Epilepsi 2021;27(1):39-46 DOI: 10.14744/epilepsi.2020.99266

ORIGINAL ARTICLE

Probable Risk Factors for Epilepsy Development Following Febrile Seizure: A Retrospective, Observational Study

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Summary

Objectives: The purpose of this study was to investigate the risk factors for epilepsy development following febrile seizure (FS).

Methods: This study included 449 patients undergoing first FS between 2014 and 2017. The sociodemographic, clinical, and electroencephalography (EEG) characteristics of the patients were retrieved from hospital records. Patients followed-up for at least 3 years after FS were divided into two groups (epilepsy and FS group; FS only group).

Results: Of the 449 patients followed-up due to FS (238 [53.2%] boys and 211 [46.8%] girls), 42 (9.4%) were diagnosed with epilepsy during follow-up. The mean age at the time of the first FS was 21.4±14.5 months. A positive family history of FS and epilepsy was observed in 217 (48.3%) and 66 (14.7%) patients, respectively. In terms of FS characteristics, the prevalence of complex FS was significantly higher in the subsequent epilepsy group. The presence of a history of perinatal asphyxia and epileptiform or background abnormality findings at first EEG was also significantly higher in the subsequent epilepsy group (p<0.001).

Conclusion: The findings of this study show that a history of perinatal asphyxia, complex FS, and epileptiform discharges at initial EEG exhibited an increased association with epilepsy development.

Keywords: EEG; epilepsy; febrile; perinatal history; seizure.

Cite this article as: Hancı F, Türay S, Kocabey H, Kabakus N. Probable Risk Factors for Epilepsy Development Following Febrile Seizure: A Retrospective, Observational Study. Epilepsi 2021;27:39-46.

Introduction

Febrile seizure (FS) represents the most frequently seen convulsive event in childhood observed in 2%–5% of infants and children. The American Academy of Pediatrics defines FS as seizures accompanied by fever (>38°C, measured by any technique) in neurologically healthy infants and children (from 6 to 60 months of age) with no intracranial infection, metabolic disturbance, or history of afebrile seizures.[1] Moreover, FS are further subdivided as simple or complex. A long duration (>15 min), focal or lateralized convulsive activity, or repeated occurrence in a 24-h interval were defined as complex FS, while simple FS was defined as generalized tonic–clonic seizure of <15 min in 24 h with fever ≥38°C at any time immediately prior, during, or after.[1] Previous FSs have been reported in 10%–15% of epileptic children.[2–4] The risk of epilepsy developing after FS ranges between 2.0% and 7.5%, while the estimated risk of developing epilepsy after complex FS is 10%–20%.[4] The predictive risk factors for epilepsy development in previous studies include developmental delay or abnormal neurological examination findings before the onset of FS; a history of complex FS (including febrile status epilepticus); presence of epilepsy in a first-degree relative; and prolonged FS, cerebral palsy, or low APGAR scores at 5 min.[5] The cohort study of Chiang et al.[6] reported that the female gender, comorbid autism with FS, and recurrent FS exhibited an increased association with epilepsy development.

Studies investigating the predictive value of electroencephalography (EEG) for epilepsy development in patients diagnosed with FS have demonstrated that focal epileptiform discharges on EEG were a significant risk factor for epilepsy

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Received 10.08.2020
Accepted 12.10.2020
Online date 22.01.2021

Febril Nöbetlerden Sonra Epilepsi Gelişimi İçin Olası Risk Faktörleri: Geriye Dönük Gözlemsel Bir Çalışma

Özet

Amaç: Bu çalışmanın amacı, febril nöbet sonrası epilepsi gelişimi için risk faktörlerini araştırmaktır.

Gereç ve Yöntem: Çalışmaya, 2014-2017 yılları arasında ilk kez febril nöbet geçiren 449 hasta dahil edilmiştir. Bu hastaların sosyodemografik, klinik ve elektroensefalografik özellikleri hastane kayıtlarından elde edilmiştir. Febril nöbet sonrası en az üç yıl takip edilen hastalar; epilepsi ve febril nöbet tanısı alanlar ve sadece febril nöbet tanısı alanlar olarak iki gruba ayrılmıştır. Çalışmada bu iki grup birbiriyle karşılaştırılmıştır.

