Epilepsy & Behavior 165 (2025) 110321

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Neurofilament light chain and glial fibrillary acidic protein as diagnostic and prognostic biomarkers in epileptic seizures and epilepsy: A systematic review

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ARTICLE INFO

Keywords:
Fluid biomarkers
NfL
GFAP
Epilepsy
Epileptic seizures

ABSTRACT

Epileptology – with epilepsy as one of the most common neurological diseases – has an urgent need for easily accessible biomarkers to improve diagnosis, prognosis and therapeutic monitoring. Neurofilament light chain (NfL) and Glial Fibrillary Acidic Protein (GFAP) have emerged as promising fluid biomarkers in various neurological disorders. Their potential role in epileptic seizures and epilepsy remains largely unexplored. To assess the current state of research on this topic we comprehensively searched the published literature for studies on GFAP and/or NfL in cerebrospinal fluid and/or blood in adult humans with epileptic seizures, status epilepticus or epilepsy (last data base search on 10th of May 2024). We identified a total of 2285 publications of which 19 fulfilled our search criteria. The studies targeted various outcomes such as prognosis in status epilepticus, differentiation of seizure semiology and etiology, differentiation of epileptic seizures from non-epileptic conditions, prediction of epilepsy in autoimmune epilepsy, after a stroke or after a first unprovoked seizure, the role of the time interval from seizure to sampling, the association with disease duration as well as seizure frequency and the influence of seizure suppressing medication. The results are heterogeneous but indicate promising applications for both NfL and GFAP in diagnosis and prognostication of patients with epileptic seizures and epilepsy.

In the present review we summarize the current evidence, future perspectives, but also limitations, of NfL and GFAP as fluid biomarkers in epilepsy and epileptic seizures.

1. Introduction

Robust and easily accessible fluid biomarkers are urgently needed to improve diagnosis, prognosis and the therapeutic monitoring of patients with epilepsy, status epilepticus and epileptic seizure. In routine clinical practice, no single fluid biomarker can be used to identify patients at a higher risk for recurrent seizures as well as of a worse course of disease, and prognostication still relies on different clinical, imaging and semiological features.

Proteins such as the astrocytic protein S100B and several inflammatory proteins such as interleukins, interferon gamma or tumor necrosis factor alpha, among others, have been assessed for their feasibility as biomarkers in epilepsy but have so far not gained significance in the clinical routine [1]. Reasons for this are various. Firstly, studies on all those proteins and epilepsy are scarce and their results inconclusive. Secondly, alterations of these biomarkers are mostly unspecific and regarding inflammatory markers could also be induced by systemic causes. Furthermore, for some proteins including S100B the short half-

Abbreviations: GFAP, glial fibrillary acidic protein; CNS, central nervous system; ILAE, International League Against Epilepsy; IQR, interquartile range; LGI1, leucine rich glioma inactivated 1; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; mRS, modified Rankin scale; NfL, neurofilament light chain; NMDA, N-methyl-D-aspartate; PREDICT, personalized screening, risk prediction, and understanding disease trajectories for early detection of disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

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https://doi.org/10.1016/j.yebeh.2025.110321
Received 7 October 2024; Received in revised form 25 January 2025; Accepted 11 February 2025
Available online 20 February 2025

life hampers the reliable use of protein levels [2]. Interestingly, several studies have shown a rise of prolactin levels after an epileptic seizure and the diagnostic value of this easy accessible protein has been proposed [3–7]. Unfortunately the feasibility of prolactin in the detection of epileptic seizures is on the one hand limited by distinct intra- and interindividual blood level fluctuations and on the other hand by a large rate of false-positive values which was shown by post-seizure sampling in patients with psychogenic non-epileptic seizures [8].

In recent years, neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) have emerged as promising biomarkers of neuroaxonal and astrocytic affection, respectively, in virtually all neurological disorders [9–14]. Indeed, their levels in cerebrospinal fluid (CSF) and blood samples were associated with disease activity and severity in multiple sclerosis, Alzheimer's disease, traumatic brain injury and neuroinfectious diseases, among others [9–11,15].

Given the large evidence in literature with concrete attempts of next clinical implementation [9,10], the use of NfL and GFAP may positively impact on the routinary management of people with epileptic seizures and epilepsy with special regards to differential diagnoses between etiologies, prognostication and treatment monitoring (Fig. 1). In contrast to the previously established blood markers for epileptic activity such as myoglobin, creatine kinases or lactate, which reflect muscular involvement due to an acute epileptic event, NfL and GFAP reflect central nervous damage or dysfunction. Another advantage of the usage of NfL and GFAP as easily accessible blood biomarkers might be in the chronic course of the disease, which could potentially allow the assessment of subclinical disease activity and therapy monitoring. As both biomarkers are known to be elevated in cerebral lesions [9–14] their use could significantly support the determination of structural seizure etiology, particularly in cases with initially negative imaging. Also, studying these biomarkers could provide further insights into the pathophysiology of epilepsy, potentially leading to the development of tailored therapeutic interventions.

So far, the role of NfL and GFAP in epilepsy and epileptic seizures has not been explored systematically and very few studies with heterogeneous results exist on this topic.

In this systematic review, we aimed to summarize and critically evaluate the existing literature on the utility of NfL and GFAP as fluid biomarkers for diagnostic and prognostic purposes in adult patients with epileptic seizures and epilepsy. Moreover, we discuss the potential application of such biomarkers as secondary outcome measures in clinical trials assessing novel therapies for epilepsies.

