which is characterized by multiple organ failure (respiratory, renal, and hepatic failure; skin necrosis; and coagulopathy) due to diffuse capillary leakage. Additionally, because the neurological manifestations of CSIDs have not been well described [40], whether diffuse capillary leakage in the CNS increases susceptibility to inflammatory mediators and the risk of subsequent seizures when brain integrity is uncompromised remains unknown. Nevertheless, our findings support the hypothesis that certain pathogens possess higher intrinsic ictogenic toxicity and epileptogenic potential than others do. However, these observations should be interpreted with caution; due to the relatively small sample size, our analysis may have limited statistical power and an increased risk of type I error. Therefore, these results should be considered preliminary and require validation in larger, multicenter cohorts.

We also evaluated the association of fever with seizures. Although fever's role in childhood seizures is well established [8, 9] and one study indicated that cytokines linked to fever, such as interleukin-1 β and interleukin-6, may predispose children to febrile seizures [41], no significant radiological differences were observed between the afebrile and febrile subgroups in the present study. This result suggests that fever may not function as a primary seizure trigger in adults by the proposed "Inverse model" in the radiological standpoint. But still there found an analogy between febrile status and prevalence of major electrolyte / glucose imbalance, which is beyond the scope of this study. This finding is particularly

notable because older adults with dementia or structural brain lesions may not exhibit typical infection symptoms [14-16].

This study has several limitations. First, the retrospective cross-sectional design restricted the conclusions to associations rather than causal relationships. Furthermore, the retrospective nature of the study may affect data precision. This is exemplified by the discrepancy where the recorded number of patients with a known epilepsy history was lower than those already receiving ASMs, suggesting an underestimation of the true prevalence of epilepsy history. Consequently, we did not perform a subgroup analysis based on the presence or absence of a prior epilepsy history. Additionally, a higher proportion of generalized tonic-clonic seizures (GTCS) was observed. We speculate that this is ascribed to the fact that seizure semiology was primarily documented based on witness accounts, most of whom were family members rather than medical professionals, potentially leading to the under-reporting of more subtle seizure types. Second, results in this study were derived from hospitalized patients and focused on non-surgical ward patients with acute symptomatic seizures rather than unprovoked seizures, which may limit the generalizability of the results to the epilepsy population. Only a minority (19.4%) of patients had prior history of epilepsy (18.6% for non-CSID, 19.7% for CSID), raising the potential for selection bias, such as Berkson's paradox. Third, while considerable effort was made to rigorously define and distinguish cases with CSIDs, challenges remain. The inclusion criteria allowed for infectious signs and diagnoses identified during the pre-ictal, ictal, or within 24 hours post-ictal period, this approach cannot fully eliminate the possibility that some infections may have been triggered or exacerbated by the seizures, such as seizure-induced aspiration pneumonia. Despite this limitation, the 24-hour window was selected as a clinically reasonable approach to enhance diagnostic sensitivity while minimizing reverse causation. Furthermore, due to the retrospective design and the resulting missing data, standard clinical scoring systems such as APACHE II or qSOFA could not be applied for CSID severity grading. Nonetheless, our simplified classification based on septic shock and bacteremia offers greater clinical utility and ease of application in real-world practice.

Fourth, missing data and a relatively small sample size may also limit the generalizability of the findings. Finally, the observations from MRIs and microbiological evaluations did not reach significance and remained suggestive, likely because the high cost of MRIs and the low yield rate of current culture techniques render such evaluations difficult to obtain large sample size [42]. Despite these limitations, the current findings support our multiple-hit hypotheses regarding the interaction between systemic inflammation and neuronal vulnerability and its implications for seizure risk assessment and targeted interventions. Future prospective studies are warranted to further clarify the temporal relationship between systemic infections and seizure onset, and to determine whether timely infection recognition and appropriate treatment may help reduce seizure burden in at-risk populations, particularly older adults with underlying brain vulnerability such as cerebral small vessel disease, chronic brain lesion or dementia.

Conclusion

Systemic infections frequently contribute to seizure occurrence and remain underrecognized, particularly in older adults with chronic brain lesions. Our findings support a multiple-hit hypothesis, in which seizures result from the combined effects of systemic inflammation and diminished brain resilience. The observed inverse association between infection severity and brain lesion burden suggests that milder infections were associated with seizures in patients with vulnerable brains, whereas more severe infections are associated with seizure occurrence in patients with structurally intact brains. GPC may also pose a higher seizure risk than GNB do. These findings underscore the importance of infection screening in older patients and those with cognitive impairment presenting with seizures, even in the absence of fever. Nevertheless, a similar analogy was also found between febrile status and prevalence of major electrolyte / glucose imbalance, rather than radiological abnormality burden. Further studies are required to validate this model and obtain findings that can inform targeted prevention strategies.

Abbreviations

ASM: antiseizure medication

BG: basal ganglion

BUN: blood urea nitrogen

CCI: Charlson Comorbidity Index

CKD: chronic kidney disease

CM: cerebral microbleed

CNS: central nervous system

Crea: creatinine

CS: centrum semiovale

CSVD: cerebral small vessel disease

CT: computed tomography

DM: diabetes mellitus

ESCI: Epilepsy-Specific Comorbidity Index

EPVS: enlarged perivascular space

GNB: Gram-negative bacilli

GPC: Gram-positive cocci

HF: heart failure

HTN: hypertension

ICC: intraclass correlation coefficient

ICD: International Classification of Diseases

IQR: interquartile range

MRI: magnetic resonance imaging

OR: odds ratio

SD: standard deviation

STRIVE: STandards for Reporting and Imaging of Small Vessel Disease

TBI: traumatic brain injury

WMHI: white matter hyperintensity

Declarations

The authors confirm that the manuscript is not being considered for publication by another journal, nor will it be submitted elsewhere while under consideration by this journal, and has not been published previously (partly or in full).

Ethics approval and consent to participate

This study was approved by the institutional review board of National Cheng Kung University Hospital (Approval number: A-ER-111-475). The requirement to obtain informed consent was not applicable because of the retrospective study design and the use of deidentified medical records and imaging data. For these reasons, the requirement to obtain written informed consent from the patients was waived.

