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Mind the Gap: Autoimmune versus Infectious Encephalitis in Children. A Retrospective Cohort Study from a Tertiary Centre, Riyadh, Saudi Arabia (2020–2026)

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Abstract

Purpose

Autoimmune encephalitis (AE) and infectious encephalitis (IE) share a presenting syndrome but require opposing treatment, often before antibody results are available. We compared children with AE and IE and developed a bedside score to distinguish them at presentation.

Methods

Children aged 0–18 years with AE or infectious encephalitis/meningoencephalitis admitted to a tertiary centre in Riyadh, Saudi Arabia (January 2020–July 2026) were retrospectively compared. A score derived by logistic regression from pre-serological variables underwent bootstrap, temporal, and subgroup validation and was compared with an adapted adult-derived (Granillo) score.

Results

Of 214 eligible children, 22 met both definitions; of the remaining 192 (70 AE, 122 IE), those with AE were older (median 9.2 vs 0.7 years) and more often had psychiatric or behavioural symptoms (51.4% vs 4.1%) and a normal cerebrospinal fluid (CSF) white cell count (84.1% vs 24.7%; both $p < 0.001$); seizures were equally frequent (49.3% vs 49.2%). Only 17.5% of children with AE, versus 64.2% with IE, were diagnosed within 1 week. The King Fahad Medical City (KFMC) AE-IE Score (age, psychiatric or behavioural symptoms, normal CSF cell count) achieved an area under the receiver operating characteristic curve of 0.93, outperformed the adapted Granillo score (0.89; $p = 0.012$), and retained discrimination in children aged ≥ 2 years (0.87) and in consensus-defined encephalitis (0.97). A score ≥ 10 had 83% sensitivity and 91% specificity.

Conclusion

Simple features available at presentation distinguish paediatric AE from IE. The KFMC AE-IE Score requires prospective external validation.

What is Known

- Autoimmune and infectious encephalitis share presenting features but need opposing treatment.
- Existing scores to distinguish them were derived in adults.

What is New:

- In children, older age, psychiatric or behavioural symptoms, and a normal CSF cell count distinguished the two; seizures did not.
- A three-item bedside score discriminated well, including in consensus-defined encephalitis.

Introduction

Encephalitis is an inflammatory syndrome of the central nervous system (CNS) whose infectious and immune-mediated forms share similar clinical signs and symptoms [1]. Autoimmune encephalitis (AE) and infectious encephalitis (IE) require different treatment, immunotherapy and antimicrobial therapy respectively, yet early in the illness their clinical presentation and cerebrospinal fluid (CSF) findings can be similar, a normal brain magnetic resonance imaging (MRI) scan does not exclude AE, and some patients have seronegative disease [2]. AE is not rare: in a US population-based study its prevalence was comparable to that of infectious encephalitis [3], and in one tertiary centre its incidence rose to rates comparable to those of all infectious causes combined [4]. AE carries median hospital charges nearly four times those of herpes simplex virus encephalitis (HSE) [5], and early treatment independently predicts a good outcome in N-methyl-D-aspartate receptor (NMDAR) encephalitis [6].

Existing discrimination tools derive predominantly from adults. Moser et al. combined fever, impaired consciousness, acute symptomatic seizures, headache, and CSF leucocyte count [7]; the score of Granillo et al., combining a Charlson comorbidity index below 2, subacute-to-chronic onset, psychiatric or memory issues, and a non-inflammatory CSF, achieved a positive predictive value of 87% for AE in a Danish nationwide validation cohort [8, 9]; and other studies have described clinical, laboratory, and imaging differences or used machine learning [10, 11]. Children differ from adults: those with NMDAR encephalitis more often present with movement abnormalities, agitation, seizures, and speech deficits, whereas memory deficits and psychiatric manifestations are more common in adults [12]. Paediatric comparative studies are few and include a prospective Spanish cohort of children with suspected AE [13], an Iranian comparison without a score [14], and a Chinese nomogram that included a feature not available at presentation and was validated internally only [15].

No paediatric tool restricted to information available at presentation has been compared directly with an adult-derived score, and paediatric data from the Middle East are lacking. We therefore aimed to compare the clinical features and diagnostic pathway of children with AE and IE, and to develop and internally validate a bedside score, based on features available before autoantibody results, that discriminates between them.