2. Methods

We conducted this study by following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for systematic reviews [16,17] and a predetermined protocol shared with all authors. The systematic search was conducted by two independent investigators (AT and LB) on the Rayyan platform (rayyan.ai) by screening publicly available online databases (PubMed and Web of Science) from database opening to the 10th of May 2024. Search strategy included Boolean search, the use of key words and MeSH terms (complete search string: **Supplementary Fig. S1**). We included in the final analysis studies with full text available in English language meeting the following inclusion criteria: 1) study population with only adult patients (≥18 years of age); 2) subjects with a history of epileptic seizures or epilepsy; 3) available data on NfL and/or GFAP in CSF and/or blood. Exclusion criteria were studies on animals, studies on subjects younger than 18 years, no history of epileptic seizures or epilepsy, preeclampsia/eclampsia and only febrile seizures as well as studies without full text availability, conference papers as well as in languages other than English. Furthermore, we excluded studies that measured NfL and/or GFAP in in vitro models or via immunohistochemical methods on human tissues from biopsies, resections or postmortem samples. Article headings and abstracts were than screened regarding relevance, eligibility criteria and duplication (PRISMA flow-chart: **Supplementary Fig. S2**). Reference lists of the selected articles were hand-searched to

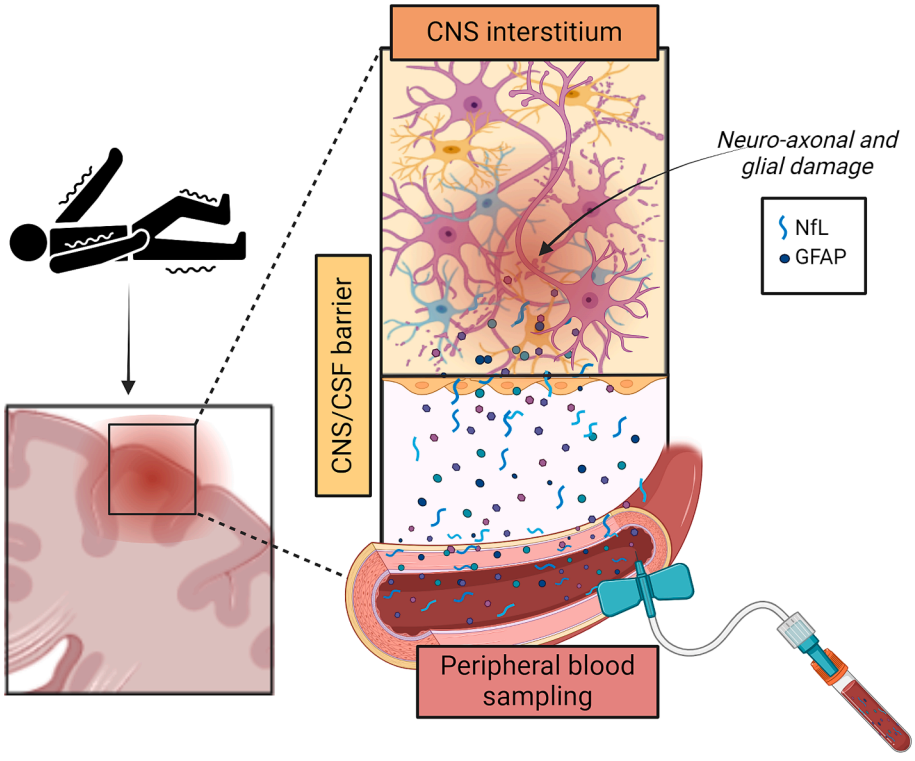

Fig. 1. Application of NfL and GFAP as blood biomarkers. Epileptic activity could trigger central nervous damage or dysfunction. This could lead to an increased release of the neuroaxonal protein neurofilament light chain and the astrocytic protein glial fibrillary acidic protein into the CNS interstitium. By crossing over the blood brain barrier, NfL and GFAP can enter the blood stream and can be detected in a peripheral blood sample.

add potentially useful data. The selection was shared between all co-authors before analysis.

3. Results

By using the reported search string, our initial search provided 2285 articles (PubMed: 790 publications, Web of Science: 1495), of which 529 duplicates were removed before screening. We screened title and abstracts of the remaining 1756 articles and selected 78 articles for full-text assessment of eligibility. Of these, we excluded 23 studies for wrong study design, 18 for wrong target population and 15 for wrong publication type. A final number of 19 publications [16–34] fulfilling our search criteria were included in the final analysis (articles are detailed in **Supplementary Table S1**).

Ten studies analyzed NfL but not GFAP [16,18,19,21–23,28–30,34], of which four studies investigated NfL levels in both CSF and serum samples [22,29,30,34], the other six studies serum NFL levels only [16,18,19,21,23,28]. We identified three studies addressing GFAP but not NfL in serum samples only [24,27,32]. The remaining six studies dealt with both NfL and GFAP [17,20,25,26,31,33]. Two studies analyzed plasma samples only [20,31], one study both plasma and serum samples [17] and three studies both CSF and serum samples [25,26,33].

NfL concentrations were measured with a digital Simoa immunoassay (Quanterix, Billerica, USA) in 11 studies [17,19,20,23,25,26,28–31,34], with a commercial immunoassay for the Ella microfluidic system (BioTechne, Minneapolis, USA) in two studies [21,22] and with a commercially available sandwich ELISA (Uman-Diagnostic, Umea, Sweden) in two studies [16,18]. In one study, information on the method of quantification was not provided [33]. For measuring GFAP, a digital Simoa immunoassay (Quanterix, Billerica, USA) was used in 5 studies [16,20,25,26,31], a commercial sandwich ELISA in two studies (Cusabio Technology LLC, USA) [27] and Abclonal Technology, ZellBio GmbH, Germany) [32]. One group described an in-house established ELISA [24] and in one study no information on the used assay was given [33].

The results of the studies could roughly be divided into three groups: The first group targeted biomarker applications in acute situations in temporal relation to an acute epileptic event (**3.1.**). The second group aims to elucidate the value of NFL and GFAP in chronic course of epileptic disease without a direct temporal relation to an acute seizure event (**3.2.**). The third group contains results that relate to both acute patients and patients with chronic conditions (**3.3.**).

Table 1 (NfL) and Table 2 (GFAP) provide an overview of the studies and their results, organized thematically according to the outcome of interest.

3.1. Application of NfL and GFAP as biomarkers in acute course of disease

12 of the 19 studies [16,17,20–22,24,25,27,31–34] evaluated the application of NfL or GFAP as biomarkers in relation to an acute seizure event, namely differentiating an epileptic seizure from a psychogenic non-epileptic seizure (**3.1.1**) [31,32], prognostication regarding seizure recurrency after a first unprovoked seizure (**3.1.2**) [16,17], establishing the optimal time point of sampling after a seizure event (**3.1.3**) [20–22,24,25,34] and prognostication in status epilepticus (**3.1.4**) [21,22,27,33,34].