Consent for publication

Not applicable. This study does not contain any individual person's data in any form (including individual details, images, or videos).

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported in part by grants from the National Science and Technology Council (112-2314-B-006 -047 -MY2), Taiwan. None of the funding sources had any role in the design, analysis, data interpretation, preparation, review, or manuscript approval of this study.

Authors' contributions

The corresponding authors of this manuscript had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Y.T. Huang, C.M. Chang, and C.W. Huang. Acquisition of data: Y.T. Huang. Manuscript drafting: Y.T. Huang and C.W. Huang. Digital plotting: Y.T. Huang. Image scoring: Y.T. Huang and T.R. Chen. Statistical consultation: S.H. Lin and T.R. Chen. Critical revision of the manuscript for important intellectual content: Y.T. Huang, T.H. Huang, Y.S. Chen, T.R. Chen, S.H. Lin, C.M. Chang, and C.W. Huang. Study supervision: C.W. Huang. All authors read and approved the final manuscript.

Acknowledgements

This manuscript was edited by Wallace Academic Editing.

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Tables

Table 1. Comparison of Demographic, Clinical, and Radiological Features Between Patients with Seizures with and without CSIDs

	Non-CSID, <i>N</i> 1 = 59	CSID, <i>N</i> 2 = 157	<i>p</i> value
Epidemiology, <i>N</i> = 216			
Age, years, range (mean ± SD)	18-96 (56.3 ± 20.4)	18-104 (65.9 ± 18.7)	0.0020*
Sex, % male	30 (50.8%)	78 (49.7%)	0.8786
CCI, range (mean ± SD)	0-13 (5.9 ± 3.8)	0-14 (6.6 ± 3.4)	0.2190
ESCI, range (mean ± SD)	0-16 (5.6 ± 4.4)	0-14 (5.6 ± 3.3)	0.9828
Past history of epilepsy (%)	11 (18.6%)	31 (19.7%)	0.8554
Seizure category (%)			
Acute symptomatic (provoked)	53 (89.8%)	157 (100%)	0.0003***
Unprovoked	6 (10.2%)	0 (0%)	0.0003***
Seizure semiology (%)			
Generalized	23 (37.1%)	86 (55.8%)	0.0386*
Focal-to-bilateral tonic-clonic	6 (9.7%)	13 (8.4%)	0.6623
Focal impaired consciousness	22 (35.5%)	45 (29.2%)	0.2220
Focal preserved consciousness	8 (12.9%)	13 (8.4%)	0.2433
Underlying disease (%)			
HTN/DM	31 (50.0%)	103 (66.9%)	0.0780
CKD/Liver disease	14 (22.6%)	33 (21.4%)	0.6672
HF/Pulmonary HTN	20 (32.3%)	59 (38.3%)	0.6167
Malignancy	27 (44.5%)	41 (26.6%)	0.0056**
Dementia	6 (9.7%)	39 (25.3%)	0.0180*
Clinical/laboratory profile (%)			
Major electrolyte/glucose imbalance	14 (23.7%)	46 (29.3%)	0.4154
Recent fever	5 (8.5%)	55 (35.0%)	0.0001***
Septic shock	1 (1.7%)	24 (15.3%)	0.0054**
Acid–base imbalance positivity	14 (23.7%)	83 (53.9%)	0.0001***
Respiratory acidosis burden	3 (5.1%)	26 (16.6%)	0.0275*
Respiratory alkalosis burden	5 (8.5%)	38 (24.2%)	0.0099**

Metabolic acidosis burden	7 (11.9%)	47 (29.9%)	0.0063**
Metabolic alkalosis burden	6 (10.2%)	15 (9.6%)	0.8918
High lactate ≥ 2.0 (mmol/L)	13 (22.0%)	56 (35.7%)	0.0555
Severe azotemia, BUN ≥ 90 (mg/dL)	3 (5.1%)	6 (3.8%)	0.7074
BUN/Crea ratio ≥ 20	29 (49.2%)	77 (49.0%)	0.9887
Brain disease condition (%)			
Recent brain injury ¹	28 (47.5%)	43 (27.4%)	0.0051**
Chronic brain injury ²	18 (30.5%)	79 (50.3%)	0.0091**
Developmental anomaly ³	5 (8.5%)	9 (5.7%)	0.5362
Radiological profile			
CT or MRI, $N = 210$	N1 = 59 (missed = 0)	N2 = 151 (missed = 6)	
Hippocampal atrophy	26 (44.1%)	94 (62.3%)	0.0167*
Lacunae positivity (%)	9 (15.3%)	37 (24.7%)	0.1452
Lacunae number, median (Q1–Q3, IQR, range)	0 (0–0, 0, 4)	0 (0–0, 0, 9)	0.2757
CT, $N = 204$	N1 = 56 (missed = 3)	N2 = 148 (missed = 9)	
CT CSVD score, 0–3, average (SD)	0.84 (1.11)	1.30 (1.16)	0.0097**
MRI, $N = 144$	N1 = 47 (missed = 12)	N2 = 97 (missed = 60)	
MRI total CSVD score, 0–4, average (SD)	0.74 (1.11)	1.18 (1.22)	0.0373*
WMHI positivity (%)	13 (27.7%)	36 (37.1%)	0.2616
Fazekas–Deep, 0–3 (SD)	0.81 (0.99)	1.22 (1.07)	0.0265*
Fazekas–Periventricular, 0–3 (SD)	1.09 (1.16)	1.63 (1.14)	0.0093**
CM positivity (%)	6 (12.8%)	24 (24.7%)	0.0971
CM, deep, median (Q1–Q3, IQR, range)	0 (0–0, 0, 8)	0 (0–0, 0, 68)	0.3271
CM, cortical, median (Q1–Q3, IQR, range)	0 (0–0, 0, 11)	0 (0–0, 0, 13)	0.6171
EPVS positivity if BG 2–4 (%)	7 (14.9%)	25 (25.8%)	0.1409
EPVS, total = BG + CS, average (SD)	1.70 (1.33)	2.18 (1.40)	0.0525
EPVS, BG, 0–4, average (SD)	0.77 (0.76)	1.07 (0.84)	0.0310*