Methods

Design and participants

This retrospective cohort study included children aged 0 to 18 years admitted to King Fahad Medical City (KFMC), a tertiary referral centre in Riyadh, Saudi Arabia, between 1 January 2020 and 31 July 2026. It is

reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and, for development of the score, the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD+AI) statement [16].

Records identified by International Classification of Diseases, 10th Revision codes for encephalitis, meningitis, and autoimmune neurological conditions were individually reviewed against three pre-specified case definitions: CNS inflammatory disease (Definition 1, the entry criterion); confirmed, probable, or clinically suspected infectious CNS disease presenting as encephalitis or meningoencephalitis (Definition 2, hereafter IE); and definite, probable, or possible AE according to the criteria of Graus et al. [17] with the paediatric adaptations of Cellucci et al. [12] (Definition 3). Where lumbar puncture (LP) was not performed, or the autoimmune antibody panel was not sent, classification relied on the remaining clinical and paraclinical findings.

Children with other autoimmune CNS diseases not meeting AE criteria (multiple sclerosis, neuromyelitis optica spectrum disorder [NMOSD], acute disseminated encephalomyelitis [ADEM], primary CNS vasculitis, neurosarcoidosis, primary CNS lymphoma, neuro-Behçet disease, and Rasmussen encephalitis), which differ from AE in pathophysiology and management, were excluded, as were children with purely metabolic, structural, toxic, or hypoxic–ischaemic encephalopathy, simple febrile seizure alone, insufficient documentation, or duplicate records. Children with myelin oligodendrocyte glycoprotein (MOG) antibodies were classified as AE when they met these AE criteria. Children meeting criteria for both AE and IE, reflecting post-infectious AE such as NMDAR encephalitis after herpes simplex virus (HSV) encephalitis [18], formed an AE–IE continuum subgroup and were excluded from comparative analyses.

Trained data collectors extracted demographic, clinical, laboratory, MRI, electroencephalography (EEG), and diagnostic pathway data (healthcare visits before diagnosis, time from symptom onset to correct diagnosis, diagnostic delay exceeding 2 weeks, and misdiagnosis) into a standardised electronic case report form.

Statistical analysis

Groups were compared with the Mann–Whitney U test and the χ^2 test (with continuity correction for 2×2 tables) or, for 2×2 tables with any cell count below 5, Fisher's exact test (two-tailed; significance $p<0.05$).

Candidate predictors were restricted to variables available before autoantibody results and were selected on clinical plausibility and univariable association: age, onset tempo, fever within 72 hours, any psychiatric or behavioural symptom, CSF pleocytosis (white cell count ≥5 cells/mm^3), MRI abnormality, and EEG abnormality (an investigation not performed was coded as not abnormal). Working-memory deficit and CSF Gram stain or culture positivity showed complete separation and movement disorder was infrequent (15 children), so these were reported descriptively. The primary model was a complete-case logistic regression with AE as the outcome, assessed by the area under the receiver operating

characteristic curve (AUROC), the Hosmer–Lemeshow test, variance inflation factors, and a least absolute shrinkage and selection operator (LASSO) model with five-fold cross-validation. Pre-specified sensitivity analyses used multiple imputation by chained equations (20 imputations, predictive mean matching, Rubin's rules; median of eight independent runs reported) and restriction to (i) definite AE and confirmed IE, (ii) children in whom the autoimmune panel was sent, and (iii) children who underwent LP; (i) and (ii) were limited to the two variables significant in the primary model.

The bedside score was derived from a reduced model containing the three most consistent variables: age, CSF pleocytosis, and psychiatric or behavioural symptoms. Coefficients were divided by the smallest (age, per year) and rounded, giving 3 points for psychiatric or behavioural symptoms and 9 points for the absence of CSF pleocytosis; age was then banded (<2, 2–7, and >7 years; 0, 3, and 6 points). In analyses that were not pre-specified, the underlying model was validated by bootstrap resampling (1,000 samples) for optimism-corrected discrimination and calibration slope [19], and temporally, by refitting it on 2020–2023 admissions and evaluating it on 2024–2026 admissions. The score was compared, using the DeLong method [20], with an adapted Granillo score [8, 9] awarding one point each for onset of 8 days or longer, absence of comorbidity, psychiatric or memory complaints, and a non-inflammatory CSF (conservatively <10 cells/mm³ and protein <0.45 g/L; liberally <100 cells/mm³ and protein ≤1.0 g/L), and clinical utility was assessed by decision curve analysis [21]. Post hoc analyses were restricted to children aged 2 years or older and to children meeting the International Encephalitis Consortium (IEC) definition of possible or probable encephalitis [22]. Annual counts for 2020–2025 were modelled by negative-binomial regression [23]. Analyses used Python 3.11 (pandas 3.0, NumPy 2.4, SciPy 1.17, statsmodels 0.15, scikit-learn 1.8).