Bulgular: Febril nöbet tanısı ile izlenen 238'i (%53.2) erkek, 211'i (%46.8) kız toplam 449 hastanın 42'sine (%9.4) takibi sırasında epilepsi tanısı konulmuştur. İlk febril nöbet zamanında ortalama yaş 21.4±14.5 ay idi. Hastaların 217'sinde (%48.3) febril nöbet aile öyküsü, 66'sında (%14.7) ailede epilepsi öyküsü vardı. Febril nöbet özellikleri açısından, epilepsi grubunda kompleks febril nöbet prevalansı anlamlı olarak daha yüksekti. Perinatal asfiksi öyküsü ve ilk elektroensefalografide epileptiform veya zemin ritmi anormalliğinin olması epilepsi grubunda anlamlı olarak daha yüksekti (p<0.001).

Sonuç: Başlangıç elektroensefalografisinde epileptiform deşarj olması, perinatal asfiksi öyküsünün olması ve ilk febril nöbetin kompleks tipte olması epilepsi gelişimi için risk faktörleri arasında sayılabilir.

Anahtar sözcükler: Elektroensefalografi; epilepsi; febril; perinatal öykü; nöbet.

after FS.[7,8] Thus, this study aims to examine the risk factors for subsequent epilepsy in patients with FS.

Materials and Methods

Participants– This study included 449 patients who were presented to the pediatric neurology clinic between 2014 and 2017 and diagnosed with FS. Medical histories and clinical and laboratory findings were retrospectively retrieved from the hospital data system.

On the one hand, the inclusion criteria were age between 6 months and 6 years, meeting the FS criteria outlined below in the Definitions section, and regular follow-up for at least 3 years. On the other hand, the exclusion criteria were patients with previous epilepsy or cerebral palsy and patients diagnosed with meningitis or encephalitis within the previous month or concurrently.

Definitions: FS was defined as a seizure occurring in association with febrile illness in the absence of any other cause of acute symptomatic seizure (e.g., infection of the central nervous system or acute electrolyte imbalance) and is the most common form of seizure in childhood.[1] Complex FS was defined as either focal or multiple seizures, seizures exceeding 15 min in duration, or a combination thereof. Consequently, simple FS was defined as a single generalized seizure occurring within 24 h and seizures <15 min in duration.[1]

Epilepsy was diagnosed based on diagnostic and clinical criteria of the International League Against Epilepsy 2017.[9] Psychosocial development and intelligence were assessed using age-appropriate psychometric tests. The standardized, Turkish-language version of the Denver Developmental Screening Test II was used to assess cognitive development.[10] Children with age-developmental delay based on the different developmental stages were diagnosed with developmental retardation.

Methods: The data collected included demographics (date of birth and gender), neonatal intensive care unit (NICU) stay (present or absent), history of asphyxia (present or absent), family history of FS (present or absent), family history of epilepsy (present or absent), age at first FS (months), total FS count, history of vaccination before FS, first seizure type (simple or complex), duration of first FS (<5, 5–15, or >15 min), body temperature during a seizure (37°C–38°C, 38.1°C–39.3°C, or >39.3°C), source of the disease (e.g., upper respiratory tract infections, otitis, lower respiratory tract infections, acute gastroenteritis, fever of unknown focus), findings at first EEG (background abnormalities or epileptiform discharges), psychiatric comorbidity (present or absent), neuromotor development (normal or abnormal = global development delay), and epilepsy after FS (present or absent).Clinical characteristics, including FS features, perinatal features, additional psychiatric comorbidity, initial interictal electroencephalographic findings, and subsequent epilepsy, were also reviewed. In addition, the odds ratio (OR) of subsequent epilepsy was estimated. The mean follow-up duration for subsequent epilepsy was 4.5 years (range, 3.1–5.6 years).

Approval for this study was granted by the Ethics Committee of Bolu Abant Izzet Baysal University (2019/253). Informed consent was received from the parents or caregivers of all children.