3.1.1. Differentiating epileptic seizures from psychogenic non-epileptic seizures

Among the main differential diagnoses of epileptic seizures, psychogenic non-epileptic seizures occur in approximately 20–30 % of patients admitted at epilepsy centers with suspected epilepsy [35].

Table 1
Key studies on CSF and blood NfL in patients with epileptic seizures and epilepsy.

Outcome	Reference	main findings
acute situations (3.1)		
Differentiation of epileptic and psychogenic non-epileptic seizures (3.1.1)	Dobson et al. 2024 [31] Simani et al. 2018 [32]	Significantly ↑ plasma NFL in epileptic vs. psychogenic non-epileptic seizures.
Seizure recurrency/ Prediction of epilepsy after a first unprovoked seizure (3.1.2)	Eriksson et al. 2021 [17] Eriksson et al. 2020 [16]	In both studies association of ↑ NfL with development of post-stroke epilepsy.
Correlation with time of sampling (3.1.3)	Giovannini et al. 2023 [21] Giovannini et al. 2022 [22] Margraf et al. 2023 [34] Nass et al. 2021 [25] Akel et al. 2023 [20]	Significant positive correlation of CSF NfL and serum NfL with time to sampling in one study [34]. Weak negative correlation of plasma NfL and time period from last seizure to sampling in one study [20]. In one study most significant ↑ of serum NfL in early postictal phase [25]. No correlation of NfL and time of sampling in two studies [21,22].
Status epilepticus (3.1.4)	Giovannini et al. 2023 [21] Giovannini et al. 2022 [22] Lybeck et al. 2021 [33] Margraf et al. 2023 [34]	↑ levels in status epilepticus compared to epilepsy and healthy controls [21]. Association of ↑ levels with greater disease severity, 30-d ay clinical outcome and therapy refractoriness [21,22]. No association of serum NfL and CSF NfL with overall mortality [34]. Correlation of NfL levels with duration of status epilepticus [22,34]. Significantly ↑ serum NfL in patients with encephalographic status epilepticus 72 h after cardiac arrest [33].
chronic situations (3.2)		
Differentiation of healthy controls and patients with epilepsy (3.2.1)	Ueda et al. 2023 [19] Gioviannini et al. 2022 [22] Dobson et al. 2024 [31]	One study with significantly ↑ plasma NfL in younger patients with epilepsy [31]. No significant differences in two other studies [19,22].
Association with disease duration (3.2.2)		No studies available.
Correlation with seizure frequency (3.2.3)	Ueda et al. 2023 [19] Akel et al. 2023 [20] Dobson et al. 2024 [31]	Significant correlation of plasma NfL with seizure frequency in one of three studies [20].
Influence of treatment with antiseizure medication (3.2.4)	Eriksson et al. 2021 [17] Ueda et al. 2023 [19] Akel et al. 2023 [20]	One study reported significantly ↓ plasma NfL in patients treated with lamotrigine vs. healthy controls and patients treated with other antiseizure drugs [20]. Two studies found no association with antiseizure medication.
Other (3.3)		
Differentiation of seizure etiology (3.3.2)	Eriksson et al. 2021 [17] Akel et al 2023 [20] Nass et al. 2021 [25] Nass et al. 2021 [26] Dobson et al. 2024 [31]	Two of five studies with association of NfL and seizure etiology [20,26]: one study with ↑ serum NfL and CSF NfL in autoimmune etiology compared to all other etiologies [26], one study with ↑ plasma NfL in younger patients with epileptogenic focus [20].Good discriminatory value of NfL for

(*continued on next page*)

Table 1 (*continued*)

Outcome	Reference	main findings
		autoimmune epilepsy vs. hippocampal sclerosis.
Occurrence of seizures in autoimmune encephalitis (3.3.2)	Luo et al. 2022 [28] Brenner et al. 2023 [30] Guasp et al. 2022 [29] Lardeux et al. 2022 [18]	No association of serum NfL with seizures in the two studies on NMDA-encephalitis, but significantly ↑ CSF NfL when seizures or status epilepticus were present [29,30]. In MOGAD: association of ↑ serum NfL with occurrence of seizures [28].
Differentiation of seizure semiology (3.3.3)	Akel et al. 2023 [20] Nass et al. 2021 [25] Margraf et al. 2023 [34] Dobson et al. 2024 [31]	No association of semiology and NfL levels in three out of four studies.In one study: significantly ↑ plasma NfL in patients with focal seizures [20]

The table shows the main findings on CSF and blood NfL in patients with epileptic seizures and epilepsy thematically ordered and numbered according to the sequence in the main text. Abbreviations: NfL: neurofilament light chain, NMDA: N-methyl-D-aspartate, MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease.

3.1.1.1. NfL in the differentiation of epileptic and non-epileptic psychogenic seizures. One study assessed NfL in the differentiation of epileptic seizures and non-epileptic psychogenic seizures [31]. Dobson et al. found significantly increased plasma NfL levels in patients after an epileptic seizure when compared to patients with a psychogenic non-epileptic seizure.

3.1.1.2. GFAP in the differentiation of epileptic and non-epileptic psychogenic seizures. Two studies assessed GFAP in the differentiation of epileptic seizures and non-epileptic psychogenic seizures [31,32]. GFAP in plasma [31] and serum samples [32] were significantly increased after an epileptic seizure compared to a psychogenic non-epileptic seizure. Patients with a psychogenic non-epileptic seizure disclosed biomarker levels similar to healthy controls.

3.1.2. Seizure recurrency after a first unprovoked seizure

Predicting the occurrence of further seizures after a first unprovoked seizure and thus diagnosing an epilepsy is up to this day a challenging undertaking [36]. With a general risk of 40–52 % for a second seizure after a first unprovoked seizure [37] this leads to an endangering of patients that cannot be diagnosed with an epilepsy after the first seizure and therefore have no indication for antiepileptic therapy.

We found two studies that examined the relation of NfL and GFAP with the development of epilepsy after a first-ever epileptic seizure [16,17]. NfL and GFAP levels were found to be elevated after a first unprovoked seizure in patients that developed post-stroke epilepsy within two years of follow-up.