The KFMC Institutional Review Board approved the study (approval number 26-343) and waived informed consent for this retrospective study of de-identified records; the study followed the Declaration of Helsinki.

Results

Participants

Of 226 children identified, one duplicate was removed and 11 were excluded: 3 did not meet Definition 1, and 8 had an alternative diagnosis (ADEM in 2, multiple sclerosis in 1, NMOSD in 4, and suspected neuro-Behçet disease in 1) (Figure S1). Of the 214 remaining children, 22 met criteria for both conditions, leaving 192 (70 AE, 122 IE) for comparison. AE was definite in 32 (45.7%), probable in 24 (34.3%), and possible in 14 (20.0%); the antibodies identified were MOG in 11, high-titre glutamic acid decarboxylase 65 (GAD65) in 10, NMDAR in 9, and other or incompletely specified antibodies in 3, and none in 37. IE was microbiologically confirmed in 52 (42.6%), probable in 32 (26.2%), clinically suspected in 37 (30.3%), and 1 had no tier recorded; the aetiology was bacterial in 40 (32.8%) and viral in 17 (13.9%). Twenty-five children with IE (20.5%) and 26 with AE (37.1%) met IEC criteria for possible or probable encephalitis. Annual numbers showed no significant temporal trend in either group (Figure S2).

Clinical features and investigations

Children with AE were older than those with IE (median 9.2 [interquartile range 7.0–12.4] vs 0.7 [0.2–6.0] years; p<0.001) (Table 1; Figure S3). Subacute onset was more frequent in AE (47.1% vs 23.0%) and hyper-acute onset in IE (27.0% vs 7.1%; p<0.001), and fever within 72 hours was less frequent in AE (34.6% vs 86.1%; p<0.001). Psychiatric or behavioural symptoms (51.4% vs 4.1%), movement disorders (18.6% vs 1.6%), and initial referral to psychiatry (10.1% vs 0%) were markedly more frequent in AE (all p<0.001), and working-memory deficit or amnesia was recorded only in AE (23.4% of assessable children). Seizures were equally frequent (49.3% vs 49.2%; p=1.000).

The CSF white cell count was normal (<5 cells/mm³) in 84.1% of children with AE and 24.7% of those with IE who were tested (p<0.001) (Table 2), and CSF Gram stain and culture were positive only in IE (20.8% and 25.0%). MRI and EEG were performed more often in AE (97.1% vs 71.3% and 75.7% vs 44.3%; both p<0.001); among those tested, MRI abnormality rates were similar (80.9% vs 80.2%; p=0.689), whereas EEG abnormalities were more frequent in AE (67.9% vs 45.5%; p=0.031).

Only 17.5% of children with AE were diagnosed within 1 week of symptom onset, compared with 64.2% of those with IE (p<0.001). Diagnostic delay exceeding 2 weeks was more common in AE (30.8% vs 12.3%; p=0.005), whereas misdiagnosis rates did not differ (29.7% vs 24.1%; p=0.527) (Table S1). Most children with AE (71.4%) received immunotherapy before antibody results were available.

Multivariable model

The complete-case model included 129 children (47 AE, 82 IE; events per variable 6.7). Age (odds ratio [OR] 1.53 per year, 95% confidence interval [CI] 1.20–1.95; p<0.001) and CSF pleocytosis (OR 0.01, 95% CI 0.00–0.18; p=0.001) were the only independent predictors, with psychiatric or behavioural symptoms borderline (OR 4.88, 95% CI 0.98–24.18; p=0.052) (Table S2; Figure S4). The model showed excellent discrimination (AUROC 0.970) and adequate calibration (Hosmer–Lemeshow p=0.87) (Figure S5), and the LASSO model retained six of the seven variables with a similar AUROC (0.971). Associations were consistent across sensitivity analyses (Table S3; Figure S6); in particular, restriction to definite AE and confirmed IE (n=66) confirmed both age (OR 1.55, 95% CI 1.21–1.99) and CSF pleocytosis (OR 0.03, 95% CI 0.00–0.22; both p<0.001).