Statistical analysis– Continuous data were expressed as mean±SD (min–max), and categorical variables as frequen-

cy and percentage for each group. A range of statistical tests was applied, depending on the normality of data distribution. Moreover, the Kolmogorov–Smirnov test was used to determine the normality of the distribution of the variables. The independent-sample t-test was applied to normally distributed variables, while Pearson's chi-square test and Fisher's exact test were applied to categorical variables. Logistic regression models (univariate and multivariate) were used to estimate crude and adjusted OR to predict the associations between FS and epilepsy. The results were assessed within 95% confidence interval and at significance level of $p < 0.05$. Analyses were performed on Statistical Package for Social Sciences, version 25.0, for Windows software (SPSS Inc., IBM, Chicago, IL, USA). Complete case analysis was used because <10% of data were missing.

Results

Of the 449 patients followed-up due to FS, 42 (9.4%) were diagnosed with epilepsy. The mean duration of follow-up for subsequent epilepsy was 4.5 years (range, 3.1–5.6 years).

The patient group consisted of 238 (53.2%) boys and 211 (46.8%) girls. The mean age at the time of first FS was 21.4±14.5 months. A positive family history of FS and epilepsy was present in 217 (48.3%) and 66 (14.7%) patients, respectively. The mean age at onset of epilepsy was 56.9±12.3 (24–78) months. The mean total FS count was 2.5±1.7. Four (0.9%) patients had a history of vaccination before FS, and 10% had a history of asphyxia during birth. Moreover, 71 (15.8%) and 73 (16.3%) patients had a history of prematurity and NICU admission. No statistically significant difference was found between patients subsequently developing epilepsy and those without epilepsy in terms of the sociodemographic parameters (e.g., age at first FS, gender, and family histories of epilepsy of patients with FS) or the perinatal characteristics of prematurity or NICU stay. However, the perinatal asphyxia rates were significantly higher in patients with subsequent epilepsy (Table 1).

Table 1. Demographic and perinatal clinical characteristics of patients with febrile seizures with or without subsequent epilepsy

Variables	Total n (%) or mean±SD (range)	Without epilepsy (n=407)	With epilepsy (n=42)	p
Age at first FS (months)	21.4±14.5 (1-78)	21.3±14.3 (2-72)	22.9±16.5 (1-78)	0.37[b]
Seizure frequency	2.5±1.7 (1-15)	2.4±1.7 (1-15)	2.8±2.1 (1-9)	0.63[b]
Gender				0.95[c]
F	211 (46.8)	191 (46.7)	20 (47.6)	
M	238 (53.2)	216 (53.1)	22 (52.4)	
Family history of epilepsy				0.84[c]
Yes	66 (14.7)	330 (84.3)	34 (81)	
No	364 (81.1)	60 (14.8)	16 (14.3)	
Missing	19 (4.2)	17 (3.9)	2 (4.8)	
Family history of FS				0.92[d]
Yes	217 (48.3)	193 (47.4)	21 (50)	
No	214 (47.7)	198 (48.6)	19 (45.2)	
Missing	18 (4)	16 (3.9)	2 (4.8)	
History of asphyxia				0.019[c]
Yes	10 (2.2)	6 (1.5)	4 (9.5)	
No	424 (94.4)	387 (95.1)	37 (88.1)	
Missing	15 (3.3)	14 (3.4)	1 (2.4)	
Gestational age				0.54[c]
Preterm	71 (15.8)	63 (15.5)	8 (19)	
Term	378 (84.2)	344 (84.5)	34 (81)	
History of admission to the NICU				0.83[d]
No	361 (80.4)	328 (80.6)	33 (78.6)	
Yes	73 (16.3)	65 (16)	8 (19)	
Missing	15 (3.3)	14 (3.4)	1 (2.4)	

Data are expressed as n (in percentage). Bold p values indicate statistical significance at α=0.05. [a]Independent samples t-test, [b]Mann–Whitney U-test, [c]Fisher's exact test, [d]Pearson's chi-square test. F: Female; M: Male; EEG: Electroencephalogram; NICU: Neonatal intensive care unit; FS: Febrile seizure.

This study had two patients who had their first seizure with febrile status. Both were followed-up in the intensive care unit, the status protocol was applied, and the patients were then started with prophylactic antiepileptic. The prognosis was good during 3–4 years of follow-up, and afebrile seizure was not observed.

