ORIGINAL ARTICLE

The Incidence and Associated Risk factors for Postencephalitic Seizures and Postencephalitic Epilepsy

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Background: Postencephalitic seizure and postencephalitic epilepsy show an association with increases in morbidity and mortality. Currently, Thailand's data regarding the incidence and associated risk factors for these conditions are limited.

Objective: To investigate the incidence of postencephalitic seizure and postencephalitic epilepsy among Thai people and identify the associated risk factors.

Materials and Methods: The present study aimed to investigate all patients who experienced acute encephalitis at the Faculty of Medicine Vajira Hospital between January 1, 2013 and December 31, 2022. Patients manifesting seizures were classified into two groups, namely, the postencephalitic seizure and postencephalitic epilepsy groups, based on the definition of International League Against Epilepsy.

Results: Of 197 patients with no history of epilepsy and who presented with acute encephalitis, 41 (20.8%) developed seizures. Specifically, 20 patients (10.1%) belonged to the postencephalitic seizure group and 21 (10.7%) to the postencephalitic epilepsy group. Multivariate analysis revealed that patients aged 60 years or younger are more likely to develop seizures than those without.

Conclusion: The incidences of postencephalitic seizures and postencephalitic epilepsy were 10.1% and 10.7%, respectively. Age ≤ 60 years old was associated more with the patients who experienced seizures compared with those who did not.

Keywords: Postencephalitic seizures; Postencephalitic epilepsy; Acute encephalitis; Seizure

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Encephalitis, which is characterized by inflammation of the brain parenchyma due to infectious or immunemediated processes, shows an association with substantial morbidity and mortality. Acute encephalitis causes seizures and epilepsy⁽¹⁻³⁾. Seizures resulting from this condition can be categorized into two types based on the 2010 definition of the International League Against Epilepsy (ILAE). Early postencephalitic seizures or acute symptomatic seizures that occur within 7 days after acute e ncephalitis are not classified as epilepsy. By contrast, postencephalitic epilepsy includes seizures that occur after day 7 following acute encephalitis^(4,5). Currently, Thailand's data regarding the

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incidence and associated risk factors of postencephalitic seizures and postencephalitic epilepsy are limited.

This retrospective cross-sectional study aimed to investigate the incidences of postencephalitic seizures and postencephalitic epilepsy among the Thai population and identify the associated risk factors.

Objectives

The primary objective of this study was to examine the incidences of postencephalitic seizures and postencephalitic epilepsy among Thai patients.

The secondary objective was to identify the associated risk factors for seizures and epilepsy in patients with acute encephalitis.

Materials and Methods Study design

This retrospective cross-sectional research was aimed at the investigation of patients who were diagnosed with acute encephalitis at the Faculty of Medicine Vajira Hospital between January 1, 2013, and December 31, 2022. Our electronic data search system was used to identify cases with a final diagnosis of encephalitis, and confirmation was made through a review of medical records. Patients who developed acute encephalitis were categorized into those with and without seizures. Subsequently, the seizure group was further classified into two subgroups: the postencephalitic seizure group and the postencephalitic epilepsy group. To identify patients who did not experience seizures, we confirmed by the follow-up information for at least three months after the diagnosis of acute encephalitis. The follow-up allowed us to gather information and identify the associated risk factors through the comparison of patients with and without seizures. The University Institutional Review Board approved the conduct of this study (study code: 020/66 E, COA 082/2566).

