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Influenza-Associated Neurological Complications in Pediatric Patients: Clinical Characteristics, Outcomes, and Risk Stratification Using the Neuroinfluenza Severity Score from the Multicenter TURK-INF Study

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Abstract

Background

Influenza-associated neurological complications (IANC) encompass a broad spectrum ranging from febrile seizures to severe encephalopathy with substantial morbidity and mortality. We aimed to describe the clinical characteristics and outcomes of pediatric IANC and evaluate the prognostic utility of the Neuroinfluenza Severity Score (NISS).

Methods

This retrospective multicenter study included children aged 1 month to 18 years hospitalized with laboratory-confirmed influenza and neurological manifestations at 21 tertiary centers in Türkiye during the 2023–2025 influenza seasons. Clinical, laboratory, neuroimaging, treatment, and six-month follow-up data were analyzed. NISS was developed using variables reflecting disease severity, and outcome analysis was performed.

Results

Among 5,093 hospitalized children with influenza, 397 (7.8%) developed neurological complications. The median age was 45.6 months, and 70.8% were younger than five years. Seizures were the most frequent manifestation (70.8%), followed by encephalopathy (10.9%) and meningoencephalitis (5.0%). Complete neurological recovery occurred in 90.2% of patients, whereas 5.0% developed long-term neurological sequelae, and overall mortality was 1.3%. ROC analysis demonstrated excellent predictive performance of NISS for unfavorable neurological outcomes, with an optimal cutoff ≥ 2 yielding 82.1% sensitivity and 91.9% specificity (AUC 0.913, 95% CI 0.856–0.969; $p < 0.001$). Patients with severe neuroinfluenza were associated with delayed oseltamivir initiation, prolonged hospitalization, elevated inflammatory markers, and more frequent high-risk neuroimaging abnormalities and had significantly long-term neurological sequelae (29.5% vs. 0.6%), and mortality (8.2% vs. 0%).

Conclusions

IANC should be considered in children presenting with acute neurological manifestations, even in the absence of respiratory symptoms. The NISS demonstrated excellent ability to identify patients at increased risk of poor neurological outcomes, long-term sequelae, and mortality, providing a practical tool for early risk stratification and timely escalation of care.

1. Introduction

Influenza represents a significant cause of respiratory illness among pediatric populations globally, affecting approximately 10–20% of the population each season (1). Although primarily associated with self-limited respiratory symptoms, influenza may also lead to severe extrapulmonary complications, with neurological involvement among the most serious because of its implications for morbidity, mortality, and long-term neurological sequelae (2, 3). Influenza-related neurological complications in hospitalized children have been reported in 1.7%–16.9% of cases, ranging from benign febrile seizures to severe conditions such as encephalopathy, status epilepticus, acute disseminated encephalomyelitis (ADEM), and acute necrotizing encephalopathy (ANE) (1). Despite growing awareness of these complications, current knowledge remains limited, as most published data come from single-center or small regional studies. This study aims to evaluate the clinical spectrum, presentation patterns, management strategies, and outcomes of influenza-associated neurological involvement in a substantial multicenter pediatric cohort from tertiary referral centers across Turkey.

2. Materials and Methods

a. Study Design and Setting

A retrospective multicenter study was conducted across 21 active centers, including tertiary referral university and state training hospitals, in 12 cities across Turkey (İzmir, Ankara, Adana, Denizli, Sakarya, Manisa, Mersin, Konya, Kocaeli, Bursa, Erzurum, and Istanbul). Hospitalized children aged 1 month to 18 years with influenza who presented with acute neurological manifestations or developed neurological complications within 48 hours of admission were included. The study period covered the 2023–2024 and 2024–2025 influenza seasons. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of İzmir City Hospital (Dated 16 October 2025, Decision No. 2025/529,).

b. Case Identification and Diagnosis of Influenza

Eligible cases were identified using hospital electronic medical records for influenza (J09–J10) and neurological conditions (G02, G04, and G05), along with microbiological confirmation records. Influenza infection was confirmed by rapid antigen testing and/or real-time reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swab specimens. In centers with available facilities, cerebrospinal fluid (CSF) samples were also tested for influenza A and B by real-time RT-PCR.

c. Data Collection and Clinical Review

Clinical data were extracted using a standardized case report form, including demographic characteristics, comorbidities, vaccination history, influenza virus subtype, clinical presentation, laboratory findings, treatment approaches (including antiepileptic drugs, antiviral therapy, and immunomodulatory treatments), timing of oseltamivir initiation, length of hospital stay, pediatric intensive care unit admission, mechanical ventilation, clinical outcomes at discharge, and clinical outcomes at 6 months of follow-up. Neuroimaging studies, including brain computed tomography and/or

magnetic resonance imaging, were reviewed, and electrophysiological findings from electroencephalography were recorded. To ensure diagnostic consistency, cases with neurological complications were reviewed by pediatric neurologists at participating centers.

