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Judul Artikel : **Preoperative sensory aura predicts risk for seizure in temporal lobe**

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From: Epilepsy & Behavior em@editorialmanager.com
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Date: 18 April 2020 00.16
To: Thohar Arifin Muhamad thohar@gmail.com



This is an automated message.

Manuscript Number: EB-D-20-00297
Sensory aura predicts risk for seizure in temporal lobe epilepsy

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Your above referenced **submission** has been assigned a manuscript number: EB-D-20-00297.

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Epilepsy & Behavior

Pre-operative Sensory aura predicts risk for seizure in temporal lobe epilepsy surgery

--Manuscript Draft--

Manuscript Number:	EB-D-20-00297R1
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Keywords:	temporal lobe epilepsy, drug-resistant, aura, sensory aura
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Abstract:	<p>Background: Patients with temporal lobe epilepsy (TLE) often report viscerosensory and experiential auras, with substantial epilepsy localization. However, few previous studies have investigated the epileptic pre-operative aura, particularly with regard to its effect on surgical outcomes in patients with drug-resistant epilepsy.</p> <p>Objective: This study investigated the potential role of pre-operative aura in predicting outcomes after surgery for TLE.</p> <p>Material and methods: This study included consecutive patients diagnosed with TLE who underwent anterior temporal lobectomy (ATL) for drug-resistant TLE during the period from January 1999 to December 2017. Data pertaining to patient age at the time of surgery, sex, age at initial seizure onset, duration of epilepsy, presence of pre-operative aura, comprehensive clinical semiology, side of surgery, and type of pathology were analyzed. Pre-operative Auras were classified as autonomic, sensory, mental and affective, or Multiple manifestations. Patients were followed at 3 and 12 months after surgery and at regular intervals thereafter.</p> <p>Results and conclusions: A total of 498 patients were included in the study. Positive pre-operative aura was observed in 386 patients (77.51%). The correlation of each variable with seizure outcomes was analyzed, and the only variable found to correlate with seizure outcome was the presence of pre-operative aura. Compared to those with negative pre-operative aura, those with positive pre-operative aura were 1.74-fold more likely to be seizure free after surgery for TLE. The analysis of patient data suggested a later onset of initial seizure in those with positive pre-operative aura, compared to those without ($p=0.04$, 95% CI 0.55–3.24). Patients with a shorter duration of disease prior to TLE surgery were more likely to achieve seizure-free status postoperatively. Pre-operative sensory aura was a good predictor that a patient would be seizure free during follow-up ($p=0.022$).</p>
Suggested Reviewers:	Garry W Mathern gmathern@ucla.edu
Response to Reviewers:	Responses to Reviewers' Comments Reviewer comment Reviewer #1: The authors report a retrospective chart study examining the association

between auras and outcomes in ATL for TLE. Several categories of auras were described: autonomic, sensory, mental and affective, or multiple manifestations. Nearly 500 patients were included. Persistent auras were seen in 77% of patients after surgery. Surprisingly, patients with auras were more likely to have disabling seizures after surgery, not less likely. Shorter duration of TLE was associated with seizure freedom as well, which has been previously described in many studies. The large size of the study and novelty of the topic are strengths. Several studies have evaluated factors associated with surgical outcome in TLE. Few look specifically at auras since most studies focus on seizures with impaired awareness which are classified as "debilitating" seizures. The report is brief but well written. The analyses are relatively simple - a univariate test to screen variables followed by a multivariate regression analyses. The description of results and discussion appear appropriate.

Author response

Thank you for this observation. First, we clarify that this study want to know the correlation of pre-operative aura with post operative outcome. We divided our subject into positive pre-operative aura or negative pre-operative aura and classify into 4 types of aura (Autonomic, Sensory, Mental and affective and multiple). From our pre-operative observation, 386 patients (77,51 %) were aura positive and 112 patients (22,48 %) were aura negative. (Table 1)

From our observation, 324/386 (80,9%) of our patients who had pre-operative aura, achieved seizure free (Engel I) and only 84/112 (75%) of patients who had negative pre-operative aura, achieved seizure free. We got correlation between pre-operative aura and seizure free status with OR 1,74 p = 0,03.

Reviewer comment

- My major concern with the paper is that I have a strong suspicion that the authors are calling many symptoms "auras" that are not epileptic auras. The percentage of auras after surgery is extremely high and not consistent with significant literature in the field. For example, symptoms such as GI issues, palpitation, mental/affective changes are likely not epileptic so I would not call them auras. This is the core finding of the paper so I think this is where the most clarification is needed. Many patients have vague symptoms after neurosurgical or even other surgical procedures that are not related to their underlying disease - epilepsy in this case. I think significant clarification of what was and what was no classified as an aura is warranted, and reconsider calling certain symptoms auras vs unspecified symptoms.