EPVS, CS, 0–4, average (SD)	0.94 (0.79)	1.11 (0.80)	0.2128
Outcome			
Mortality or critical discharge/transfer to other facility (%)	9 (15.3%)	27 (17.2%)	0.7328
ASM status for survivors, <i>N</i> = 180	N1 = 50	N2 = 130	
Past history of epilepsy among survivors	9 (18.0%)	29 (22.3%)	0.5259
ASM number (before admission) (%)			
0 (Non-user)	38 (76.0%)	87 (66.9%)	0.2364
User	12 (24.0%)	43 (33.1%)	0.2364
1	4 (8.0%)	22 (16.9%)	0.1586
2	4 (8.0%)	15 (11.5%)	0.5960
3	2 (4.0%)	4 (3.1%)	0.6704
4	1 (2.0%)	1 (0.8%)	0.4795
5	0 (0%)	1 (0.8%)	1.0000
6	1 (2%)	0 (0%)	0.2778
Average ASM class number (SD)	0.56 (1.23)	0.56 (0.96)	0.9937
ASM number (discharge) (%)			
0 (Non-user)	8 (16.0%)	14 (10.8%)	0.3372
User	42 (84.0%)	116 (89.2%)	0.3372
1	30 (60.0%)	72 (55.4%)	0.5757
2	7 (14.0%)	27 (20.8%)	0.2987
3	3 (6.0%)	9 (6.9%)	1.0000
4	0 (0%)	5 (3.8%)	0.3242
5	0 (0%)	2 (1.5%)	1.0000
6	2 (4.0%)	1 (0.8%)	0.1871
Average ASM class number (SD)	1.30 (1.22)	1.45 (1.09)	0.4363
Added on average ASM class number (SD)	0.74 (0.63)	0.92 (0.85)	0.1355

ASM: antiseizure medication. BG: basal ganglion. BUN: blood urea nitrogen. CCI: Charlson Comorbidity Index. CKD: chronic kidney disease. CM: cerebral microbleed. Crea: creatinine. CS: centrum semiovale. CSVD: cerebral small vessel disease. CT: computed tomography. DM: diabetes mellitus. EPVS: enlarged

perivascular space. ESCI: Epilepsy-Specific Comorbidity Index. HF: heart failure. HTN: hypertension. IQR: interquartile range. MRI: magnetic resonance imaging. Q1: the first quartile. Q3: the third quartile. SD: standard deviation. WMHI: white matter hyperintensity.

¹Recent brain injury: recent stroke, brain tumor, or anoxic brain injury

²Chronic brain injury: old stroke, encephalomalacia, traumatic brain injury, or surgical brain injury

³Developmental anomaly: cortical dysplasia, mesial temporal sclerosis, vascular anomaly, or microcephaly

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table legends: Patients with CSIDs had significantly more prevalent hippocampal atrophy, severe CT CSVD scores, and severe MRI CSVD scores than did those without CSIDs. The features that differed significantly on MRI were deep white matter hyperintensity, periventricular white matter hyperintensity, and basal ganglion EPVS. No significant differences were observed between groups in survival rates and ASM prescriptions.

Table 2. Clinical and Radiological Profiles of Patients with Seizures with Mild versus Severe CSIDs

	Without septic shock or bacteremia, N1 = 108	With septic shock or bacteremia, N2 = 49	<i>p</i> value
Epidemiology, N = 157			
Age, years, range (mean ± SD)	22-95 (65.7 ± 18.3)	18-104 (66.3 ± 19.7)	0.8493
Sex, % male	53 (49.1%)	25 (51.0%)	0.8212
CCI, range (mean ± SD)	0-14 (6.3 ± 3.2)	0-14 (7.5 ± 3.6)	0.0398*
ESCI, range (mean ± SD)	0-13 (5.2 ± 3.1)	1-14 (6.3 ± 3.6)	0.0722
Past history of epilepsy (%)	23 (21.3%)	8 (16.3%)	0.4686
Seizure semiology (%)			
Generalized	59 (54.6%)	27 (55.1%)	0.9561
Focal-to-bilateral tonic-clonic	10 (9.3%)	3 (6.1%)	0.7558
Focal impaired consciousness	30 (27.8%)	15 (30.6%)	0.7159
Focal preserved consciousness	9 (8.3%)	4 (8.2%)	1.0000
Underlying disease (%)			
HTN/DM	74 (68.5%)	29 (59.2%)	0.2539
CKD/Liver disease	20 (18.5%)	14 (28.6%)	0.1565
HF/Pulmonary HTN	33 (30.6%)	26 (53.1%)	0.0070**
Malignancy	26 (24.1%)	15 (30.6%)	0.3875
Dementia	30 (27.8%)	9 (18.4%)	0.2061
Clinical/laboratory profile (%)			
Major electrolyte/glucose imbalance	34 (31.5%)	11 (22.4%)	0.2462
Recent fever	32 (29.6%)	24 (49.0%)	0.0190*
Acid–base imbalance positivity	54 (50.0%)	29 (59.2%)	0.2855
Respiratory acidosis burden	20 (18.5%)	6 (12.2%)	0.3272
Respiratory alkalosis burden	21 (19.4%)	17 (34.7%)	0.0387*
Metabolic acidosis burden	32 (29.6%)	15 (30.6%)	0.9009
Metabolic alkalosis burden	10 (9.3%)	5 (10.2%)	1.0000