d. Definitions of Neurological Complications

Influenza-associated neurological complication (IANC) was defined as the onset or progression of a neurological symptom that cannot be otherwise explained in a patient with laboratory-confirmed influenza. These complications included central and peripheral nervous system manifestations and were classified as seizures, encephalopathy, meningoencephalitis, ADEM, and other neurological abnormalities such as ataxia, involuntary movements, syncope, and dystonia. Seizures were classified as febrile seizures, new-onset seizures, provoked seizures in patients with known epilepsy, repetitive seizures, or status epilepticus. Acute encephalopathy is defined as an altered mental state lasting > 24 hours and represents a heterogeneous spectrum of clinicoradiological syndromes with variable severity. For severity classification, cases were operationally categorized as mild encephalopathy based on clinical course and outcomes. Mild encephalopathy was defined as complete clinical recovery within 24 hours of symptom onset, with normalization of consciousness and no residual neurological sequelae. Severe encephalopathy was defined as prolonged impaired consciousness and/or the need for intensive care, and was associated with adverse neurological outcomes. Specific syndromes, including ANE, mild encephalitis/encephalopathy with reversible splenial lesion (MERS), meningoencephalitis, and ADEM, were diagnosed according to established clinical and radiological criteria (4, 5, 6, 7, 8, 9).

To categorize disease severity, a Neuroinfluenza Severity Score (NISS) was developed using predefined clinical, radiological, and therapeutic variables, as detailed in Table 1, with each criterion receiving one point if present. Abnormal magnetic resonance imaging (MRI) findings were classified as low-risk (non-severe) or high-risk (severe) based on previously described radiological predictors of disease severity and prognosis in pediatric IANC (10, 11, 12, 13, 14). Clinical outcomes were evaluated at hospital discharge and at 6-month follow-up. A good outcome was defined as complete neurological recovery without residual deficits. A poor outcome was defined as death or neurological sequelae at follow-up, with an unfavorable neurological outcome operationalized as a Pediatric Cerebral Performance Category (PCPC) score of ≥ 2 at 6 months (15). The association between NISS categories and neurological outcomes was examined.

Table 1
The Neuroinfluenza Severity Score (NISS) is used to assess disease severity and outcomes.

Neuroinfluenza Severity Score (NISS)	**Score**
Status epilepticus	1
Encephalopathy or altered consciousness lasting longer than 24 hours	1
Pediatric intensive care unit (PICU) admission	1
Requirement for mechanical ventilation	1
High-risk (severe) neuroimaging features on brain MRI*	1
Use of immunomodulatory therapy (intravenous immunoglobulin and/or pulse corticosteroids and/or plasmapheresis)	1
Total	**0–6**
***Abnormal MRI findings**	
Low-risk imaging (non-severe) neuroimaging features	
Isolated cortical/subcortical involvement	
Isolated periventricular white matter involvement	
Isolated splenial lesion (MERS)	
High-risk imaging (severe) neuroimaging features	
Thalamus and/or basal ganglia involvement	
Brainstem involvement	
ANE pattern	
ADEM/demyelinating pattern	
Multifocal diffusion restriction	

e. Statistical Analysis

Statistical analyses were performed using IBM SPSS version 27. Continuous variables were reported as mean ± standard deviation or median (range), and categorical variables as number and percentages. Normality was assessed using the Shapiro–Wilk test. Group comparisons were performed using appropriate parametric or nonparametric tests (t-test, Mann–Whitney U, ANOVA, or Kruskal–Wallis), and categorical variables were compared using chi-square or Fisher's exact test. ROC curve analysis was used to evaluate the predictive performance of the Neuroinfluenza Severity Score (NISS). A p-value < 0.05 was considered statistically significant.