The KFMC AE-IE Score

The reduced three-variable model, applicable to 156 children (63 AE, 93 IE), yielded the KFMC AE-IE Score: 0, 3, or 6 points for age <2, 2–7, and >7 years; 3 points for any psychiatric or behavioural symptom; and 9 points for a CSF white cell count <5 cells/mm³ (range 0–18). The score achieved an AUROC of 0.933 (95% CI 0.90–0.97) (Table 3; Figure 1). No child scoring 0 had AE, and a score of 10 or more had a sensitivity of 83%, a specificity of 91%, and a positive predictive value of 87%. The observed proportion with AE rose from 0% at a score of 0 to 96% at 18 (Figure 1B).

On bootstrap validation, the optimism-corrected AUROC of the underlying model was 0.947 (apparent 0.951), with a median calibration slope of 0.81. In temporal validation, the model refitted on 2020–2023 admissions (n=97; 41 AE) retained its discrimination in 2024–2026 admissions (n=59; 22 AE; AUROC 0.94, 95% CI 0.88–1.00), although its calibration slope (0.68) and calibration-in-the-large (−0.73) indicated some over-prediction of AE; the score performed similarly in both periods (AUROC 0.95 and 0.90) (Figure 1C). In 150 children with complete data for both scores, the KFMC AE-IE Score had a higher AUROC than the adapted Granillo score (0.93 vs 0.89; p=0.012), although not significantly in children aged 2 years or older (0.87 vs 0.84; p=0.29) (Figure 1A). On decision curve analysis, it provided the greater net benefit at threshold probabilities of 40% or more, and the adapted Granillo score between 15% and 35% (Figure 1D).

In children aged 2 years or older (n=116; 69 AE, 47 IE), psychiatric or behavioural symptoms remained more frequent (52.2% vs 10.6%) and CSF pleocytosis less frequent (16.1% vs 75.8%) in AE (both p<0.001), and the score retained good discrimination (AUROC 0.874). In the 40 children meeting IEC criteria for encephalitis with complete data (22 AE, 18 IE), the AUROC was 0.97 (95% CI 0.92–1.00); at a threshold of 10 or more, sensitivity was 68% and specificity 100%.

Discussion

In this paediatric cohort, older age and the absence of CSF pleocytosis were the most consistent discriminators of AE from IE before antibody results were available, whereas seizures and MRI abnormality did not discriminate, and a three-item bedside score maintained its discrimination on internal, temporal, and subgroup validation. To our knowledge, this is the first paediatric comparison of AE and IE from Saudi Arabia.

Age was the strongest single discriminator, consistent with NMDAR encephalitis occurring mostly in children and young adults [2, 24] and infectious CNS disease being concentrated in infancy. Because age separates many patients, and because our IE group included the full spectrum of infectious CNS disease, discrimination could be easier than in the encephalopathic child in whom the dilemma is greatest. However, in children aged 2 years or older the score retained good discrimination, although the lower AUROC (0.874) indicates that part of its accuracy reflects age, and in children meeting IEC criteria for encephalitis it remained excellent (AUROC 0.97).

Psychiatric or behavioural symptoms, movement disorders, and memory deficit were the features most strongly associated with AE, consistent with previous work [8–10]. In children, psychiatric involvement often takes the form of tantrums, aggression, agitation, and regression and only rarely of psychosis [12, 25], and almost half of the children with AE (48.6%) had no psychiatric features at presentation. These features are therefore red flags that should prompt consideration of AE rather than criteria whose absence excludes it. Seizures did not discriminate, in contrast to the adult-derived tool of Moser et al. [7], reflecting their frequency both in CNS infection in infancy and in paediatric AE [25], and fever, present in one-third of children with AE and absent in 13.9% of those with IE, excludes neither diagnosis.

A normal CSF cell count was the prevailing pattern in AE (84.1%), with normal protein in 78.6% and oligoclonal bands in only 26.4% of those tested, in contrast to the frequent CSF abnormalities of NMDAR encephalitis [2]. Conversely, 24.7% of children with IE had a normal cell count, most of them (13 of 23) clinically suspected rather than confirmed cases, and antibiotic pre-treatment (11 of 23) may have blunted the CSF response. A normal CSF therefore argues against, but does not exclude, infection, particularly early HSE, for which a repeat LP within 3–7 days is recommended when concern persists [22]. Because CSF findings contribute to the definition of probable IE, the pleocytosis association could be partly definitional; however, it persisted when the analysis was restricted to definite AE and microbiologically confirmed IE (OR 0.03).