3.1.2.1. NfL in the prediction of epilepsy after a first unprovoked seizure. After an unprovoked new-onset seizure, plasma NfL measured within 48 days (IQR 64) were found to be increased in patients who received a diagnosis of post-stroke epilepsy, but not other types of epilepsy, within two years compared to patients with a single seizure at follow-up [17]. Moreover, higher serum NfL levels at month three after the stroke event were associated with the development of post stroke epilepsy within two years in a cohort of 90 patients with acute ischemic stroke [median age: 72 (IQR: 65–80) years, median National Institute of Health Stroke Scale, NIHSS: 18 (IQR: 15–22)] undergoing mechanical thrombectomy (successful in 90 %) [16].

Table 2
Key studies on CSF and blood GFAP in patients with epileptic seizures and epilepsy.

Outcome	Reference	main findings
acute situations (3.1)		
Differentiation of epileptic and psychogenic non-epileptic seizures (3.1.1)	Dobson et al. 2024 [31] Simani et al. 2018 [32]	Significantly ↑ plasma GFAP and serum GFAP in epileptic vs. psychogenic non-epileptic seizures.
Seizure recurrency/ Prediction of epilepsy after a first unprovoked seizure (3.1.2)	Eriksson et al. 2021 [17]] Eriksson et al. 2020 [16]	Association with development of post-stroke epilepsy [17].
Correlation with time of sampling (3.1.3)	Mochol et al. 2023 [24] Nass et al. 2021 [25] Akel et al. 2023 [20]	In one study weak negative correlation of plasma GFAP and time period from last seizure to sampling [20]. In one study most significant ↑ of serum GFAP in early postictal phase [25]. No correlation in one study [24].
Status epilepticus (3.1.4)	Lybeck et al. 2021 [33] Mahama et al. 2023 [27]	No differences of serum GFAP in treatment responsive vs. not-responsive status epilepticus [27]. Significantly ↑ serum GFAP in patients with electroencephalographic status epilepticus 72 h after cardiac arrest [33]
chronic situations (3.2)		
Differentiation of healthy controls and patients with epilepsy (3.2.1)	Dobson et al. 2024 [31] Mochol et al. 2023 [24]	Significantly ↑ GFAP in patients with epilepsy compared to healthy controls [24]
Association with disease duration (3.2.2)	Mochol et al. 2023 [24] Simani et al 2018 [32]	No significant associations.
Correlation with seizure frequency (3.2.3)	Simani et al. 2018 [32] Akel et al. 2023 [20] Dobson et al. 2024 [31]	Significant correlation of plasma GFAP with seizure frequency in one of three studies when post-stroke epilepsy was excluded [20].
Influence of treatment with antiseizure medication (3.2.4)	Eriksson et al. 2021 [17] Akel et al. 2023 [20] Mochol et al. 2023 [24]	No association with antiseizure medication was reported.
other		
Differentiation of seizure etiology (3.3.2)	Eriksson et al. 2021 [17] Akel et al 2023 [20] Nass et al. 2021 [25] Nass et al. 2021 [26] Dobson et al. 2024 [31]	One out of five studies with association of ↑ GFAP and seizure etiology [20].Radiological result (structural epileptogenic lesion) was significant predictor of plasma GFAP levels.
Occurrence of seizures in autoimmune encephalitis (3.3.2)	No studies available.	
Differentiation of seizure semiology (3.3.3)	Akel et al. 2023 [20] Mochol et al. 2023 [24] Nass et al. 2021 [25] Dobson et al. 2024 [31]	No association of semiology and GFAP levels in three out of four studies.In one study: significantly ↑ plasma GFAP in patients with focal seizures [20].

The table shows the main findings on CSF and blood GFAP in patients with epileptic seizures and epilepsy thematically ordered and numbered according to

the sequence in the text. Abbreviations: GFAP: glial fibrillary acidic protein, NMDA: N-methyl-D-aspartate, MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease.

3.1.2.2. GFAP in the prediction of epilepsy after a first unprovoked seizure. In the cohort of patients with unprovoked new-onset seizures described for NfL above (**3.1.2.1.**), plasma GFAP was found to be increased in patients who received a diagnosis of post-stroke epilepsy, but not other types of epilepsy, within two years compared to patients with a single seizure at follow-up [17].

3.1.3. Establishment of the optimal time point for sampling

For different acute CNS damages such as stroke it has been shown, that NfL and GFAP reach their maximum levels in CSF and blood not at the time of the event but days (GFAP) or even weeks (NfL) after the event as discussed below. To assess the dynamics of this process in relation to an epileptic seizure and to determine the exact time-point at which biomarker levels reach their peak before declining again would be crucial to generate comparable results. Six studies targeted the influence of the time interval between the onset of an epileptic seizure or a status epilepticus and sampling [20–22,24,25,34]. The results on this are heterogenous. Further studies on this topic with consistent sampling time points over longer time ranges following an epileptic event are much needed. Because of the recurrent sample taking, which would be necessary for this study design, only blood but not CSF biomarkers would be applicable.

3.1.3.1. Time dependent course of NfL levels after an epileptic seizure. Five studies assessed the time dependent course of NfL levels after an epileptic seizure. In two studies no correlation of the time it took to draw the serum samples after the onset of the epileptic seizure and NfL levels were found [21,22]. Three further studies detected alterations in biomarker levels contingent on the time interval it took from seizure onset to sample taking: Margraf et al. found a significant positive correlation for CSF NfL and serum NfL and the time it took from the beginning of the seizure to sampling (CSF NfL: rho = 0.64, serum NfL: rho = 0.55 [34]), Akel et al. a weak negative correlation of plasma NfL and the time period from the last seizure to sampling (rho = -0.22) [20] and Nass et al. the most significant elevation of serum NfL in the early postictal phase directly after a tonic-clonic seizure [25].

3.1.3.2. Time dependent course of GFAP levels after an epileptic seizure. We found three studies on the time dependent course of GFAP levels after an epileptic seizure [20,24,25]. In one of the studies no correlation of the time interval to sample taking and serum GFAP levels [24] was found. However, the other two studies detected alterations in biomarker levels contingent on the sampling time: Akel et al. found a weak negative correlation of plasma GFAP and the time period from the last seizure to sampling (rho = − 0.167) [20] and Nass et al. the most significant elevation of serum GFAP in the early postictal phase directly after a tonic-clonic seizure [25].