3. Results

a. Demographics and Clinical Characteristics

Neurological manifestations associated with influenza were identified in 397 of 5.093 hospitalized patients with laboratory-confirmed influenza (7.79%). A total of 397 children were included in this study. Data were collected from centers across Turkey, enhancing the generalizability of our findings. Seasonal clustering was observed in December (16.88%) and January (36.78%), with case numbers peaking in 2025 (58.7%, n = 233), compared with 2024 (31.0%, n = 123) and 2023 (10.3%, n = 41). Children < 5 years constituted 70.78% of the cohort, representing the predominant risk group. Male patients slightly predominated, comprising 55.92% of the cohort (Table 2).

b. Laboratory and Imaging Findings

Admission laboratory findings, including complete blood count, serum biochemistry, and CSF analyses, are summarized in Table 3. Among hematological abnormalities, lymphopenia was the most frequent finding, observed in 51.9% of patients.

c. Outcomes and Sequelae

A favorable outcome was observed, while 39 patients (9.8%) had a poor outcome. At six-month follow-up, reversible neurological impairment was observed in 14 patients (3.5%), and 20 patients (5%) exhibited persistent long-term neurological sequelae. The overall mortality rate was 1.3% (n = 5). Among 37 patients who received adjunctive therapy, 15 (40.5%) achieved complete recovery, 7 (18.9%) had reversible neurological sequelae at 6 months, 10 (27.0%) developed long-term sequelae, and mortality was observed in 5 patients (13.5%).

d. Distinct Clinical Characteristics and Outcomes in Patients with Encephalopathy

Development of encephalopathy was significantly associated with older age. Age ≥ 5 years was significantly more prevalent among patients with encephalopathy. The encephalopathy group had a markedly stronger inflammatory profile, with higher ALT, AST, and ferritin levels and lower lymphocyte and white blood cell counts at presentation (Table 4).

Antiviral treatment was initiated later in the encephalopathy group. Oseltamivir therapy lasted longer in patients with encephalopathy. Approximately 25% of patients with encephalopathy received adjunctive treatments. Combination regimens (IVIG plus corticosteroids, with or without plasmapheresis) were most common in the encephalopathy subgroup.

Clinically, encephalopathy was associated with a more severe disease course. Hospital stay and duration of neurological symptoms were more than twice as long as in patients without encephalopathy. Outcome analysis showed lower rates of complete recovery in the encephalopathy group and significantly higher rates of long-term sequelae and mortality.

e. Subgroup Analysis: Mild and Severe Encephalopathy

Age increased significantly with encephalopathy severity, with the highest mean age in the severe group. Severe encephalopathy was associated with lower platelet counts, higher liver enzyme levels, and higher CSF glucose.

Clinical severity correlated with worse outcomes: severe encephalopathy was associated with longer hospitalization, markedly higher ICU admission and mechanical ventilation rates, greater need for immunomodulatory therapy, lower rates of complete recovery, and substantially higher rates of long-term sequelae and mortality (Table 5).

f. Clinical Outcomes According to NISS Score

The predictive performance of the Neuroinfluenza Severity Score (NISS) for poor outcome was evaluated using receiver operating characteristic (ROC) curve analysis (Table 6). The optimal cutoff was 1.5, yielding a sensitivity of 82.05% and a specificity of 91.90% (AUC: 0.913; 95% CI: 0.856–0.969; p <0.001) (Table 7). As the NISS consists of integer values, patients with scores ≥2 were classified as having severe neuroinfluenza.

Severe neuroinfluenza was associated with older age, a higher proportion of children aged ≥ 5 years, and more frequent underlying comorbidities.

Severe cases showed greater systemic involvement, with more frequent lower respiratory and extrapulmonary manifestations, and were accompanied by a markedly stronger inflammatory response, including higher leukocyte counts and elevated liver enzymes, ferritin, and CSF abnormalities in glucose and protein.

Clinically, severe neuroinfluenza is characterized by delayed initiation of antiviral therapy, prolonged recovery, extended hospitalization, significantly increased rates of ICU admission and mechanical ventilation, and notably poorer outcomes. These adverse outcomes include lower rates of complete recovery, increased long-term neurological sequelae, and higher mortality rates, observed exclusively in patients with severe neuroinfluenza (Table 7).

4. Discussion

Influenza-associated neurological complications (IANC) represent a broad and heterogeneous clinical spectrum in children. A key strength of this multicenter study is the identification of a distinct high-risk neuroinfluenza phenotype characterized by severe clinical presentation, laboratory abnormalities, neuroimaging findings, and poorer outcomes.

Previous studies reported neurological involvement in 1.7%–15% of hospitalized influenza cases (16). The prevalence was 7.79%, similar to the 7.6% reported in a large multicenter study from the United States and to rates in other pediatric cohorts (17, 18). Seasonal clustering in January (36.78%) and

December (16.88%) aligns with the established peak of influenza activity (19), during which most IANCs occur between January and March (20). However, the progressive increase in cases toward 2025 (n = 233, 58.7%) suggests intensified viral circulation and may reflect shifts in seasonal dynamics or declining population immunity in the post-pandemic period (3).