High lactate ≥ 2.0 (mmol/L)	36 (33.3%)	20 (40.8%)	0.3644
Severe azotemia, BUN ≥ 90 (mg/dL)	2 (1.9%)	4 (8.2%)	0.0765
BUN/Crea ratio ≥ 20	50 (46.3%)	27 (55.1%)	0.3065
Brain disease condition (%)			
Recent brain injury ¹	28 (25.9%)	15 (30.6%)	0.5418
Chronic brain injury ²	61 (56.5%)	28 (57.1%)	0.9382
Developmental anomaly ³	6 (5.6%)	3 (6.1%)	1.0000
Radiological profile (%)			
CT or MRI, $N = 151$	N1 = 103 (missed = 5)	N2 = 48 (missed = 1)	
Hippocampal atrophy	64 (62.1%)	29 (60.4%)	0.8397
Lacunae positivity (%)	23 (22.3%)	15 (31.3%)	0.2395
Lacunae number, median (Q1–Q3, IQR, range)	0 (0–0, 0, 9)	0 (0–0, 0, 4)	0.2757
CT, $N = 148$	N1 = 100 (missed = 8)	N2 = 48 (missed = 1)	0.9164
CT CSVD score, 0–3, average (SD)	1.41 (1.20)	1.06 (1.06)	0.0767
MRI, $N = 97$	N1 = 71 (missed = 37)	N2 = 26 (missed = 23)	
MRI total CSVD score, 0–4, average (SD)	1.20 (1.24)	1.19 (1.23)	0.9863
WMHI positivity (%)	30 (42.3%)	5 (19.2%)	0.0365*
Fazekas–Deep, 0–3 (SD)	1.34 (1.13)	0.85 (0.78)	0.0190*
Fazekas–Periventricular, 0–3 (SD)	1.70 (1.18)	1.38 (1.02)	0.1968
CM positivity (%)	18 (25.4%)	7 (26.9%)	0.8755
CM, deep, median (Q1–Q3, IQR, range)	0 (0–0, 0, 68)	0 (0–0, 0, 2)	0.9283
CM, cortical, median (Q1–Q3, IQR, range)	0 (0–0, 0, 13)	0 (0–0, 0, 3)	0.8572
EPVS positivity if BG 2–4 (%)	19 (26.8%)	7 (26.9%)	0.9872
EPVS, total = BG + CS (SD)	2.20 (1.35)	2.23 (1.66)	0.9266
EPVS, BG, 0–4 (SD)	1.11 (0.85)	1.00 (0.85)	0.5660

EPVS, CS, 0–4 (SD)	1.10 (0.78)	1.23 (0.95)	0.5291
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BG: basal ganglion. BUN: blood urea nitrogen. CCI: Charlson Comorbidity Index. CKD: chronic kidney disease. CM: cerebral microbleed. Crea: creatinine. CS: centrum semiovale. CSVD: cerebral small vessel disease. CT: computed tomography. DM: diabetes mellitus. EPVS: enlarged perivascular space. ESCI: Epilepsy-Specific Comorbidity Index. HF: heart failure. HTN: hypertension. IQR: interquartile range. MRI: magnetic resonance imaging. Q1: the first quartile. Q3: the third quartile. SD: standard deviation. WMHI: white matter hyperintensity.

¹Recent brain injury: recent stroke, brain tumor, or anoxic brain injury

²Chronic brain injury: old stroke, encephalomalacia, traumatic brain injury or surgical brain injury

³Developmental anomaly: cortical dysplasia, mesial temporal sclerosis, vascular anomaly, or microcephaly

* $p < 0.05$, ** $p < 0.01$

Table legends: Among the patients with CSIDs, those with severe infections were more likely to have higher comorbidity scores, including higher Charlson Comorbidity Index values and greater heart failure or pulmonary hypertension than those without severe infections were. Additionally, these patients had a lower burden of deep WMHI than did the mild CSID group, as well as less WMHI overall, suggesting an inverse association between infection severity and chronic brain lesion burden.

Table 3. Univariate and logistic regression analysis of factors associated with mild CSID among patients with CSID

	Mild CSID, N1 = 71	Severe CSID, N2 = 26	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted <i>p</i> value
High CCI, ≥ 7	37 (52.1%)	18 (69.2%)	0.48 (0.19-1.26)	0.57 (0.13- 2.56)	0.4617
High ESCI, ≥ 6	30 (42.3%)	15 (57.7%)	0.54 (0.22-1.33)	1.24 (0.30-5.08)	0.7652
HF/Pulmonary HTN	24 (33.8%)	15 (57.7%)	0.37 (0.15-0.94)	0.32 (0.10-1.02)	0.0534
Recent fever	16 (22.5%)	14 (53.8%)	0.25 (0.10-0.65)	0.25 (0.08-0.76)	0.0143*
Respiratory alkalosis burden	13 (18.3%)	12 (46.2%)	0.26 (0.10-0.70)	0.47 (0.15-1.50)	0.2031
WMHI positivity	30 (42.3%)	5 (19.2%)	3.07 (1.04-9.08)	1.11 (0.19-6.39)	0.9071
Fazekas–Deep, severe (2-3)	25 (35.2%)	2 (7.7%)	6.52 (1.42-29.89)	10.2 (1.06-99.4)	0.0448*

CCI: Charlson Comorbidity Index. CI: confidence interval. ESCI: Epilepsy-Specific Comorbidity Index. HF: heart failure. HTN: hypertension. OR: odds ratio. WMHI: white matter hyperintensity.

* $p < 0.05$

Table legends: In the multivariable logistic regression analysis, the presence of fever showed a significant negative association with mild CSID, whereas a high Fazekas score-Deep (2–3) was significantly and positively associated with mild CSID, consistent with our earlier observations. Other variables that initially presented with $p < 0.1$ in Table 2 lost their statistical significance after adjustment.