Author response

Thank you for your observation. We want to clarify that aura in this study was observed pre-operatively. Aura following the patient's seizure was observed directly by epilepsy team during pre-operative step. Data of aura were compared to clinical history in medical record. Unmatched data were re-observed directly to the patients. Final decision of aura and type were taken by epilepsy team meeting before operation. Post-operatively, outcome was measured using Engel class (Seizure free (IA-ID) and seizure (II,III,IV)). After surgery we didn't re-evaluate the aura. We add chart flow of our study to make it clear (Figure 1)

Reviewer comment

- The title does not mention surgery, so it's unclear the study is about surgical outcomes. Would recommend revising. Perhaps just add "surgery" at the end.

Author response

We agree and have added the word "surgery" in title for making it clear.

Reviewer comment

- The authors state seizure outcomes were classified using the Engel scale. I believe that must mean seizure freedom was defined as any Engel I (Engel IA-D?) and not just Engel 1A, since patients with auras are not classified as 1A. Can the authors clarify in greater detail?

Author response

Your suggestion is noted. We agree and use Engel I (Engel IA-ID) to describe good outcome (seizure free). Patients who had aura symptoms only postoperatively during followup (Engel IB), categorized as seizure free. We have re-checked and corrected our data and manuscript related with this change.

Reviewer comment

- The authors may be interested there was also a study showing simple partial studies such as auras were the seizure types least affected by surgery, just FYI:
<https://www.ncbi.nlm.nih.gov/pubmed/23892416>

Author response

Thank you for your suggestion. In our study, most of our patients (275 patients, 55,22%) presented with Focal Impaired Awareness Seizure (FIAS) and Focal to Bilateral Tonic Clonic Seizure (183 patients, 36,74 %). Only 2 patients who developed focal aware seizure/simple partial seizure. As we mentioned before, our study focused on the correlation between pre-operative aura analysis to predict the outcome of surgery.

June 11, 2020
S.C. Schachter, MD
Editor-in-Chief:
Epilepsy & Behavior

Dear Dr. Schachter,

Please find enclosed “**Pre-operative Sensory aura predicts risk for seizure in temporal lobe epilepsy surgery**”, which we had **revise and rewrite as reviewer comment**, and request you to consider for publication as *Original Research Article* in *Epilepsy & Behavior*.

Patients with temporal lobe epilepsy (TLE) often report viscerosensory and experiential auras, with substantial epilepsy localization. However, few previous studies have investigated the epileptic aura, particularly with regard to its effect on surgical outcomes in patients with drug-resistant epilepsy. This study investigated the potential role of aura in predicting outcomes after surgery for TLE.

A total of 498 patients were included in the study. Positive pre-operative aura was observed in 386 patients (77.51%). The correlation of each variable with seizure outcomes was analyzed, and the only variable found to correlate with seizure outcome was the presence of pre-operative aura. Compared to those with negative pre-operative aura, those with positive pre-operative aura were 1.74-fold more likely to be seizure free after surgery for TLE. The analysis of patient data suggested a later onset of initial seizure in those with positive pre-operative aura, compared to those without ($p=0.04$, 95% CI 0.55–3.24). Patients with a shorter duration of disease prior to TLE surgery were more likely to achieve seizure-free status postoperatively. Pre-operative sensory aura was a good predictor that a patient would be seizure free during follow-up ($p=0.022$).

This manuscript has not been published elsewhere and is not under consideration by another journal. We have approved the manuscript and agree with submission to *Epilepsy & Behavior*. There are no conflicts of interest to declare.

We believe that the findings of this study are relevant to the scope of your journal and will be of interest to its readership. The manuscript has been carefully reviewed by an experienced editor whose first language is English and who specializes in editing papers written by scientists whose

native language is not English.

We look forward to hearing from you at your earliest convenience.

Sincerely,

Correspondence to:

Muhamad Thohar Arifin

Department of Neurosurgery, Faculty of Medicine, Diponegoro University,

Jl. Prof Soedarto Tembalang Indonesia

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Responses to Reviewers' Comments

Reviewer comment

Reviewer #1: The authors report a retrospective chart study examining the association between auras and outcomes in ATL for TLE. Several categories of auras were described: autonomic, sensory, mental and affective, or multiple manifestations. Nearly 500 patients were included. Persistent auras were seen in 77% of patients after surgery. Surprisingly, patients with auras were more likely to have disabling seizures after surgery, not less likely. Shorter duration of TLE was associated with seizure freedom as well, which has been previously described in many studies.