Younger age is a well-established risk factor for influenza, with the highest risk observed in children under 5 years of age, who constitute 72.8% of our cohort (21). Nevertheless, one of the most noteworthy findings is the severity–age paradox: despite the predominance of younger patients, severe neurological involvement was more prevalent among older patients, consistent with previous reports indicating that influenza-associated encephalopathy occurs at a higher mean age than uncomplicated influenza or benign neurological manifestations (18, 22, 23). This phenomenon may reflect age-related differences in immune response, whereby a more mature immune system elicits a more pronounced inflammatory reaction, leading to blood–brain barrier disruption and secondary neuronal injury (24).

The clinical profile of the cohort highlights a dual-risk pattern. The disease frequently affected previously healthy children (62.4%), showing that neurological complications can occur even in children without comorbidities. However, underlying diseases were significantly associated with higher disease severity and NISS scores ≥ 2. While previous studies identify children with underlying neurodevelopmental disorders as a vulnerable population—reporting a 3.7- to 6.5-fold increased risk of IANC—our findings suggest a more nuanced relationship (1, 17, 25). Specifically, comorbidities do not determine disease occurrence but instead critically affect disease severity and clinical outcomes once severe illness develops.

Neuroinfluenza presents with a broad clinical spectrum, ranging from simple febrile seizures to fulminant encephalopathy. Notably, 25.9% of patients present without respiratory symptoms, consistent with previous reports indicating that 12.2%–38.7% of children with neuroinfluenza may present without typical respiratory signs, such as cough or rhinorrhea (7, 26, 27). Seizures were the most common manifestation, predominantly simple febrile seizures; however, complicated and recurrent seizures have also been observed, indicating a lowered seizure threshold during infection. Gastrointestinal symptoms, particularly vomiting and feeding difficulties, were common and may reflect early systemic involvement preceding neurological deterioration, as described in ANE (28). The most severe presentations included ANE and severe encephalopathy, conditions associated with mortality rates of 30%–40% and requiring prompt recognition and early neurocritical management during influenza outbreaks (18, 29).

Influenza A predominated among children with neurological complications; however, no significant differences were observed between Influenza A and B in neurological manifestations or outcomes, suggesting that both strains can cause a similar spectrum of neuroinfluenza (1, 6, 7, 30). Despite the limited number of CSF PCR samples analyzed (n = 15), Influenza A RNA was detected in 11 patients. While several studies have suggested that Influenza A is more strongly associated with neurotropic and severe neurological manifestations, others have reported comparable rates of neurological complications between Influenza A and B (1). Earlier studies reported viral RNA positivity in 50%–71% of

encephalopathy cases, whereas more recent international studies demonstrated entirely negative CSF PCR results, underscoring the heterogeneous nature of IANC (16, 23, 31, 32). Nevertheless, patients with positive CSF Influenza A PCR exhibited severe neurological phenotypes, including NISS scores ≥ 2 and characteristic neuroimaging abnormalities such as bilateral thalamic involvement, diffusion restriction in the hippocampus and brainstem, and acute necrotizing encephalopathy, supporting a potential association between viral neuroinvasion and severe neuroinfluenza phenotypes. Elevated ferritin and transaminase levels in severe cases, together with lower respiratory tract involvement and hepatic, cardiac, and hematological manifestations, suggest that immune- mediated injury also plays a major pathogenic role. Clinical studies have further shown that excessive cytokine release from activated glial cells, particularly in genetically susceptible individuals, may contribute to neurotoxicity (26). Taken together, these findings indicate that both direct viral neuroinvasion and immune-mediated mechanisms may contribute to the pathogenesis of severe neuroinfluenza.

Lymphopenia was present in 51.9% of patients and was more pronounced in those with encephalopathy, supporting previous reports that identify it as a marker of severe influenza and poor prognosis (19). Among encephalopathy cases, thrombocytopenia was more pronounced in severe forms, whereas elevated CSF glucose distinguished severe from mild encephalopathy (19, 33, 34). In patients with a NISS score ≥ 2, white blood cell and neutrophil counts were higher, and CSF protein and glucose levels were elevated, reflecting systemic inflammation and blood–brain barrier dysfunction (20). These early hematological and biochemical abnormalities may serve as practical prognostic markers to predict disease severity and guide timely escalation of care.