Study definitions

Encephalitis was defined via the presentation of an altered mental status (decreased or altered level of consciousness, lethargy, or personality change) lasting more than 24 h, with at least three of the following associated manifestations: (1) temperature $\geq 38^{\circ}$ C within 72 h of presentation, (2) focal, generalized, or unknown onset seizures not attributable to a preexisting seizure disorder, (3) new onset focal neurologic deficits, (4) cerebrospinal fluid (CSF) white blood cell count \geq 5/mm³, (5) abnormal brain parenchyma during neuroimaging, and (6) abnormal electroencephalography (EEG) consistent with encephalitis and is not attributable to another cause^(6,7). An immunocompromised state was defined as a diagnosis with human immunodeficiency virus infection or acquired immunodeficiency syndrome (HIV/ AIDS), posttransplantation, or receiving chemotherapy or chronic immunosuppressant medications. Patients were categorized into four groups: viral encephalitis, autoimmune encephalitis, cerebritis, and encephalitis of unknown/other etiology groups. The patients were categorized into the viral encephalitis group only if their CSF showed a positive antibody titer, positive polymerase chain reaction result, CSF culture, or confirmatory histopathologic findings. Autoimmune encephalitis was defined by the presence of an antigen-specific antibody in serum/CSF or by histopathological evidence compatible with the diagnosis in brain biopsy. Cerebritis was defined using CSF culture or hemoculture of positive bacteria or other nonviral pathogens. All other patients who could not be categorized into any of the three categories were segregated into a fourth category. Coma was defined as a Glasgow Coma Scale (GCS) sum score ≤ 8 . Seizures were defined clinically or via EEG confirmation. Status epilepticus (SE) refers to a tonic-clonic seizure activity lasting longer than 5 min or focal seizures without regaining consciousness between seizures for >10 min or absence of seizure activity lasting longer than 5 to 10 min⁽⁸⁾.

Inclusion criteria

1) All patients meeting the specified criteria for acute encephalitis were admitted to the hospital.

2) Age ≥ 15 years.

Exclusion criteria

1) Patients with a previous or present history of brain tumors.

2) Patients with a history of neurosurgical procedures.

3) Patients with traumatic intracranial bleeding.

4) Patients with a history of toxic substance abuse.

5) Patients with a history of epilepsy before admission.

6) Patients with encephalopathy secondary to other causes, such as toxins, sepsis, or metabolic factors.

Data analysis

Baseline characteristics were analyzed using percentages and p-values. The study on the incidence of postencephalitic seizures and epilepsy reported the results in percentages. In addition, the investigation of associated risk factors, which involved the comparison of patients with and without seizures, initially utilized the Chi-squared test. Subsequently, binary logistic regression analysis was conducted, and the results were presented as odds ratios (OR) with a 95% confidence interval (CI). IBM SPSS Statistics, version 29.0 was used in the analyses.

Selection bias

The sample group, where ICD10 encephalitis was the primary diagnosis and seizures were complications, was recorded by medical personnel from various fields. However, this data might not accurately reflect the true condition. Therefore, it was corrected by manually reviewing the medical history of the entire sample.

Bias from data collection and questionnaires

From a review of samples recorded in the Ephis database and patient medical records, it was evident that certain factors associated with postencephalitic seizure and postencephalitic epilepsy remained unclear. To rectify this, additional information was gathered by studying laboratory test results and consulting with the physicians responsible for recording the information.

Results

A total of 197 patients had acute encephalitis. Among these patients, 50.3% were male. The majority of patients were aged over 60 years, and 97% were Thai. The three major comorbidities were hypertension (31%), immunocompromised host (27.4%), and type 2 diabetes mellitus (23.9%). Among immunocompromised hosts, 61.1% were HIV patients, and 38.9% were non-HIV individuals (Table 1).

 Table 1. Demographic and clinical characteristics of patients (n=197)

Characteristics	n (%)
Sex	
Male	99 (50.3)
Female	98 (49.7)
Age (years)	
16 to 40	55 (27.9)
40 to 60	63 (32.0)
>60	79 (40.1)
Race	
Thai	191 (97.0)
Foreigner	6 (3.0)
Comorbidity	
Immunocompromised host	54 (27.4)
Hypertension	61 (31.0)
Diabetic mellitus	47 (23.9)
Dyslipidemia	38 (19.3)
Cardiovascular disease	14 (7.1)
Old cerebrovascular disease	11 (5.6)
Atrial fibrillation	7 (3.6)
Immunocompromised host, (n=54)	
HIV disease	33 (61.1)
Other	21 (38.9)
HIV disease, (n=33)	
CD4 level	
≤100	10 (30.3)
101 to 200	8 (24.2)
201 to 500	7 (21.2)
>500	2 (6.1)
Not exam	6 (18.2)
on Antiretroviral drugs	
Yes	9 (27.3)
No	24 (72.7)
Glasgow Coma Scale (GCS)	
<8	40 (20.3)
>8	157 (79.7)
Fever	142 (72.1)
Time before admission	()
<1 week	186 (94.4)
>1 week	11 (5.6)
Etiology of encephalitis	(0.0)
Viral infection	41 (20.8)
Autoimmune encenhalitis	4 (2.0)
Encephalitis of unknown/other etiology	62 (31 5)
Cerebritis	90 (45 7)
Bacterial cerebritis	77 (39.1)
Fungus cerebritis	7 (3.6)
Parasite cerebritis	1 (0.5)
Protozoa cerebritis	10 (5 1)
	10 (0.1)

Table 1. Cont.