Table 4. Comparison of Patients with and without Fever in the Mild CSID Subgroup

	Afebrile, N1 = 76	Febrile, N2 = 32	<i>p</i> value
Epidemiology, N= 108			
Age, years, range (mean ± SD)	22-92 (66.7 ± 17.5)	22-95 (63.4 ± 20.2)	0.4336
Sex, % male	34 (44.7%)	19 (59.4%)	0.1647
CCI, range (mean ± SD)	0-12 (6.3 ± 2.9)	0-14 (6.1 ± 3.8)	0.8121
ESCI, range (mean ± SD)	0-13 (5.2 ± 2.9)	0-13 (5.3 ± 3.6)	0.8377
Underlying disease (%)			
HTN/DM	56 (73.7%)	18 (56.3%)	0.0749
CKD/Liver disease	14 (18.4%)	5 (15.6%)	0.7902
HF/Pulmonary HTN	28 (36.8%)	5 (15.6%)	0.0288*
Malignancy	15 (19.7%)	11 (34.4%)	0.1042
Dementia	25 (32.9%)	5 (15.6%)	0.0673
Clinical/laboratory profile (%)			
Major electrolyte/glucose imbalance	29 (38.2%)	6 (18.8%)	0.0491*
Acid–base imbalance positivity	37 (48.7%)	17 (53.1%)	0.6734
Respiratory acidosis burden	12 (15.8%)	8 (25.0%)	0.2605
Respiratory alkalosis burden	14 (18.4%)	7 (21.9%)	0.6231
Metabolic acidosis burden	21 (27.6%)	11 (34.4%)	0.4834
Metabolic alkalosis burden	8 (10.5%)	2 (6.25%)	0.7200
High lactate ≥ 2.0 (mmol/L)	21 (27.6%)	15 (46.9%)	0.0527
Severe azotemia, BUN ≥ 90 (mg/dL)	1 (1.3%)	1 (3.1%)	0.5067
BUN/Crea ratio ≥ 20	34 (44.7%)	16 (50.0%)	0.6165
Brain disease condition (%)			
Recent brain injury ¹	19 (25.0%)	9 (28.1%)	0.7351
Chronic brain injury ²	42 (55.3%)	14 (43.8%)	0.2742
Developmental anomaly ³	3 (3.9%)	3 (9.4%)	0.3585
Radiological profile (%)			
CT or MRI, N = 103	N1 = 74 (missed = 2)	N2 = 29 (missed = 3)	

Hippocampal atrophy	47 (61.8%)	17 (58.6%)	0.3999
Lacunae positivity (%)	16 (21.6%)	7 (24.1%)	0.6452
Lacunae number, median (Q1–Q3, IQR, range)	0 (0–0, 0, 9)	0 (0–0.5, 0.5, 6)	0.8808
CT, <i>N</i> = 101	N1 = 72 (missed = 4)	N2 = 29 (missed = 3)	
CT CSVD score, 0–3, average (SD)	1.47 (1.22)	1.21 (1.15)	0.3062
MRI, <i>N</i> = 71	N1 = 55 (missed = 21)	N2 = 16 (missed = 16)	
MRI total CSVD score, 0–4, average (SD)	1.20 (1.24)	1.19 (1.28)	0.9726
WMHI positivity (%)	23 (41.8%)	7 (43.8%)	0.8905
Fazekas–Deep, 0–3 (SD)	1.35 (1.13)	1.31 (1.20)	0.9225
Fazekas–Periventricular, 0–3 (SD)	1.71 (1.21)	1.69 (1.08)	0.9459
CM positivity (%)	14 (25.5%)	4 (25.0%)	1.0000
CM, deep, median (Q1–Q3, IQR, range)	0 (0–0, 0, 68)	0 (0–0.5, 0.5, 3)	0.9203
CM, cortical, median (Q1–Q3, IQR, range)	0 (0–0, 0, 13)	0 (0–0, 0, 11)	0.8729
EPVS positivity if BG 2–4 (%)	15 (27.3%)	4 (25.0%)	1.0000
EPVS, total = BG + CS (SD)	2.16 (1.36)	2.31 (1.35)	0.7020
EPVS, BG, 0–4 (SD)	1.05 (0.80)	1.31 (1.01)	0.3603
EPVS, CS, 0–4 (SD)	1.13 (0.77)	1.00 (0.82)	0.5838

BG: basal ganglion. BUN: blood urea nitrogen. CCI: Charlson Comorbidity Index. CKD: chronic kidney disease. CM: cerebral microbleed. Crea: creatinine. CS: centrum semiovale. CSVD: cerebral small vessel disease. CT: computed tomography. DM: diabetes mellitus. EPVS: enlarged perivascular space. ESCI: Epilepsy-Specific Comorbidity Index. HF: heart failure. HTN: hypertension. IQR: interquartile range. MRI: magnetic resonance imaging. Q1: the first quartile. Q3: the third quartile. SD: standard deviation. WMHI: white matter hyperintensity.

¹Recent brain injury: recent stroke, brain tumor, or anoxic brain injury

²Chronic brain injury: old stroke, encephalomalacia, traumatic brain injury, or surgical brain injury

³Developmental anomaly: cortical dysplasia, mesial temporal sclerosis, vascular anomaly, or microcephaly

* $p < 0.05$

Table legends: Patients with CSID and fever had significantly lower rates of heart failure and pulmonary hypertension and less electrolyte or glucose imbalance than did those without. Nevertheless, no significant differences in neuroimaging markers were observed, suggesting that fever had a neutral effect on seizure risk.

Table 5. Clinical and Imaging Differences Between Patients with GPC and GNB Infections with Seizures and CSIDs

	Pure GPC, <i>N</i> 1 = 18	Pure GNB, <i>N</i> 2 = 53	<i>p</i> value
Epidemiology, <i>N</i> = 71			
Age, years, range (mean ± SD)	22-104 (66.9 ± 22.1)	25-95 (68.7 ± 16.7)	0.7533
Sex, % male	7 (38.9%)	24 (45.3%)	0.6365
CCI, range (mean ± SD)	0-12 (6.1 ± 3.9)	0-13 (6.8 ± 3.3)	0.5006
ESCI, range (mean ± SD)	0-14 (5.9 ± 4.1)	0-13 (5.3 ± 2.9)	0.5438
Underlying disease (%)			
HTN/DM	9 (50.0%)	39 (73.6%)	0.0647
CKD/Liver disease	6 (33.3%)	9 (17.0%)	0.1837
HF/Pulmonary HTN	9 (50.0%)	21 (39.6%)	0.4413
Malignancy	5 (27.8%)	12 (22.6%)	0.7514
Dementia	5 (27.8%)	11 (20.8%)	0.5306
Clinical/laboratory profile (%)			
Major electrolyte/glucose imbalance	3 (16.7%)	15 (28.3%)	0.5313
Recent fever	5 (27.8%)	19 (35.8%)	0.5317
Infection location			
Pneumonia	11 (61.1%)	25 (47.2%)	0.3067
UTI	4 (22.2%)	26 (49.1%)	0.0465*
Septic shock	3 (16.7%)	6 (11.3%)	0.6833
Bacteremia	5 (27.8%)	15 (28.3%)	0.9659
Acid–base imbalance positivity	7 (38.9%)	28 (52.8%)	0.3067
Respiratory acidosis burden	2 (11.1%)	12 (22.6%)	0.4937
Respiratory alkalosis burden	3 (16.7%)	12 (22.6%)	0.7450
Metabolic acidosis burden	6 (33.3%)	14 (26.4%)	0.5729
Metabolic alkalosis burden	0 (0%)	5 (9.4%)	0.3199
High lactate ≥ 2.0 (mmol/L)	4 (22.2%)	18 (34.0%)	0.3521
Severe azotemia, BUN ≥ 90 (mg/dL)	1 (5.56%)	3 (5.7%)	1.0000
BUN/Crea ratio ≥ 20	9 (50.0%)	8 (15.1%)	0.0080**