3.1.4. Prognostication in status epilepticus

3.1.4.1. Application of NfL in prognostication in status epilepticus. We found four studies regarding the prognostic potential of NfL in status epilepticus [21,22,33,34]. Giovannini et al. compared NfL levels in CSF and plasma of patients with status epilepticus to patients with epilepsy and healthy controls. Elevated biomarker levels were associated with greater disease severity. Indeed, serum NfL levels were found to be significantly higher in refractory or super-refractory status epilepticus than in therapy-responsive status epilepticus (113 pg/mL vs. 64.7 pg/mL, $p = 0.016$), in status epilepticus with duration > 24 h vs. < 24 h ($p = 0.013$) as well as status epilepticus with vs. without clinical worsening within 30 days (as defined by an increase of at least one point on the modified Ranking scale (mRS) within 30 days compared to baseline mRS [22]. In another study from the same group, serum NfL was evaluated in a cohort of patients with status epilepticus, epilepsy and in healthy controls and found to be higher in status epilepticus compared to the latter groups ($p < 0.001$ for both) [21]. Moreover, similar to their previous study [22], the authors found significant associations between elevated serum NfL levels and severity of alterations of consciousness, refractoriness to treatment and 30-d ay clinical outcome. Here, a cutoff of 33.4 pg/ml was found to be a predictor for the 30-d ay clinical outcome.

Concerning the prognostic value of NfL, Markgraf et al. found no significant association of serum NfL and CSF NfL with overall mortality and with the "EMSE" (Epidemiology-based Mortality score in Status Epilepticus) score in 28 patients with status epilepticus [34]. Instead, similarly to the study of Giovannini et al. [22], NfL levels correlated positively with the duration of status epilepticus in hours (serum NfL: rho = 0.59, $p = 0.001$; CSF NfL: rho = 0.58, $p = 0.002$). Both groups (Giovannini et al. rho = 0.68, $p < 0.001$, Margraf et al. rho = 0.73, $p < 0.001$) found a high correlation of serum NfL and CSF NfL levels [22,34].

In a cohort of 128 patients with cardiac arrest, serum NfL measured 72 h after the event were reported to be significantly higher in patients who developed encephalographic status epilepticus [n = 26, 20.6 %, median age: 72 years (IQR: 65–81)] compared to patients without encephalographic status epilepticus [n = 102, 79.4 %, median age: 64 years (IQR: 56–71)] [33].

3.1.4.2. Application of GFAP in prognostication in status epilepticus. On another issue, GFAP in patients with status epilepticus was investigated only in two studies [27,33]. Serum GFAP levels were not significantly different in patients with status epilepticus treatment-responsive vs. non-responsive status epilepticus [27]. In the cohort of 128 patients with cardiac arrest (as described above under **3.1.1.1.** for NfL), serum GFAP measured 72 h after the event was significantly higher in patients who developed encephalographic status epilepticus compared to patients without encephalographic status epilepticus [33]. No further studies on GFAP in status epilepticus were found.

3.2. Application of NfL and GFAP as biomarkers in chronic course of disease

7 of the 19 studies [17,19,20,24,31,32] evaluated the application of NfL or GFAP as biomarkers in chronic course of disease. Topics addressed in chronic epileptic disease were the differentiation of patients with epilepsy to healthy controls (**3.2.1**) [20–22,24,25,34], the association of biomarker levels with disease duration (**3.2.2**) [17], the correlation of biomarker levels with seizure frequency (**3.2.3**) [19,20,31,32] and the influence of antiseizure medication on biomarker levels (**3.2.4**) [17,19,20,24].

3.2.1. Differentiation of patients with epilepsy and healthy controls

A total of four studies investigated the potential of NfL and GFAP to differentiate between patients with epilepsy and healthy controls [19,22,24,31]. In this respect, three of the four studies assessed NfL [19,22,31] and only one study GFAP [24].

3.2.1.1. Application of NfL in the differentiation of patients with epilepsy to healthy controls. Of the three studies on this topic two publications found no significant differences in serum or CSF NfL levels between the two groups [19,22]. However, Dobson et al. found higher plasma NfL levels in the 95th age matched percentile compared to the control group with 97 % positive predictive value for epilepsy, especially in patients < 60 years [31].

3.2.1.2. Application of NfL in the differentiation of patients with epilepsy to healthy controls. In the one study on GFAP, the patient group had higher

serum GFAP levels than the control group (190 pg/mL vs. 170 pg/mL, p = 0.042) [24].

3.2.2. Biomarker levels and disease duration

Only two studies addressed the question of the association of biomarker levels and disease duration[24,32]. Both studies were on serum GFAP and found no significant association of serum GFAP levels and disease duration. No studies on NfL regarding this topic could be found.

3.2.3. Influence of seizure frequency on fluid biomarker levels

To determine the seizure frequency physicians are dependent on the history taking information of patients or their caretakers which is often not reliable. On the patient's side reasons for this might be amnesia for the event or deliberate concealment for fear of restrictions such as ban from driving, among others. Currently there is no dependable marker to assess seizure frequency. Four studies investigated the relation of fluid biomarkers and seizure frequency [19,20,31,32].

3.2.3.1. Seizure frequency and NfL levels. In the three of the four studies that assessed seizure frequency and NfL [19,20,31] only one [20] found a significant but weak correlation (rho = 0.162) of plasma NfL and seizure frequency whereas the other two studies did not find any correlation of seizure frequency and NfL levels.

3.2.3.2. Seizure frequency and GFAP levels. In the same study that was positive for the correlation of plasma NfL levels and seizure frequency, plasma GFAP levels correlated with seizure frequency but only when post-stroke epilepsy was excluded from the analysis. As was for NfL, the correlation was very weak (rho = 0.176) [20]. The other two studies on GFAP did not find any correlation of GFAP levels and seizure frequency [20,31,32].

3.2.4. Influence of treatment with antiseizure medication on fluid biomarkers

The monitoring of the treatment with antiseizure medication is mostly based on the anamnestic information of the patient, the course of disease and on determination of drug blood levels. Admitted dosages of antiseizure medication are mostly estimations considering different factors such a patients age and weight, side effects of the therapy or possible interactions with other medical drugs. The determination of the most accurate individual dosage of antiseizure medication is virtually impossible and most patients are probably treated with dosages that are higher or lower than necessary. Fluid biomarkers could help to find the correct individual dosage of antiseizure drugs and to monitor the effects of antiseizure treatments. Furthermore, fluid biomarkers could be used for surveillance of patients in clinical trials, could help to determine effects of a certain therapy and guarantee patient compliance.