Characteristics	n (%)
Seizure classification	
Convulsive Seizure	41 (20.9)
Focal onset	33 (80.5)
Generalize onset	2 (4.9)
Unknown onset	6 (14.6)
Status epilepticus	4 (9.8)
Onset of seizure	
≤1 week	20 (10.1)
>1 week	21 (10.6)
Anti-seizure medications (ASMs)	
Monotherapy	33 (80.5)
Polytherapy	7 (17.1)
Cerebrospinal fluid (CSF) finding	
CFS protein abnormality	165 (83.8)
CFS glucose abnormality	96 (48.7)
CSF nucleated cell abnormality	175 (88.8)
Viral panel abnormality	41 (20.8)
Autoimmune panel abnormality	4 (2.0)
Imaging abnormalities	
Normal	119 (60.4)
Abnormal	78 (39.6)
Lesion, (n=78)	
Cortical involvement	20 (25.6)
No cortical involvement	58 (74.4)
Electroencephalogram (EEG)	
Normal	6 (3.0)
Abnormal	25 (12.7)
Not done	166 (84.3)

Table 2. Incidence of postencephalitic seizure and epilepsy (n=197)

Variables	n (%)
Seizure	41 (20.8)
Postencephalitic epilepsy	21 (10.7)
Death at admission	5 (2.5)
Postencephalitic seizure	20 (10.1)
Death at admission	8 (4.0)
No seizure	156 (79.2)
Death at admission	26 (13.2)
No follow-up	47 (23.9)
Follow at least 3 months, no seizure	83 (42.1)

A total of 41 patients (20.8%) developed seizures. The incidence of postencephalitic seizures and epilepsy was 10.1% and 10.7%, respectively (Table 2).

Analysis of the general characteristics of patients with seizures revealed an even distribution between males and females. Postencephalitic seizures and postencephalitic epilepsy exhibited similar age distributions and predominantly affected individuals under 60 years of age, particularly the Thai population. No significant differences were observed in comorbidities between postencephalitic seizures and postencephalitic epilepsy. Both groups displayed a GCS above 8, and the time before admission was less than one week. The major etiologies in this study included bacterial infection, unknown etiology, viral infection, and autoimmune causes, In subsequent analysis, seizure classifications in both groups encompassed focal onset, unknown onset, and generalized onset. SE occurred similarly in each group. The postencephalitic seizure group demonstrated a higher incidence of abnormal imaging (p=0.041). Conversely, lesions involving the cortex were more prevalent in the postencephalitic epilepsy group (p=0.041) (Table 3).

Mortality between patients with postencephalitic seizures and those with postencephalitic epilepsy showed no significant difference in the present study (Table 4).

Comparison of patients with and without seizures through crude analysis revealed the statistical significance of associated risk factors, with p<0.05. GCS higher than 8 exhibited an association with the absence of seizures in patients with acute encephalitis (p=0.040).

In the univariate analysis, simple logistic regression identified ages 16 to 40 years (unadjusted OR=2.8, 95% CI: 1.09 to 7.19, and p=0.033) and GCS \leq 8 (unadjusted OR=4.07, 95% CI: 1.12 to 14.81, and p=0.033) as risk factors for postencephalitic seizure and postencephalitic epilepsy but on multivariate analysis using multiple logistic regression detected only ages less than 60 (16 to 40 years, adjusted OR=3.56, 95% CI: 1.28 to 9.89, p=0.015; 40 to 60 years, adjusted OR=3.03, 95% CI: 1.12 to 8.24, p=0.030) was defined as a risk factor for postencephalitic seizure and postencephalitic epilepsy (Table 5).

Discussion

This study aimed to determine the incidence of postencephalitic seizures and postencephalitic epilepsy based on the 2010 ILAE definition of acute symptomatic seizures^(4,5). In the past, the definition of seizure and epilepsy was unclear until the 2010 ILAE definition was released, so the incidence and the potentially associated risk factors of acute symptomatic seizure and epilepsy need to be clarified due to the difference in management.