Because misdiagnosis rates were similar despite much longer times to diagnosis, delay in AE appears to reflect late recognition rather than diagnostic error. Although 71.4% of children with AE received immunotherapy before antibody results, in line with recommendations [12, 17], the interval before AE is first considered remains a challenge, and part of it precedes referral: almost half (48.6%) had been unwell for more than 2 weeks before admission. We therefore propose an institutional pathway (Figure S7) in which a score of 10 or more triggers urgent neurology review and, once infection has been reasonably excluded, consideration of first-line immunotherapy without awaiting antibody results. Linking immunotherapy to infectious exclusion is important, because the specificity of AE criteria is low before infectious results are available and reaches approximately 90% once both polymerase chain reaction (PCR) and infectious serology results are available [26]. The score is intended to prompt earlier consideration of immunotherapy, not to justify withholding antimicrobial treatment, and the pathway requires prospective evaluation.

The score shares core elements with existing tools [7–9] but was developed in children, uses age in place of comorbidity, requires neither MRI nor EEG, and, unlike a recent paediatric nomogram [15], uses only features available at presentation. Its positive predictive value of 87% at a threshold of 10 or more matched that of the Granillo score in the Danish cohort [9], but predictive values depend on prevalence (40.4% for AE in the scored subset) and will be lower in general emergency departments. The score also requires LP, because the CSF item contributes half of the points.

This study has limitations. It was retrospective, so behavioural and cognitive symptoms may have been under-recorded, and was conducted in a single tertiary centre in which about one-third of patients were transferred from other hospitals. The autoimmune panel was sent in 92.9% of children with AE but in only 9.0% of those with IE, and possible and seronegative AE were included, so some misclassification is possible; MRI and EEG were also performed preferentially in suspected AE. The score's components were selected from a model with a low events-per-variable ratio (6.7), and the sample size was not set in advance; a post hoc calculation using the criteria of Riley et al. [27] showed that the sample was sufficient to limit overfitting (minimum 54 children for the three-predictor score model and 123 for the seven-predictor primary model) but not to estimate overall risk precisely (minimum 370), although these minima rely on the models' own, likely optimistic, explained variation; bootstrap optimism was probably underestimated because variable selection was not repeated within resamples; and temporal validation

was not fully independent because the score was derived from the whole cohort. Its performance, and its advantage over the approximated Granillo score, are therefore likely to be optimistic. Finally, the 22 children in the AE–IE continuum were excluded; post-infectious AE should be considered in any child who deteriorates with new movement or psychiatric features after treated encephalitis [18]. Prospective multicentre external validation reported according to TRIPOD+AI [16] is required before clinical adoption.

Conclusion

Older age, neuropsychiatric features, and a normal CSF cell count distinguished AE from IE before antibody results were available, and the KFMC AE-IE Score condenses these findings into a simple bedside tool that should be regarded as hypothesis-generating until externally validated.

Abbreviations

AE, autoimmune encephalitis; AUROC, area under the receiver operating characteristic curve; CSF, cerebrospinal fluid; IE, infectious encephalitis; IEC, International Encephalitis Consortium; KFMC, King Fahad Medical City; LP, lumbar puncture; NMDAR, N-methyl-D-aspartate receptor.

Declarations

Funding: This study was funded by the Research Center, King Fahad Medical City (IRF 026-020). The funder had no role in study design, data collection, analysis, interpretation, or manuscript preparation.

Competing interests: The authors declare no competing interests.

Ethics approval: This study was approved by the Institutional Review Board of King Fahad Medical City (IRB approval number: 26-343) and was conducted in accordance with the Declaration of Helsinki.

Consent to participate: Individual informed consent was waived by the Institutional Review Board given the retrospective design and use of de-identified records.

Consent for publication: Not applicable.

Data availability: The de-identified data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to institutional and IRB approval. The study protocol and data analysis plan are also available on request.

Author contributions: F.A.A.: Conceptualization, Methodology, Formal analysis, Developing Bedside Score, Writing – original draft, Writing – review & editing, Project administration, Visualization, and submission. B.S., L.A., & Z.K.: Literature review and data collection, drafting the introduction and

methods. S.T., A.A.: Clinical interpretation; S.T.: writing discussion. All authors have read and approved the final manuscript.