We found four publications on the influence of treatment with antiseizure medication on NfL and/or GFAP levels in patients with epilepsy [17,19,20,24], with two publications on both NfL and GFAP [17,19] as well as each one publication on NfL [19] and GFAP [24].

3.2.4.0.1. Impact of antiseizure medication on NfL. Overall, NfL [17,19] concentrations in blood samples were found unchanged in treated vs. untreated subjects with epilepsy. In one study only the number (1/2/≥3 drugs) but not the kind of antiseizure medication was given [19]. In one study no details on the antiseizure medication was given at all [17]. On the contrary to those two studies, one study reported significantly lower levels of plasma NfL in patients younger than 65 treated with lamotrigine compared to patients treated with carbamazepine, lacosamide, topiramate, valproate or levetiracetam [20].

3.2.4.1. Impact of antiseizure medication on GFAP. Likewise, GFAP concentrations in blood samples were found unchanged in treated vs. untreated subjects with epilepsy independent on the number or type of drugs used [17,20,24].

3.3. Demographic and clinical associations in patients with acute and chronic epileptic disease

11 of the 19 studies [17,18,20,24–26,28–31,34] include issues that are not exclusively related to either of the first two groups. This involves demographical aspects such as age relation [17,20,23,26] and sex differences in biomarker levels [21,34] (**3.3.1**), studies on etiology of seizures and epilepsy (**3.3.2**) [17,18,20,25,26,28,30,31] as well as studies on seizure semiology (**3.3.3**) [20,24,25,31,34].

3.3.1. Demographical aspects

As in healthy subjects and patients with other neurological diseases, blood NfL levels were also found to be positively correlated with age in patients with epileptic conditions [17,20,23,26].

Moreover, one study found overall higher sNfL levels in female vs. male patients (serum NfL: 90.85 pg/mL vs. cohort median of 64.7 pg/mL, p = 0.001) [21], whereas one study did not find any sex related differences in NfL levels [34]. None of the other studies reported on sex related differences in biomarker levels.

3.3.1.1. Differentiation of seizure etiology. Five studies dealt with NfL and GFAP and the differentiation of seizure etiologies [17,20,25,26,31]. Two of these studies reported an association of NfL with seizure etiology [20,26] and only one study of GFAP with seizure etiology [20].

Nass et al. [26] examined serum and CSF NfL and GFAP levels in subgroups (autoimmune encephalitis, genetic generalized epilepsy, psychogenic non-epileptic seizures, hippocampal sclerosis) in a cohort of patients with epilepsy. They found significantly higher serum NfL and CSF NfL levels in autoimmune encephalitis compared to all other groups. There was no difference in serum GFAP or CSF GFAP levels between the groups. No age adjustment was done although NfL correlated positively with age and the group with autoimmune encephalitis was significantly older (median age 64) than all other groups (median age 32). Serum NfL had a good discriminatory value for autoimmune etiology vs. hippocampal sclerosis (AUC: 0.88). With a cut-off value of 11.75 pg/mL, sensitivity was 84.6 % and specificity was 84.6 % [26]. Akel et al. found significantly higher plasma NfL and levels in patients < 65 years (but not in patients > 65 years) when they had an epileptogenic focus. The radiological result with detection of an epileptic lesion was a significant predictor of the plasma NfL and plasma GFAP levels [20]. Interestingly, Eriksson et al. found no significant differences of plasma GFAP and plasma NfL levels comparing cohorts of patients with post stroke epilepsy and with epilepsy without relation to stroke [17].

3.3.1.2. NfL levels in autoimmune etiology. We further identified four studies that focused exclusively on NfL in epileptic seizures in autoimmune encephalitis [18,28–30]. Two studies examined both serum NfL and CSF NfL levels in patients with and without seizures in NMDA-encephalitis [29,30]. Both Brenner et al. and Guasp et al. found no significant differences for serum NfL levels when comparing patients with epileptic seizures to patients without seizures [29,30]. However CSF NfL levels where significantly higher in patients with seizures or status epilepticus [29]. In one study on NfL and seizures in LGI1-encephalitis CSF NfL levels were significantly higher in patients with seizures compared to patients without seizures [18]. One study evaluated serum NfL levels in myelin oligodendrocyte glycoprotein antibody-associated disease [28]. Here serum NfL levels were associated with the occurrence of seizures and significantly higher serum NfL levels were found in patients with seizures compared to patients without seizures and healthy controls.

3.3.2. Differentiation of seizure semiology

According to the ILAE (International League Against Epilepsy) 2017

operational classification of seizure types, epileptic seizures can be distinguished in seizures with focal, generalized or unknown onset with further discrimination into focal onset with impaired/unimpaired awareness and motor/nonmotor symptoms and evolution into a bilateral tonic-tonic presentation, generalized onset with motor/nonmotor symptoms as well as unknown onset with motor/nonmotor symptoms or unclassified presentation [38]. Based upon this is the classification of the epilepsies with focal, generalized, combined generalized & focal and unknown epilepsies [39]. Classifying semiology, which often relies on anamnestic information, can be a challenging undertaking.

3.3.2.1. Application of NfL in the differentiation of seizure semiology. Four studies [20,25,31,34] evaluated the potential of NfL to differentiate between seizure semiologies. Only one of these studies reported an association of NfL with seizure semiology with significantly higher plasma NfL in patients with focal compared to generalized or bilateral tonic-clonic seizures [20]. These results could not be confirmed by other authors when comparing patients with focal to patients with generalized seizures [25], seizure types (no further discrimination given) [31] or serum NfL and CSF NfL levels in motoric versus non-motoric status epilepticus [34].

3.3.2.2. Application of GFAP in the differentiation of seizure semiology. Four studies [20,24,25,31] evaluated the potential of GFAP to differentiate between seizure semiologies. No association of GFAP and seizure semiology could be found in three of the four studies[24,25,31]. As for NfL, only one study reported an association of GFAP with seizure semiology with significantly higher plasma NfL in patients with focal compared to generalized or bilateral tonic-clonic seizures [20].