In the present study, it was found that one-fourth of Thai people diagnosed with acute encephalitis experienced seizures, which was relatively low when compared to the prior study^(9,10). One reason for the difference in incidence could be the difference in the definition of epilepsy. Additionally, the present study only considered patients who had clinical seizures, and the number of EEG recordings was only 15.7%, which could result in some patients with non-convulsive seizures being missed.

The present study found that there were no significant differences in comorbidities between the postencephalitic seizure and postencephalitic epilepsy groups. Both groups had a balanced gender distribution and prevalence in individuals under 60 years of age, particularly in the Thai population. The etiologies comprised bacterial infection, viral infection, unknown/other etiology, and autoimmune causes, and they were the same in both groups. The group with postencephalitic seizures displayed more abnormal imaging results, while the postencephalitic epilepsy group showed more lesions in the cortex and abnormal electroencephalography. Seizure classifications, SE, and mortality rates were comparable.

Multivariable analysis using multiple logistic regression identified age ≤ 60 years as a risk factor for both seizure subgroups (postencephalitic seizure and postencephalitic epilepsy) when compared with the no-seizure group. However, this differs from the prior study, which found that abnormal MRI and the presence of early seizure were the potential risks associated with postencephalitic epilepsy. The longer follow-up period of at least 1 year after the onset of acute encephalitis may increase the incidence of postencephalitic epilepsy⁽⁵⁾. The difference between the age groups may reflect the different causes of encephalitis that could not be identified, such as some of the autoimmune encephalitis antibodies that were identified in the recent past or other viruses rather than the herpes group. Some cases might have been diagnosed as unknown causes.

The present study encountered some limitations, such as the retrospective nature of the work and certain incomplete information limiting conclusive findings. An autoimmune panel was conducted in only 2% of all acute encephalitis patients, as well as and an EEG was performed in only 15.7%. Additionally, the study predominantly involved Thai patients in a single center, which might not be representative of other populations. Finally, the low occurrence of developing seizures resulted in insufficient statistical significance during subgroup analysis to identify the potential predictors of postencephalitic seizures and epilepsy.

Identifying the clear causes of acute encephalitis and awareness of nonconvulsive seizures by EEG monitoring in postencephalitic patients, especially those who had altered mental status or changes in behavior, are vital for improving patient care by early management and can significantly impact the quality of life and neurological recovery in affected individuals.

Conclusion

Postencephalitic seizures and postencephalitic epilepsy achieved occurrence rates of 10.1% and 10.7%, respectively. Patients aged ≤ 60 years showed an association

Table 3. Comparison of demographic and clinical characteristics between patients with postencephalitic seizure and those with postencephalitic epilepsy