Table 2. Patients' febrile seizure characteristics

Variables	Total n (%) or mean±SD (range)	Without epilepsy (n=407)	With epilepsy (n=42)	p
First seizure type				0.015[a]
Simple	399 (88.9)	366 (89.9)	33 (78.6)	
Complex	46 (10.2)	39 (9.6)	7 (16.7)	
Missing	4 (0.9)	2 (0.5)	2 (4.8)	
Duration of first FS				0.004[b]
<5 min	294 (65.5)	269 (66.1)	25 (59.5)	
5–15 min	96 (21.4)	91 (22.4)	5 (11.9)	
>15 min	44 (9.8)	37 (9.1)	7 (16.7)	
Missing	15 (3.3)	10 (2.5)	5 (11.9)	
Body temperature during seizure (°C)				0.055[a]
37–38	34 (7.6)	30(7.4)	4 (9.5)	
38.1–39.3	377 (84)	341(83.8)	36 (85.7)	
>39.3	37 (8.2)	36 (8.8)	1 (2.4)	
Missing	1 (0.2)	0 (0)	1 (2.4)	
Origin of disease				0.56[a]
Upper respiratory tract infection	200 (44.5)	179 (44)	20 (47.6)	
Otitis	12 (2.7)	11 (2.7)	1 (2.4)	
Low respiratory tract infection	23 (5.1)	20 (4.9)	3 (7.1)	
Acute gastroenteritis	16 (3.6)	15 (3.7)	1 (2.4)	
Fever of unknown origin	198 (44.1)	173 (42.5)	17 (40.5)	
Other	9 (2)	9 (2.1)	0 (0)	

Data are expressed as n (in percenrage). Bold p values indicate statistical significance at α=0.05. [a]Fisher's exact test, [b]Pearson's chi-square test.
F: Female; M: Male; EEG: Electroencephalogram; FS: Febrile seizure.

Table 3. Initial EEG findings and additional psychiatric comorbidities

Variables	Total n (%) or mean±SD (range)	Without epilepsy (n=407)	With epilepsy (n=42)	p
EEG findings				0.022[a]
Normal	200 (44.5)	188 (47.6)	12 (28.6)	
Background abnormalities (diffuse or focal slowing)	191 (42.5)	170 (43)	21 (50)	
Epileptiform discharges	43 (9.6)	34 (8.6)	9 (21.4)	
Missing	15 (3.4)	3 (0.8)	0 (0)	
Neuromotor development				0.22[a]
Normal	408 (91.9)	372 (91.4)	36 (85.7)	
Abnormal	41 (9.1)	35 (8.6)	6 (14.3)	
Additional psychiatric comorbidity				0.055[a]
No	400(89.1)	35 (8.6)	8 (19)	
Yes	43 (9.6)	367 (90.2)	33 (78.6)	
Missing	6 (1.3)	5 (1.2)	1 (2.4)	

Data are expressed as n (in percentage). Bold p values indicate statistical significance at α=0.05. [a]Fisher's exact test, [b]Pearson's chi-square test.
EEG: Electroencephalogram.

All patients received antipyretics. In addition, 45 patients received prophylactic antiepileptic drugs. No difference in prognosis was noted between patients who received prophylactic antiepileptics and those who did not.

In terms of FS characteristics, the prevalence of complex FS and duration of seizure >15 min were significantly higher in the subsequent epilepsy group ($p<0.05$). However, no significant differences were observed between the FS with subsequent epilepsy and FS without epilepsy groups in terms of fever during seizure or source of infection (Table 2).

The rates of epileptiform and background abnormality at first EEG were higher in the FS with subsequent epilepsy compared with the group without epilepsy. No statistically significant difference was determined between patients with and without additional psychiatric comorbidity according to these two groups. No statistically significant difference between the two groups was also found in terms of patients with normal neuromotor development and global developmental delay (Table 3).

The multivariate analysis results for independent risk factors predicting epilepsy after FS are shown in Table 4. On the one hand, a crude OR of 6.97 for epilepsy was calculated in children with histories of perinatal asphyxia (95% CI, 1.88–25.8; p=0.004). On the other hand, a crude OR of 4.1 for epilepsy after FS was determined in children with epileptiform EEG (95% CI, 1.6–10.59; p=0.003).