4. Discussion

In this review we provided an extensive overview of currently available data on CSF and blood NfL and GFAP in epilepsy and epileptic seizures. We tried to shed light on different aspects of the potential application of NfL and GFAP as biomarkers regarding the diagnostic and prognostic value in acute and chronic epileptic disease stages (Fig. 2). The results acquired revealed very variable data, especially considering the overall small size of study populations (mean n = 36.7) and the great heterogeneity in terms of seizure type and time points of sample collection.

In addition, different methods for protein measurement were used and possible influencing factors (such as age, sex, renal function, BMI) were not always taken into consideration, which hampers the generalizability of individual results. For instance, sex specific differences in biomarker levels have exclusively been described in two of the 19 studies discussed in this review. The aspect of sex dimorphism in biomarker levels is currently the subject of debate in the scientific community, with increasing evidence of gender-specific differences in biomarker levels [40–42]. Establishing this also for patients with epileptic conditions would be crucial for the implementation of NfL and GFAP into clinical practice.

In status epilepticus, serum NfL could be a valuable biomarker to assess responsiveness to therapy and functional outcome. Higher blood NfL levels in patients with status epilepticus could indicate a time dependent neuronal damage underlying epileptic activity, as suggested by the correlations between serum NfL and CSF total tau proteins [22]. Moreover, blood–brain barrier affection, which occurs as a consequence of status epilepticus [43], may also contribute to protein leakage from CSF to blood and lead to increased NfL/GFAP levels in serum and plasma. The mechanism of this have been widely investigated and possible pathomechanisms range from neuroinflammation and hypoxia to oxidative stress as well as imbalance of neurotransmitters [44]. Numerous preclinical studies, particularly in rodents, have focused on the development and spreading of epileptic seizures, the pathophysiology and consequences of status epilepticus and biochemical changes

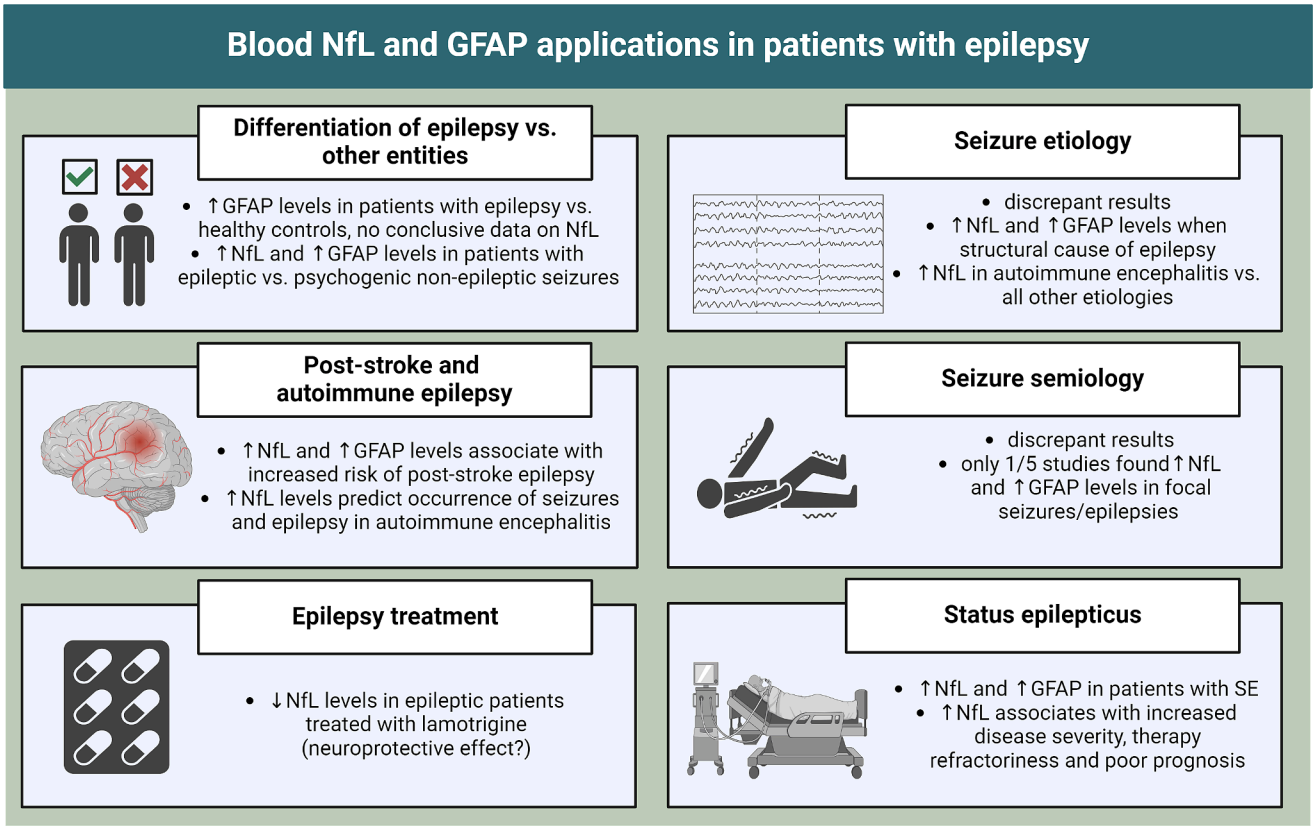

Fig. 2. Main findings on NfL and GFAP in patients with epileptic seizures and epilepsy.

associated with epilepsy. Common models include chemical (e. g. kainic acid or pilocarpine exposure) and electrical (e. g. amygdala or hippocampal stimulation) methods for inducing epilepsy through status epilepticus [45] Also, NfL levels in CSF and blood have been investigated and an association with epileptic activity has been described [46]. Furthermore, significant increases in GFAP expression prompted by epileptogenic activity in pilocarpine-induced status epilepticus have been reported [47] as consequence of reactive astrogliosis which is considered a hallmark of epilepsy [48]. The implications of these findings for humans are to date not clear [49].