Variables	Total (n=41)	Postencephalitic seizure (n=20)	Postencephalitic epilepsy (n=21)	p-value
	n (%)	n (%)	n (%)	
Sex				
Male	19 (46.3)	10 (50.0)	9 (42.9)	0.647
Female	22 (53.7)	10 (50.0)	12 (57.1)	
Age (years)				
16 to 40	15 (36.6)	8 (40.0)	7 (33.3)	0.905
41 to 60	15 (36.6)	7 (35.0)	8 (38.1)	
>60	11 (26.8)	5 (25.0)	6 (28.6)	
Race				
Thai	40 (97.6)	19 (95.0)	21 (100)	0.488
Foreigner	1 (2.4)	1 (5.0)	0 (0.0)	
Comorbidity				
Immunocompromised host	11 (26.8)	5 (25.0)	6 (28.6)	0.796
Hypertension	10 (24.4)	4 (20.0)	6 (28.6)	0.719
Diabetic mellitus	8 (19.5)	5 (25.0)	3 (14.3)	0.454
Dyslipidemia	6 (14.6)	1 (5.0)	5 (23.8)	0.184
Cardiovascular disease	1 (2.4)	0 (0.0)	1 (4.8)	1.000
Old cerebrovascular disease	2 (4.9)	0 (0.0)	2 (9.5)	0.488
Atrial fibrillation	1 (2.4)	0 (0.0)	1 (4.8)	1.000
Immunocompromised host, (n=11)				
HIV disease	8 (72.7)	4 (80.0)	4 (66.7)	1.000
Other	3 (27.3)	1 (20.0)	2 (33.3)	
HIV disease, (n=8)				
CD4 level				
≤100	3 (37.5)	0 (0.0)	3 (75.0)	0.143
101 to 200	2 (25.0)	1 (25.0)	1 (25.0)	
201 to 500	2 (25.0)	2 (50.0)	0 (0.0)	
Not exam	1 (12.5)	1 (25.0)	0 (0.0)	
on Antiretroviral drugs				
Yes	4 (50.0)	3 (75.0)	1 (25.0)	0.486
No	4 (50.0)	1 (25.0)	3 (75.0)	
Glasgow Coma Scale (GCS)				
≤8	7 (17.1)	3 (15.0)	4 (19.0)	1.000
>8	34 (82.9)	17 (85.0)	17 (81.0)	
Fever	32 (78.0)	15 (75.0)	17 (81.0)	0.719
Time before admission	26 (05 0)	45 (05 0)	10 (00 5)	0.670
≤1 week	36 (87.8)	17 (85.0)	19 (90.5)	0.663
>1 week	5 (12.2)	3 (15.0)	2 (9.5)	
Etiology of encephalitis	11 (2(0)	F (2F 0)	((20, ()	0.707
	11 (26.8)	5 (25.0)	6 (28.6)	0.796
Autoimmune encephailtis	2 (4.9)	0 (0.0)	2 (9.5)	0.488
Carebritie	10 (24.4)	5 (25.0)	5 (23.8)	0.442
Cerebrius Pactavial carebritia	18 (43.9)	10 (50.0)	δ (38.1) 6 (20.4)	0.443
Datterial Cerebritic	14 (34.1)	δ (40.0) 1 (E 0)	0 (28.6)	0.440
Parasite corebritie	3 (7.3)	1 (3.0)	2 (9.5)	1.000
Protozoa cerebritis	3 (7 3)	1 (5.0)	2 (9 5)	1 000
i rotozou terebitus	5 (7.5)	1 (3.0)	2 (9.5)	1.000

The p-value corresponds to the Chi-square test or Fisher's exact test.

Table 3. Cont.

Variables	Total (n=41)	Postencephalitic seizure (n=20)	Postencephalitic epilepsy (n=21)	p-value
	n (%)	n (%)	n (%)	
Seizure classification				
Focal onset	33 (80.5)	16 (80.0)	17 (81.0)	1.000
Generalize onset	2 (4.9)	0 (0.0)	2 (9.5)	0.488
Unknown onset	6 (14.6)	4 (20.0)	2 (9.5)	0.410
Status epilepticus	4 (9.8)	2 (10.0)	2 (9.5)	1.000
Anti-seizure medications (ASMs)				
Monotherapy	33 (80.5)	17 (85.0)	16 (76.2)	1.000
Polytherapy	7 (17.1)	3 (15.0)	4 (19.0)	
Cerebrospinal fluid (CSF) finding				
CFS protein abnormality	36 (87.8)	18 (90.0)	18 (85.7)	0.606
CFS glucose abnormality	20 (48.8)	12 (60.0)	8 (38.1)	0.158
CSF nucleated cell abnormality	38 (92.7)	19 (95.0)	19 (90.5)	0.488
Viral panel abnormality	10 (24.4)	3 (15.0)	7 (33.3)	0.277
Autoimmune panel abnormality	2 (4.9)	0 (0.0)	2 (9.5)	0.356
Imaging abnormalities				
Normal	22 (53.7)	14 (70.0)	8 (38.1)	0.041
Abnormal	19 (46.3)	6 (30.0)	13 (61.9)	
Lesion, (n=19)				
Cortical involvement	11 (57.9)	1 (16.7)	10 (76.9)	0.041
No cortical involvement	8 (42.1)	5 (83.3)	3 (23.1)	
Electroencephalogram (EEG)				
Abnormal	12 (29.3)	4 (20.0)	8 (38.1)	0.203
Not done	29 (70.7)	16 (80.0)	13 (61.9)	

The p-value corresponds to the Chi-square test or Fisher's exact test.