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Tables

Table 1: Baseline characteristics and clinical presentation at admission of children with autoimmune encephalitis (AE, n=70) and infectious encephalitis (IE, n=122)

Variable	AE	IE	p	Missing, n (AE/IE)
Age at presentation, years	9.2 (7.0–12.4)	0.7 (0.2–6.0)	<0.001***	0/0
Male sex	35 (50.0%)	73 (59.8%)	0.242	0/0
Nationality			0.677	0/0
Saudi	68 (97.1%)	116 (95.1%)		
Non-Saudi	2 (2.9%)	5 (4.1%)		
Unknown	0 (0.0%)	1 (0.8%)		
Any comorbidity present	9 (12.9%)	32 (26.2%)	0.046*	0/0
Onset tempo			<0.001***	0/0
Hyper-acute (less than 48 hours)	5 (7.1%)	33 (27.0%)		
Acute (2–7 days)	22 (31.4%)	60 (49.2%)		
Subacute (8 days – 3 months)	33 (47.1%)	28 (23.0%)		
Insidious (more than 3 months)	10 (14.3%)	1 (0.8%)		
Duration of illness before admission			<0.001***	0/0
less than 24 hours	1 (1.4%)	20 (16.4%)		
24–48 hours	9 (12.9%)	26 (21.3%)		
2–7 days	15 (21.4%)	32 (26.2%)		
8–14 days	10 (14.3%)	24 (19.7%)		
more than 14 days	34 (48.6%)	14 (11.5%)		
unknown	1 (1.4%)	6 (4.9%)		
Referral pathway			0.017*	0/0
Via emergency department	32 (45.7%)	69 (56.6%)		
Direct to neurology / neuropaediatrics	14 (20.0%)	8 (6.6%)		
Inpatient transfer from another facility	24 (34.3%)	45 (36.9%)		
Fever ≥38.0°C at/within 72 h	18 (34.6%)	93 (86.1%)	<0.001***	18/14
Overall vaccination status			<0.001***	0/0
Fully vaccinated for age	52 (74.3%)	67 (54.9%)		
Partially vaccinated	2 (2.9%)	20 (16.4%)		

Variable	AE	IE	p	Missing, n (AE/IE)
Unvaccinated	0 (0.0%)	11 (9.0%)		
Unknown	16 (22.9%)	24 (19.7%)		
Prior HSV encephalitis episode	0 (0.0%)	3 (2.5%)	0.555	0/0
Clinical presentation at admission				
GCS <12 at any point	19 (30.2%)	22 (19.6%)	0.164	7/10
Altered mental status ≥24h	32 (45.7%)	26 (21.3%)	<0.001***	0/0
Working memory deficit/amnesia	11 (23.4%)	0 (0.0%)	<0.001***	23/52
Meningeal sign	5 (8.5%)	17 (19.5%)	0.110	11/35
Seizure	34 (49.3%)	60 (49.2%)	1.000	1/0
New focal neurological deficit	23 (32.9%)	22 (18.0%)	0.031*	0/0
Petechial or purpuric rash	2 (2.9%)	2 (1.6%)	0.623	0/0
Papilloedema	3 (6.0%)	8 (14.5%)	0.207	20/67
Psychiatric/behavioural symptom	36 (51.4%)	5 (4.1%)	<0.001***	0/0
Initially referred to psychiatry	7 (10.1%)	0 (0.0%)	<0.001***	1/2
Movement disorder	13 (18.6%)	2 (1.6%)	<0.001***	0/0
Autonomic dysfunction	5 (7.1%)	9 (7.4%)	1.000	0/0

*Continuous variable reported as median (IQR), Mann–Whitney U test. Categorical variables as n (%), chi-square test (with continuity correction for 2×2 tables) or, for 2×2 tables with any cell count <5, Fisher's exact test. The Missing column reports counts shown as AE/IE. *p<0.05, **p<0.01, ***p<0.001. Abbreviations: AE, autoimmune encephalitis; IE, infectious encephalitis; IQR, interquartile range.*

Working-memory deficit/amnesia (11 of 47 assessable AE patients vs 0 of 70 assessable IE patients; 23/52 not assessable) showed complete separation, and any movement disorder (13/70 vs 2/122) was too infrequent to be modelled reliably; both were excluded from the multivariable model. Abbreviation: GCS, Glasgow Coma Scale.