Discussion

The present study found that the prevalence of epilepsy development in patients followed-up due to FS was 9.4% (42/449) and was higher than in the previous studies (2%–7.5%).[2–4,6] One study comparing patients with FS with the healthy control group reported a significantly higher association with epilepsy (18.76-fold) in individuals with FS compared to controls and that epilepsy developed in 3.3% (32/952) of patients followed-up due to FS.[6] Another study searching epilepsy development in patients undergoing first FS >5 years old reported epilepsy development in 14% (n=64) of patients.[11] Similar to the present study, Lee et al.[12] reported the incidence of subsequent epilepsy after FS at 10% (25/249) in children with a mean age of 21.8±13.8 months. The generally higher incidence of epilepsy development in the present study compared with the previous literature may be due to the closer follow-up of at-risk patients and to the sample group selected in this study.

Chiang et al.[6] found a higher risk of developing epilepsy in female patients (female gender) undergoing FS in their cohort study. However, another study found no gender difference similar to the present research in terms of FS development.[11]

No relationship between age at first FS or seizure frequency (mean, 2.5±1.7) and epilepsy development was determined. In one study, the subsequent occurrence of epilepsy in patients with a history of FS was associated with a seizure frequency >10 in the first 2 years after seizure onset.[12]

Table 4. Results of multivariate analysis for predicting independent risk factors for epilepsy after febrile seizures

Variables	p value	Odds ratio (95% CI)
Age	0.83	0.97 (0.76–1.24)
Gender (male)	0.38	0.41 (0.06–2.9)
Birth week (preterm)	0.54	1.28 (0.56–2.9)
History of admission to the neonatal ICU	0.74	0.7 (0.09–5.5)
Family history of epilepsy	0.85	1.96 (0.001–2968.3)
First seizure type	0.08	2.1 (0.89–5.32)
Duration of first FS		
5–15 min	0.28	0.58 (0.21–1.57)
>15 min	0.09	2.21 (0.88–5.5)
Asphyxia	0.004	6.97 (1.88–25.8)
Additional psychiatric comorbidity	0.47	2.22 (0.25–19.6)
EEG (epileptiform)	0.003	4.1 (1.6–10.59)

Results of multivariate logistic regression analysis for epilepsy after febrile convulsion as the dependent variable. The goodness of fit of the model in the logistic regression analysis was confirmed by a p value of 0.819 with the Hosmer–Lemeshow test. CI: Confidence interval; ICU: Intensive care unit; EEG: Electroencephalogram; FS: Febrile seizure.

Moreover, in Chiang et al.'s[6] cohort study of 952 patients diagnosed with FS and 3,808 age- and sex-matched controls from Taiwan, the frequency of subsequent development of epilepsy among patients who experienced FS was 4.846-fold greater in patients with recurrent FS. Similar to another study, recurrent FS was identified as a risk factor for subsequent afebrile seizure.[13] The failure of the present study to determine a relationship between seizure frequency and epilepsy development may be due to the mean seizure frequency of this study being lower than in those studies (2.5±1.7).

A family history of epilepsy has been linked to subsequent epilepsy in some studies,[5,13] while subsequent epilepsy was reported to be independent of a family history of epilepsy in others.[11] This study found no association between family histories of epilepsy or FS and epilepsy development.

In terms of perinatal characteristics, no association between history of prematurity (gestational age) or history of NICU stay and epilepsy development was observed, although a history of asphyxia in the perinatal period and epilepsy development were associated. The history of asphyxia is a risk factor for epilepsy development after FS. In addition, Lee et al.[12] reported that a history of preterm birth (p=0.001) was associated with the subsequent occurrence of epilepsy. In another study, the long-term risk of epilepsy after FS was higher among patients with low APGAR scores at 5 min.[5] One study investigating the risk factors for epilepsy in children undergoing first FS after 5 years old reported a higher incidence of subsequent epilepsy after FS, and that this was independent of prenatal and natal history.[11] The APGAR scores were not included because these were lacking in the records, and only a history of asphyxia was higher among patients developing epilepsy among the perinatal factors.

The relationship between complex FS and the duration of seizure exceeding 15 min and subsequent development of epilepsy has not been well described in the literature. Kim et al.[7] reported a significantly higher incidence of prolonged (>10 min) seizure or the presence of multiple seizures for 24 h in patients with subsequent epilepsy in their study of 183 patients diagnosed with complex FS, while no such association was observed for the presence of focal seizure. Consequently, Nelson et al.[14] described the characteristics of the first FS (longer than 15 min, multiple or focal) as important predictors. Another study reported the initial FS within 1 h of developing fever and focal FS as risk factors for subsequent afebrile seizure.[13] In this study, the incidence of complex FS and duration of seizure exceeding 15 min were significantly higher in the subsequent epilepsy group. However, no significant difference in fever during FS and infection source was observed between the FS with subsequent epilepsy and FS without epilepsy groups.