 Table 4. Mortality between patients with postencephalitic seizures

 and those with postencephalitic epilepsy

Variables	Mortality		p-value
	Survive (n=28)	Death (n=13)	
·	n (%)	n (%)	
Postencephalitic epilepsy	16 (76.2)	5 (23.8)	0.326
Postencephalitic seizure	12 (60)	8 (40)	

The p-value corresponds to Fisher's exact test

with the experience of seizures compared with those without. However, the study encountered a limitation in the identification of the potential predictors of postencephalitic seizures and epilepsy because of the low incidence of seizures identified.

What is already known on this topic?

Encephalitis is a common cause of seizures and epilepsy. However, in 2010, the ILAE introduced new definitions for seizures and epilepsy, which has resulted in various treatment plans. A clear description is crucial for the identification of risk factors for patients with encephalitis who may develop seizures or epilepsy later on. However, information regarding the incidence of seizures and epilepsy in Thai people who suffer from encephalitis is limited. Having access to such information can lead to effective treatment planning.

What this study adds?

This study revealed a lower incidence of seizures and epilepsy after encephalitis in Thai people than in populations of other countries. However, given the low incidence of seizures, risk factors that differentiate between seizures and postencephalitic epilepsy are difficult to identify. Nevertheless, new data suggest that individuals under the age of 60 years and with encephalitis are more likely to experience seizures after encephalitis.

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Conflicts of interest

The authors declare no conflict of interest.

Table 5. Univariate and multivariate analyses using multiple logistic regression analysis of risk factors associated with postencephalitic
seizures and postencephalitic epilepsy with no seizures

r Univariable analysis		lysis	Multivariable analysis		
	Crude OR ¹ (95% CI)	p-value	Adjusted OR ² (95% CI)	p-value	
Female	1.03 (0.49 to 2.17)	0.946			
Age (years)					
16 to 40	2.80 (1.09 to 7.19)	0.033	3.56 (1.28 to 9.89)	0.015	
41 to 60	2.54 (1.00 to 6.47)	0.050	3.03 (1.12 to 8.24)	0.030	
>60	1.00 Reference		1.00 Reference		
Race					
Thai	1.00 Reference				
Foreigner	1.01 (0.09 to 11.50)	0.992			
Comorbidity					
Immunocompromised host	1.16 (0.49 to 2.72)	0.741			
Hypertension	0.60 (0.26 to 1.40)	0.236			
Diabetic mellitus	0.53 (0.22 to 1.31)	0.169			
Dyslipidemia	0.54 (0.20 to 1.47)	0.228			
Cardiovascular disease	0.32 (0.04 to 2.76)	0.300			
Old Cerebrovascular disease	1.01 (0.18 to 5.77)	0.989			
Atrial fibrillation	0.67 (0.07 to 6.62)	0.729			
GSC ≤8	4.07 (1.12 to 14.81)	0.033	2.59 (0.68 to 9.88)	0.163	
Fever	1.45 (0.60 to 3.48)	0.410			
The time before admission >1 week	2.74 (0.70 to 10.82)	0.150			
Etiology of encephalitis					
Viral infection	0.96 (0.41 to 2.22)	0.918			
Autoimmune encephalitis	2.08 (0.28 to 15.3)	0.473			
Encephalitis of unknown/other etiology	0.54 (0.23 to 1.25)	0.152			
Cerebritis	1.62 (0.75 to 3.50)	0.217			
Cerebrospinal fluid (CSF) finding					
CFS protein abnormality	1.13 (0.32 to 3.90)	0.853			
CFS glucose abnormality	1.31 (0.62 to 2.81)	0.481			
CSF nucleated cell abnormality	0.99 (0.17 to 5.63)	0.988			
Viral panel abnormality	0.95 (0.40 to 2.28)	0.913			
Autoimmune panel abnormality	0.33 (0.01 to 12.82) ^a	0.555			
Imaging abnormalities	1.89 (0.88 to 4.09)	0.104			

OR=odds ratio; ORadj=Adjusted Odds Ratio; CI=confident interval; NA=data not applicable.

¹ Crude Odds Ratio estimated by Binary logistic regression model or logistic regression model with the Firth method (Firth's Bias Reduced Logistic Regressions)^a.

² Adjusted Odds Ratio estimated by Multiple logistic regression model with the Firth method (Firth's Bias Reduced Logistic Regression).

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