Table 2: Cerebrospinal fluid, blood, neuroimaging, and electroencephalography findings — AE (n=70) vs IE (n=122)

Variable	AE	IE	p	Missing, n (AE/IE)
LP performed	69 (98.6%)	105 (86.1%)	0.004**	0/0
CSF WBC			<0.001***	7/29
≥1000	0 (0.0%)	8 (8.6%)		
100–999	0 (0.0%)	27 (29.0%)		
10–99	6 (9.5%)	31 (33.3%)		
5–9	4 (6.3%)	4 (4.3%)		
<5	53 (84.1%)	23 (24.7%)		
CSF protein			<0.001***	0/0
normal <0.45 g/L	55 (78.6%)	30 (24.6%)		
mildly elevated 0.45–1.0 g/L	5 (7.1%)	17 (13.9%)		
markedly elevated >1.0 g/L	7 (10.0%)	45 (36.9%)		
Not done	3 (4.3%)	30 (24.6%)		
CSF glucose			<0.001***	5/32
normal ≥2.2 mmol/L	64 (98.5%)	58 (64.4%)		
low 1.1–2.1 mmol/L	0 (0.0%)	14 (15.6%)		
very low <1.1 mmol/L	1 (1.5%)	18 (20.0%)		
CSF differential			0.017*	55/70
Lymphocytic (more than 50% lymphocytes — favours viral or autoimmune)	8 (53.3%)	27 (51.9%)		
Neutrophilic (more than 50% PMN — favours bacterial)	2 (13.3%)	21 (40.4%)		
Mixed	5 (33.3%)	4 (7.7%)		

Variable	AE	IE	p	Missing, n (AE/IE)
CSF Gram stain positive	0 (0.0%)	20 (20.8%)	<0.001***	5/26
CSF culture positive	0 (0.0%)	26 (25.0%)	<0.001***	4/18
Oligoclonal bands positive	14 (26.4%)	3 (15.0%)	0.368	17/102
Brain MRI performed	68 (97.1%)	87 (71.3%)	<0.001***	0/0
MRI result			0.689	2/36
Normal	11 (16.2%)	16 (18.6%)		
Equivocal	2 (2.9%)	1 (1.2%)		
Abnormal	55 (80.9%)	69 (80.2%)		
EEG performed	53 (75.7%)	54 (44.3%)	<0.001***	0/0
EEG result			0.031*	17/67
Normal	17 (32.1%)	30 (54.5%)		
Abnormal	36 (67.9%)	25 (45.5%)		
Blood culture positive	4 (6.7%)	18 (15.7%)	0.099	10/7
CRP category			<0.001***	8/13
<10 mg/L	47 (75.8%)	39 (35.8%)		
10–49	10 (16.1%)	25 (22.9%)		
50–99	3 (4.8%)	16 (14.7%)		
≥100 mg/L	2 (3.2%)	29 (26.6%)		

CRP was recorded in the source case report form as a mix of numeric values and range categories and was normalised into consistent bands. CSF Gram stain and culture positivity are, by definition, zero in the AE group. Abbreviations: CSF, cerebrospinal fluid; WBC, white cell count; MRI, magnetic resonance imaging;

EEG, electroencephalography; CRP, C-reactive protein; LP, lumbar puncture; PMN, polymorphonuclear leucocytes.

Table 3: Performance of the KFMC AE-IE Score at candidate thresholds (n=156: 63 AE, 93 IE)

Score threshold	Sensitivity	Specificity	PPV	NPV
≥ 1	100%	48%	57%	100%
≥ 4	98%	56%	60%	98%
≥ 7	90%	73%	70%	92%
≥ 10	83%	91%	87%	89%
≥ 13	73%	96%	92%	84%
≥ 16	38%	99%	96%	70%

KFMC AE-IE Score = age points (<2y=0; 2–7y=+3; >7y=+6) + 3 if any psychiatric/behavioural symptom present + 9 if CSF WBC <5 cells/mm³ (no pleocytosis) once LP performed; range 0–18. AUROC 0.933. Derived and evaluated in the same n=156 subset of this single-centre cohort (63 AE, 93 IE); not yet externally validated. Abbreviations: PPV, positive predictive value; NPV, negative predictive value; LP, lumbar puncture; KFMC, King Fahad Medical City; AUROC, area under the receiver operating characteristic curve.