Brain disease condition (%)			
Recent brain injury ¹	6 (33.3%)	11 (20.8%)	0.3414
Chronic brain injury ²	6 (33.3%)	36 (67.9%)	0.0099**
Developmental anomaly ³	2 (11.1%)	3 (5.7%)	0.5952
Radiological profile			
CT or MRI, <i>N</i> = 69	N1 = 18 (missed = 0)	N2 = 51 (missed = 2)	
Hippocampal atrophy	7 (38.9%)	34 (66.7%)	0.0391*
Lacunae positivity (%)	4 (22.2%)	19 (37.3%)	0.2448
Lacunae number, median (Q1–Q3, IQR, range)	0 (0–0, 0, 9)	0 (0–1, 1, 6)	0.3628
CT, <i>N</i> = 69	N1 = 18 (missed = 0)	N2 = 51 (missed = 2)	
CT CSVD score, 0–3, average (SD)	1.06 (1.21)	1.47 (1.14)	0.2146
MRI, <i>N</i> = 41	N1 = 10 (missed = 8)	N2 = 31 (missed = 22)	
MRI total CSVD score, 0–4, average (SD)	0.80 (1.32)	1.32 (1.01)	0.2714
WMHI positivity (%)	4 (40.0%)	13 (41.9%)	1.0000
Fazekas–Deep, 0–3 (SD)	1.00 (1.05)	1.48 (1.06)	0.2264
Fazekas–Periventricular, 0–3 (SD)	1.4 (1.35)	1.97 (0.98)	0.2422
CM positivity (%)	1 (10.0%)	8 (25.8%)	0.1274
CM, deep, median (Q1–Q3, IQR, range)	0 (0–0, 0, 12)	0 (0–0, 0, 10)	0.8415
CM, cortical, median (Q1–Q3, IQR, range)	0 (0–0, 0, 1)	0 (0–0, 0, 8)	0.5029
EPVS positivity if BG 2–4 (%)	1 (10.0%)	6 (19.4%)	0.6599
EPVS, total = BG + CS (SD)	1.70 (1.64)	2.23 (1.18)	0.3651
EPVS, BG, 0–4 (SD)	0.70 (0.67)	1.06 (0.68)	0.1585
EPVS, CS, 0–4 (SD)	1.00 (1.05)	1.16 (0.73)	0.6608
Offending antibiotics (Cefepime, imipenem, ertapenem & meropenem)	0 (0%)	6 (11.3%)	0.3072

BG: basal ganglion. BUN: blood urea nitrogen. CCI: Charlson Comorbidity Index. CKD: chronic kidney disease. CM: cerebral microbleed. Crea: creatinine. CS: centrum semiovale. CSVD: cerebral small vessel

disease. CT: computed tomography. DM: diabetes mellitus. EPVS: enlarged perivascular space. ESCI: Epilepsy-Specific Comorbidity Index. GNB: Gram-negative bacillus. GPC: Gram-positive coccus. HF: heart failure. IQR: interquartile range. HTN: hypertension. MRI: magnetic resonance imaging. Q1: the first quartile. Q3: the third quartile. SD: standard deviation. WMHI: white matter hyperintensity.

¹Recent brain injury: recent stroke, brain tumor, or anoxic brain injury

²Chronic brain injury: old stroke, encephalomalacia, traumatic brain injury, or surgical brain injury

³Developmental anomaly: cortical dysplasia, mesial temporal sclerosis, vascular anomaly, or microcephaly

* $p < 0.05$, ** $p < 0.01$

Table legends: In patients with CSID with positive cultures, the pure GNB subgroup had significantly more UTIs and a less extreme BUN/creatinine ratio than the pure GPC group did. Patients with GPC infections exhibited a significantly lower burden of chronic brain injury and hippocampal atrophy than did those with GNB infections, suggesting that GPC-related seizures may be observed in the setting of less extensive preexisting brain pathology, supporting the proposed “Inverse model” of systemic inflammation and seizure susceptibility.