Regarding seizure semiology the results on NfL and GFAP were heterogeneous. A likely explanation for elevated NfL and GFAP levels in younger patients with focal epilepsies [20] seems to be the etiology of focal seizures/focal epilepsies, which is more often than not structural [43]. Structural damage such as ischemia or traumatic brain injury could lead to higher long-term levels of neuro-axonal and astrocytic injury markers. However, when considering that in the population of the PREDICT study, which was used here, 22 patients with an apparent structural brain damage such as stroke, trauma and tumor had plasma NfL levels below the calculated cut-off value but only 9 of these patients had plasma NfL levels above the cut-off value, this hypothesis seems to be invalid. Therefore, the reason for elevated neuro-axonal and astrocytic destruction markers in patients with focal seizures only remains cryptic. This is somewhat consistent with the results on seizure etiologies. Here, three of five studies did not find any differences in NfL and GFAP levels for various seizure etiologies [17,26,31]. One study found higher NfL levels with good discriminatory values to other etiologies in autoimmune encephalitis but did not adjust to age with significantly older individuals in the autoimmune encephalitis cohort, so the significance of the results is highly questionable [26]. Only one of five studies found higher NfL and GFAP levels in younger patients with structural etiology [20]. Clinical differentiation is often difficult and the latency of diagnosis is seven to nine years on average [35], as patients with psychogenic non-epileptic seizures are often classified as treatment refractory epilepsy and receive therefore inadequate pharmacological therapy. Data on the discrimination of epileptic seizures to psychogenic non-epileptic seizures or healthy individuals is rare and inhomogeneous. Two studies found elevated GFAP levels and one study elevated NfL levels in patients with epileptic seizures compared to psychogenic non-epileptic seizures and a healthy control group [31,32]. However, two studies found no differences in NfL levels of patients with epileptic seizures compared to healthy individuals [19,21]. Still, GFAP and NfL might be useful biomarkers in the differentiation of epileptic seizures to other non-epileptic conditions, but further studies on this topic are dearly needed.

The elevation of GFAP and NfL in patients with post-stroke epilepsy compared to patients with a single seizure might not be the result of epileptic activity but of the structural damage done by ischemia as such. This would be consistent with findings on NfL [50] and GFAP in stroke patients [51,52]. Studies have shown, that NfL and GFAP levels rise after a stroke event and reach the maximum peak at three weeks (NfL) [50] and 2–5 days (GFAP) [51,52], respectively. In addition, in other causes, the structural damage as such and not the epileptic activity could lead to an increase of NfL and GFAP levels.

For autoimmune encephalitis CSF NfL – and potentially serum NfL also – could develop into a valuable marker for the occurrence of epileptic seizures. Three of four studies on this topic found elevated CSF NfL or serum NfL levels in patients with autoimmune encephalitis when epileptic seizures where present compared to autoimmune encephalitis without epileptic seizures [18,29,53]. These results could become relevant not only in the acute phase of an autoimmune encephalitis but especially in the course of disease since it could help to discriminate patients with a higher risk for recurrent seizures and therefore the need for further seizure suppressing therapy. This topic is currently under further investigation in another study on anti-LGI1 encephalitis (ClinicalTrials.gov ID: NCT04001270).

Interesting is the connotation of low NfL levels, lower even than in healthy controls, under therapy with lamotrigine, suggesting a neuroprotective effect of this drug [17]. On the one hand, preclinical evidence supports this assumption [43,50,51]. On the other hand, lamotrigine is used as a first-choice treatment for focal seizures, which may have higher blood NfL levels compared to generalized seizures [20] given that they are more frequently caused by structural lesions. If confirmed by further studies, the reduction of biomarker level under lamotrigine therapy could be used to monitor the degree of the neuronal damage and, eventually, the effects of lamotrigine or other antiseizure medication in the longitudinal management of patients with epilepsy. Indeed, fluid biomarkers could be implemented as primary or secondary outcome measures in clinical trials evaluating new seizure suppressing drugs.

Implementing biomarkers such as NfL and GFAP in clinical practice for the management of epileptic seizures and epilepsy is hampered by several challenges. First, the temporal trajectories of NfL and GFAP in blood as well as the best time point for biomarker assessment for prognostic purposes after focal and generalized epileptic seizures are still unclear. Moreover, whether physiological and paraphysiological factors may influence biomarker concentrations in subjects with epilepsy similarly to healthy subjects [54] has not been comprehensively explored. Finally, as already mentioned, the neuroaxonal and glial response to pharmacological treatment needs further experimental clarification for a better use in clinical trials.

5. Conclusion

In conclusion, literature on fluid NfL and GFAP levels in epilepsy is to date limited. Elevated biomarker levels may suggest an underlying structural cause, a higher risk of developing status epilepticus and an overall worse clinical outcome. NfL and GFAP could ameliorate the prognostic evaluation of patients with epilepsy but larger studies with homogeneous study populations and accounting for possible influencing factors are needed. Finally, such biomarkers have the potential to aid clinicians in the choice and monitoring of antiseizure medication on an individual level.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CRediT authorship contribution statement

Annemarie Thaele: Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **Lorenzo Barba:** Writing – review & editing, Project administration, Methodology, Data curation. **Samir Abu-Rumeileh:** Writing – review & editing. **Matteo Foschi:** Writing – review & editing, Visualization, Software. **Markus Otto:** Writing – review & editing, Supervision.

Funding

L.B. received research support from the Medical Faculty of Martin-Luther-University Halle-Wittenberg (Junior-Clinician-Scientist-Program No. JCS24/02). S.A.R was supported by the Medical Faculty of Martin-Luther-University Halle-Wittenberg (Clinician-Scientist-Program No. CS22/06). A.T. was supported by the Medical Faculty of Martin-Luther-University Halle-Wittenberg (Clinician-Scientist-Program No. CS23/03).

Declaration of competing interest

M.O. received research support from the EU Joint Programme

Neurodegenerative Diseases networks Genfi-Prox, the EU (MOOD-MARKER), the German Research Foundation/ DFG (SFB1279), the foundation of the state Baden-Württemberg (D.3830), Boehringer Ingelheim Ulm University BioCenter (D.5009), and the Thierry Latran Foundation. There is no conflict of interest with the current work. A.T. receives compensations for travel expenses and congress fees from Novartis Pharma GmbH. There is no conflict of interest with current work. None of the other authors has any conflict of interest to disclose.

Acknowledgments

We thank the medical faculty of Martin-Luther-University Halle-Wittenberg for supporting AT, LB and SAR within the Clinician Scientist Program.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2025.110321.

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