In their study of 119 patients, Kanemura et al.[15] reported subsequent epilepsy in three of the 93 patients with normal EEG and six of the 26 patients with abnormal EEGs. Their study of EEG localization abnormality in patients developing epilepsy suggested that patients with FS presenting with frontal paroxysmal EEG abnormalities may be at risk for epilepsy. Some studies in the literature have reported that epileptiform discharges on EEG were associated with subsequent occurrence of epilepsy[12] and that the incidence of epileptiform discharges (focal in all cases) was significantly higher in patients with subsequent epilepsy.[7] Similar to that study, focal EEG discharges in patients with FS have been described as predictive of later epilepsy, but not generalized discharges.[8] Furthermore, epileptiform discharges were not differentiated as focal or generalized in the present study because the incidence of epilepsy development was higher in patients with epileptiform discharges and slow background activity.

The relationship between epilepsy and autism spectrum disorders (ASD) has been well described in previous studies.[16,17] However, in one of the few studies of FS and epilepsy development following FS, Chiang et al.[6] reported a higher risk of epilepsy development in patients with comorbid ASD in their cohort study of patients diagnosed with FS. Furthermore, no association between comorbid psychiatric diseases (ASD, attention deficit hyperactivity disorder, or behavioral problems) and epilepsy development was detected.

Studies have reported a higher rate of epilepsy development in children with neurodevelopmental delay together with FS.[12,13] In addition, Nelson et al.[14] described previous neurological and developmental status as a significant predictor of epilepsy after FS in one of the studies on that subject. However, no difference in terms of epilepsy development was determined in the present study between patients with and without neurodevelopmental delay. This study had very few patients with global developmental delay (41/449), and most patients had simple and very few FS. In the literature, no significant difference was found when patients with febrile status epilepticus and simple febrile convulsion were compared in terms of cognitive functions after 1 month and 1 year.

In the present study, the frequency of subsequent development of epilepsy among FS patients was 6.97-fold great-

er among patients with a history of asphyxia and 4.1-fold higher in patients with epileptiform discharges on initial EEG.

Study limitations– The limitations of this study include its retrospective nature, the absence of MRI findings, the absence of localized EEG characteristics, epilepsy was not grouped according to types, and the short follow-up time.

Moreover, the strengths of this study include the adequate patient number, it is one of the few investigations into the subject, and patients were assessed from several perspectives.

Conclusion– In light of the results of this study, patients diagnosed with FS should be followed-up more closely in terms of potential epilepsy development in case of a history of asphyxia in the perinatal period if the first FS is complex and exceeds 15 min in duration or epileptiform discharges and background abnormalities were present at first EEG performed 7–20 days after the first FS. In addition, prophylactic antiepileptic use is recommended in patients with these findings to reduce the recurrence of FS or to prevent the development of febrile status. However, previous studies have reported that the use of prophylactic antiepileptic drugs has been reported not to prevent the development of epilepsy.[18–20]

FS is frequently seen and is generally regarded as a benign entity. However, further prospective studies with patients diagnosed with FS and receiving long-term follow-up (10–15 years) are now needed to investigate the relationship with epilepsy at long-term follow-up and search for neurocognitive and behavioral outcomes. It may be appropriate to perform neuroimaging for hippocampal abnormality, especially in patients with recurrent complex FSs and developing febrile status, and to follow-up these patients more closely for epilepsy development.[19]

Funding– This research received no specific grant from any public or commercial funding agency.

Ethics Committee Approval– Ethics committee approved.

Peer-review– Externally peer-reviewed.

Conflict of interest– The authors declare that they have no conflict of interest.

Authorship Contributions– Concept: F.H., S.T., N.K.; Design: F.H., N.K.; Supervision: F.H., H.K.; Materials: F.H., H.K.; Data collection &/or processing: F.H., S.T., H.K.; Analysis and/or interpretation: F.H., N.K.; Literature search: F.H., S.T.; Writing: F.H., S.T.; Critical review: N.K., F.H.

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