Figures

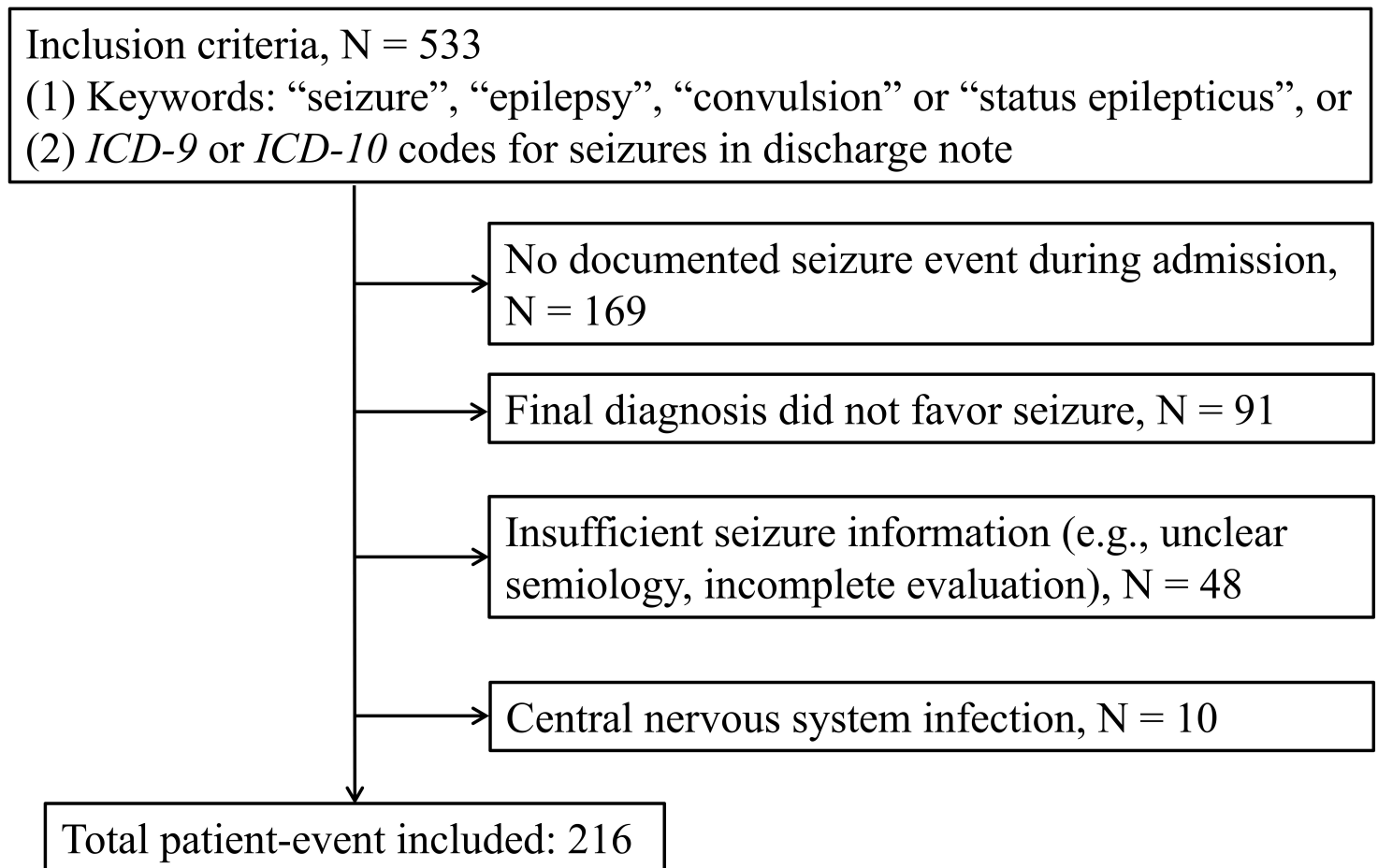
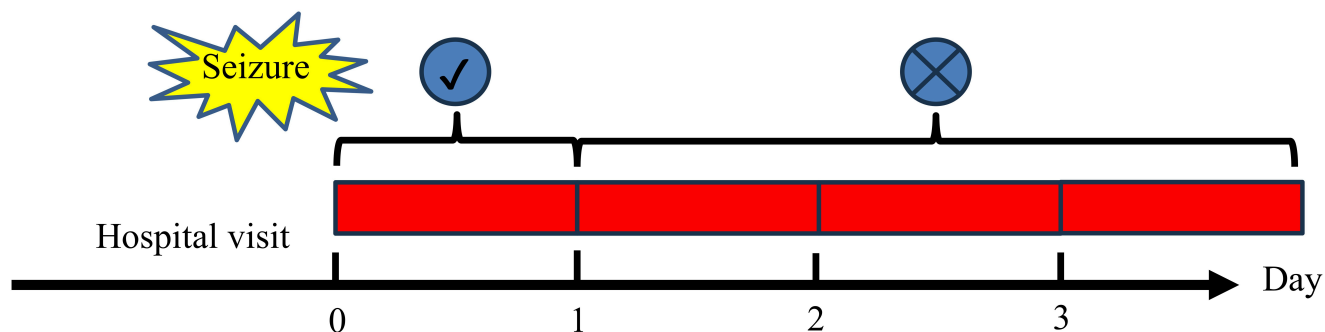


Figure 1

Flowchart of Patient Inclusion and Exclusion

After medical record and *International Classification of Diseases* code database screening, 533 patients met the inclusion criteria. After manual selection, 169 patients were excluded for having no seizure events, 91 were excluded for having received final diagnoses other than seizure, 48 were excluded for lacking critical information, and 10 were excluded for having received a diagnosis of a central nervous system infection. Ultimately, 216 patient–events were included in the analysis. Figures were created using *PowerPoint, Microsoft* for digital illustration

a. Infection concurrent or shortly after seizure



b. Seizure within treatment course of infection

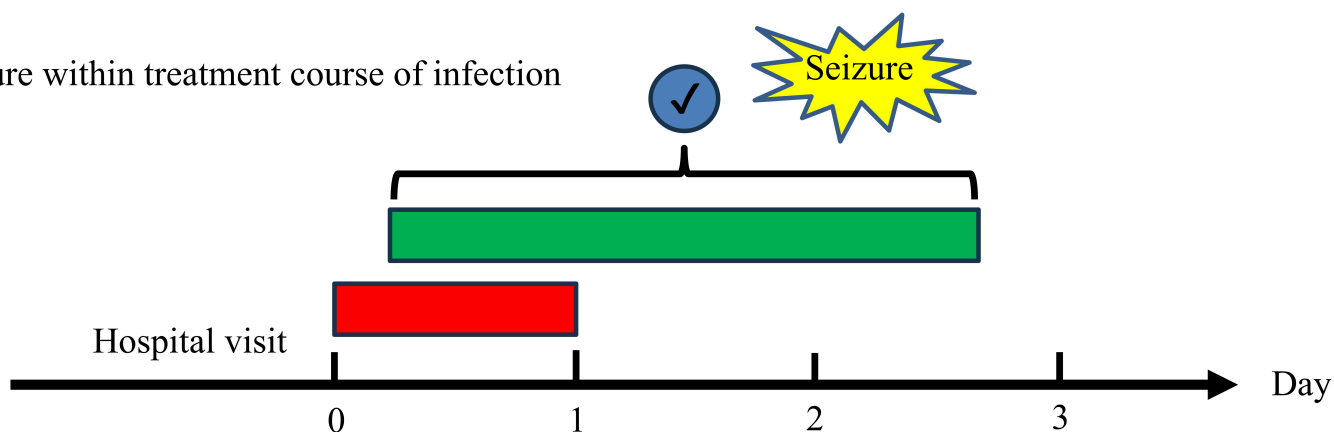


Figure 2

CSID Inclusion and Exclusion Criteria

Figure 2 illustrates the inclusion criteria for CSID. The definition emphasizes “concurrent” occurrence of systemic infection and seizure. a. CSID was defined when systemic infection was detected at the time of seizure onset or within 24 hours thereafter, as confirmed by clinical signs, antibiotic initiation, and microbiologic workup. Infections developing more than 24 hours post-seizure were excluded. b. CSID was also defined when seizures occurred during the ongoing treatment of a documented systemic infection. Figures were created using *PowerPoint, Microsoft* for digital illustration