Figures

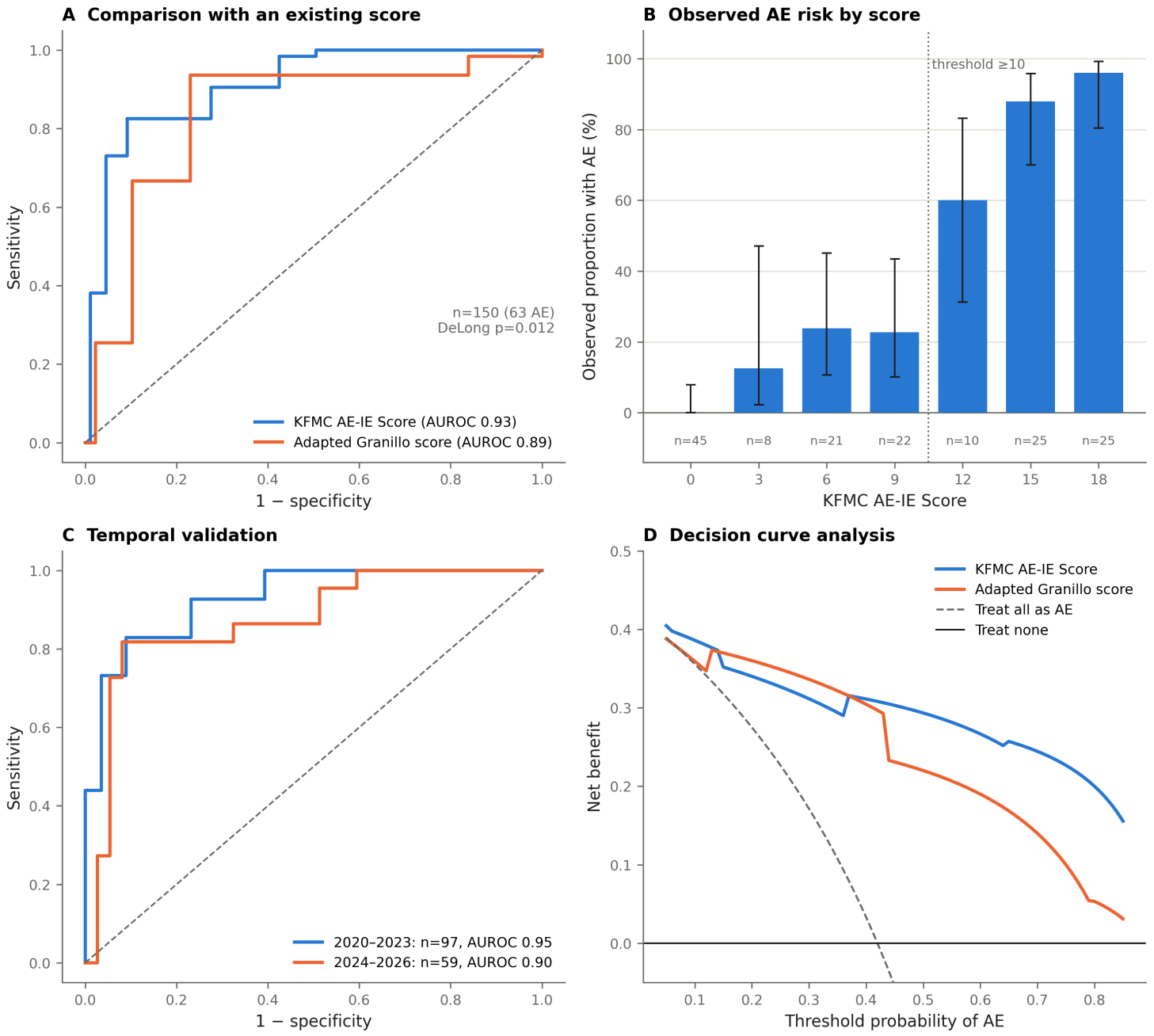

Figure 1

Validation and clinical utility of the KFMC AE-IE Score. (A) Receiver operating characteristic curves for the KFMC AE-IE Score and an adapted Granillo score in the 150 children with complete data for both (DeLong test). (B) Observed proportion of children with AE at each score value, with 95% Wilson confidence intervals and number of children; the dotted line marks the threshold of 10 or more. (C) Temporal validation: score performance in admissions from 2020–2023 and from 2024–2026. (D) Decision curve analysis comparing the net benefit of the two scores with strategies of treating all or no children as AE.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AEvsIEEurJPediatrSupplementaryInformation3.docx