Neuroimaging findings varied across the clinical spectrum, with several patterns strongly associated with severe disease and should be regarded as red flags for poor prognosis. Notably, bilateral thalamic involvement, the hallmark radiological feature of ANE, remains the most characteristic radiological finding, and its association with the influenza virus has been widely recognized since 1995 (18, 29). Basal ganglia, brainstem, and, in particular, hippocampal involvement were also more frequent in severe neuroinfluenza. Among patients with hippocampal involvement, half had bilateral lesions and were associated with reversible neurological sequelae at 6 months, indicating potential prognostic value and the need for long-term follow-up. The mechanisms underlying hippocampal involvement in IANC are only partially understood and may serve as a marker of disease severity and prognostic significance (35).

Oseltamivir was initiated in 91.94% of patients, with a mean initiation time of 1.75 days after symptom onset, within the critical 48-hour window recommended by current guidelines (25). Although antiviral therapy is routinely recommended for all hospitalized children with suspected influenza, its efficacy in altering the course of established CNS manifestations remains uncertain, and the optimal duration of oseltamivir therapy in this setting has not been clearly defined (36, 37). Antiviral therapy was initiated later in severe cases, likely due to atypical presentations without respiratory symptoms. This delay is clinically significant, as early antiviral treatment is known to reduce disease severity. Severe cases required immunomodulatory treatments, and only 40% of these patients achieved complete recovery. Given the proposed role of dysregulated inflammation in pathogenesis, immunomodulatory therapies

may attenuate excessive inflammation and limit secondary neuronal injury, although current evidence remains inconsistent and varied regarding mortality and morbidity (2, 32, 38, 39). Therefore, early recognition, timely initiation of treatment, and prompt clinical decision-making regarding immunomodulatory therapy appear to be critical to improving outcomes (39, 40).

IANC represents a broad clinical spectrum. The overall prognosis is generally favorable. Neurological symptoms typically resolve within 48–72 hours, and 90.2% of patients achieve complete recovery, closely paralleling international series (7, 18). However, these results should not obscure the substantial clinical burden of severe disease. The frequent need for newly initiated antiepileptic therapy (17%), continuation of antiepileptic treatment at discharge (39.8%), intensive care admission (15.9%), and mechanical ventilation (7.6%) in severe cases underscores substantial healthcare utilization and clinical burden. A poor outcome was observed in 9.82% of patients (n = 39), with a mortality rate of 1.3% (n = 5). Although lower than reports in encephalopathy-focused cohorts—where mortality reaches 13% or higher—it remains higher than that observed in broader populations (17, 20, 29, 30, 41).

A major strength of this study is the incorporation of a six-month neurological follow-up, addressing an important limitation of many previous studies focused on short-term outcomes. Prior reports indicate that up to 50% of children with infective encephalitis develop neurological sequelae, with approximately 20% experiencing severe impairment. It is recommended that all children diagnosed with encephalitis undergo follow-up evaluations for at least one year (42). Neurological recovery may be delayed or incomplete, particularly in children with severe disease, underscoring the potential severity of neuroinfluenza and the need for structured long-term neurological surveillance. In this context, a key novel contribution of our study is the development of the NISS, designed to predict follow-up outcomes. The NISS demonstrated excellent predictive performance, with 82.05% sensitivity and 91.9% specificity at a score ≥ 2. Notably, all fatal outcomes occurred exclusively among patients classified as severe neuroinfluenza by NISS, supporting its practicality as an effective scoring system for early risk stratification and timely escalation of care. As its use becomes increasingly prevalent, its clinical utility and impact on patient outcomes may be more precisely defined.

This study has several limitations. Its retrospective design may have introduced selection and information bias. Variations in diagnostic approaches, treatment strategies, and resource availability across participating centers may also have affected data consistency. CSF analysis and influenza PCR testing were not performed uniformly, limiting assessment of viral neuroinvasion. Although six-month follow-up data were available, longer-term neurological outcomes could not be evaluated. Differences in healthcare systems, clinical practices, and resource availability may limit the generalizability of these findings to other settings.

Conclusion

IANC represents a potentially life-threatening spectrum of conditions in and requires a high index of clinical suspicion. Influenza should be considered in children presenting with neurological

manifestations, even in the absence of fever or respiratory symptoms. Early recognition, timely neuroimaging, and prompt initiation of antiviral therapy are critical for improving outcomes. Laboratory findings at presentation, together with the NISS, may provide a practical approach to early risk stratification (21).

The low vaccination rate represents a critical and preventable gap. Influenza vaccination remains the most effective strategy for preventing influenza-related morbidity and IANC (21). Furthermore, because neuroinfluenza may affect a broader age range, vaccination strategies and increased awareness among healthcare providers are essential. The heterogeneous nature of neuroinfluenza highlights the need for larger studies to better understand its clinical spectrum, while public health actions are essential to reduce its impact.

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Tables

Tables 2 to 7 are available in the Supplementary Files section.

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