*Red bar: onset of certain systemic infectious diseases

*Green bar: treatment course for certain systemic infectious diseases

*Tick mark: systemic infectious disease included as CSID

*Cross mark: systemic infectious disease excluded from CSID

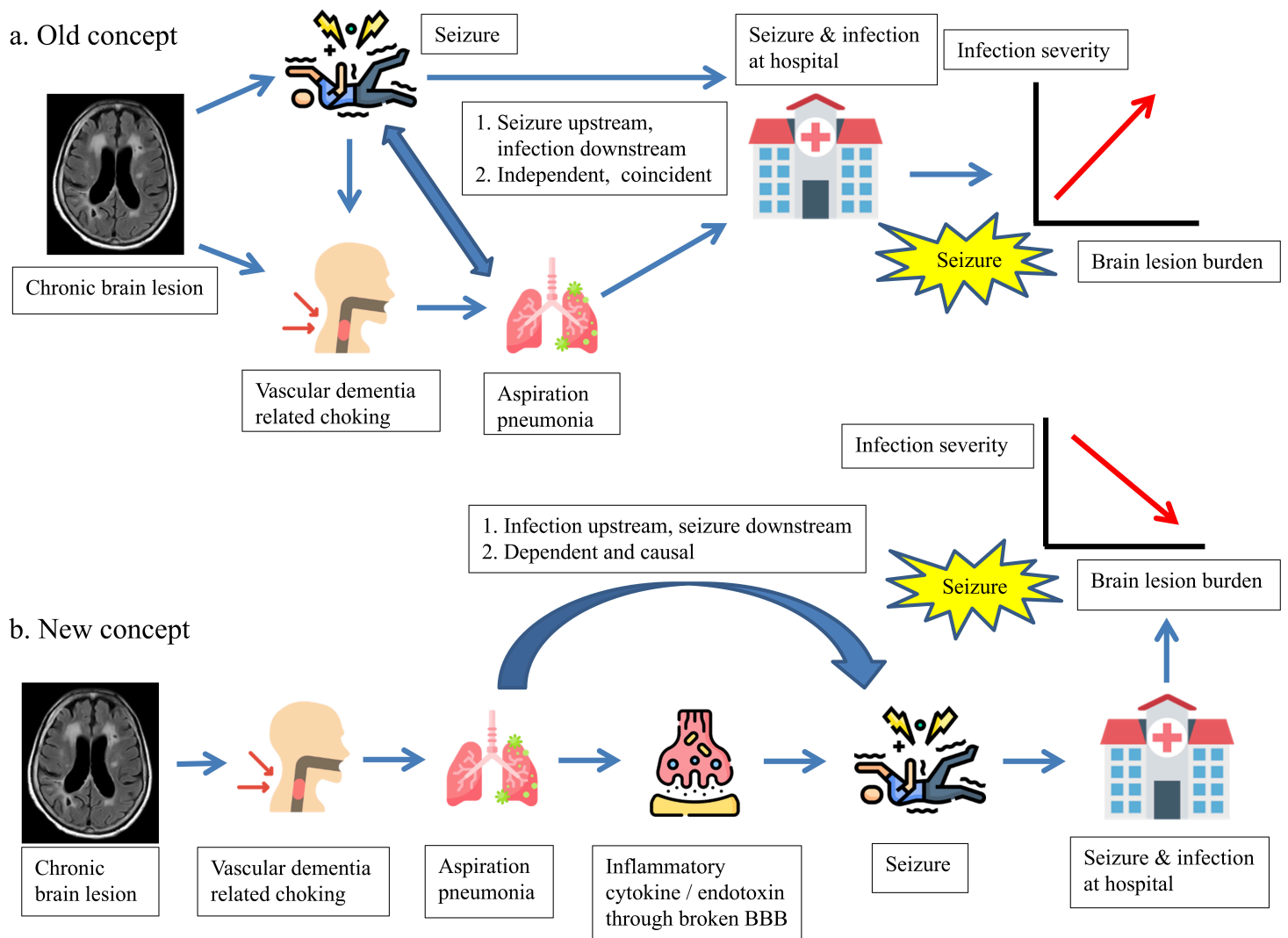


Figure 3

Hypothesis A: Parallel Increase Versus Hypothesis B: Inverse Model

a. In the traditional conception of seizures, in the relationship between seizures and systemic infectious diseases, seizures are considered to be antecedents of diseases or coincidences. When presenting at medical institutions with seizure and concurrent systemic infectious diseases, patients with frailty typically experience more severe infections and more extensive brain pathology than those without frailty do, whereas more robust patients present with milder infection and fewer imaging abnormalities (parallel increase). b. In the newer "Inverse model" conception of seizures advocated for in the present study, in the relationship between seizures and systemic infectious disease, infections are considered antecedents, seizures sequelae, and infection-related inflammatory cytokines or pathogenic toxins mediators through the breaking of the blood–brain barrier. When presenting at medical institutions with seizures and concurrent systemic infectious diseases, patients with more resilient brains and fewer structural abnormalities tend to present with more severe systemic inflammation when seizures occur, whereas those with more vulnerable brains may develop seizures in association with even mild

infections (inverse model). Figures were created using *FlatIcon* and *PowerPoint, Microsoft* for digital illustration.

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