The large size of the study and novelty of the topic are strengths. Several studies have evaluated factors associated with surgical outcome in TLE. Few look specifically at auras since most studies focus on seizures with impaired awareness which are classified as "debilitating" seizures. The report is brief but well written. The analyses are relatively simple - a univariate test to screen variables followed by a multivariate regression analyses. The description of results and discussion appear appropriate.

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Reviewer comment

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Reviewer comment

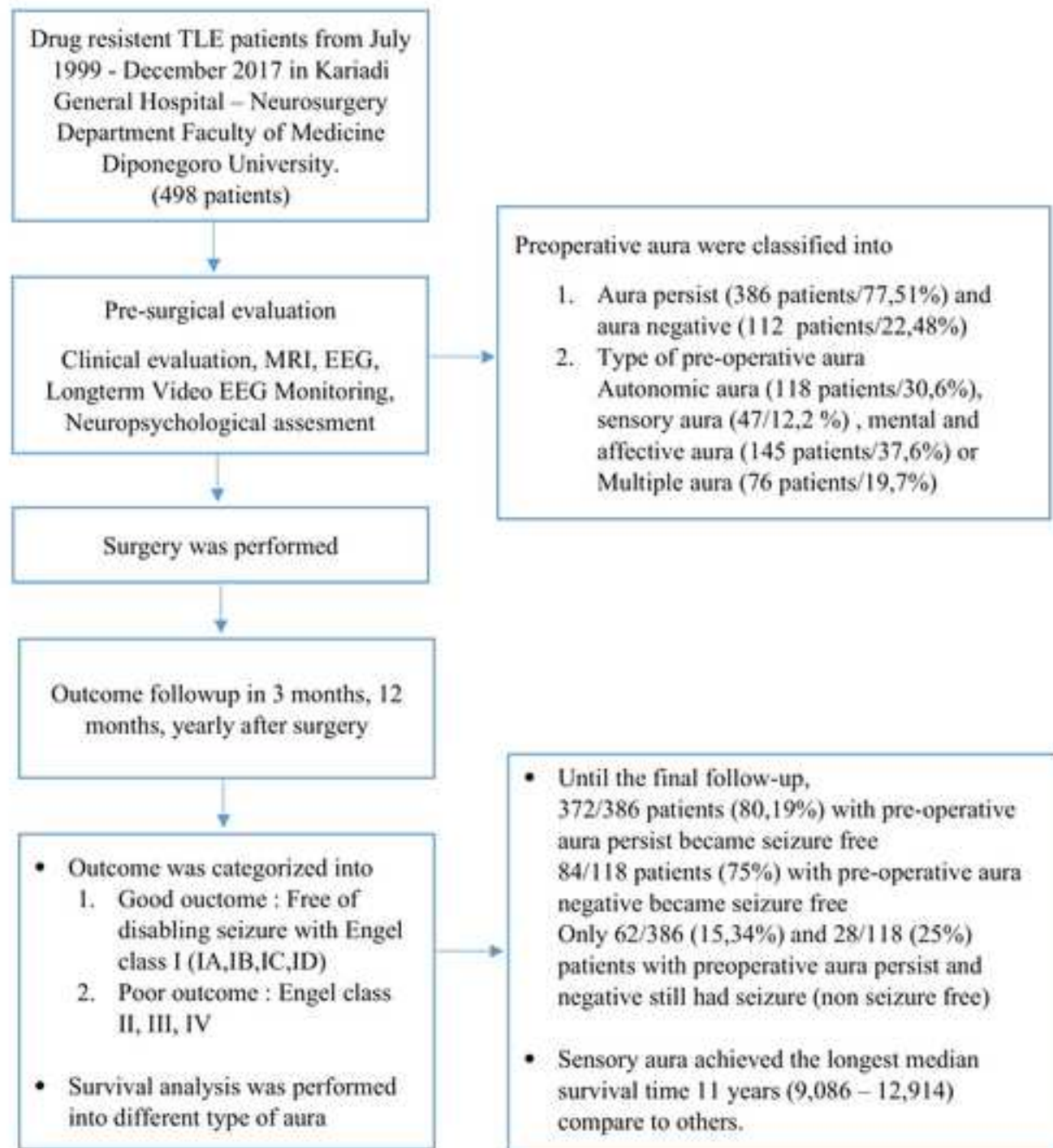
- The authors may be interested there was also a study showing simple partial seizures such as auras were the seizure types least affected by surgery, just FYI: <https://www.ncbi.nlm.nih.gov/pubmed/23892416>

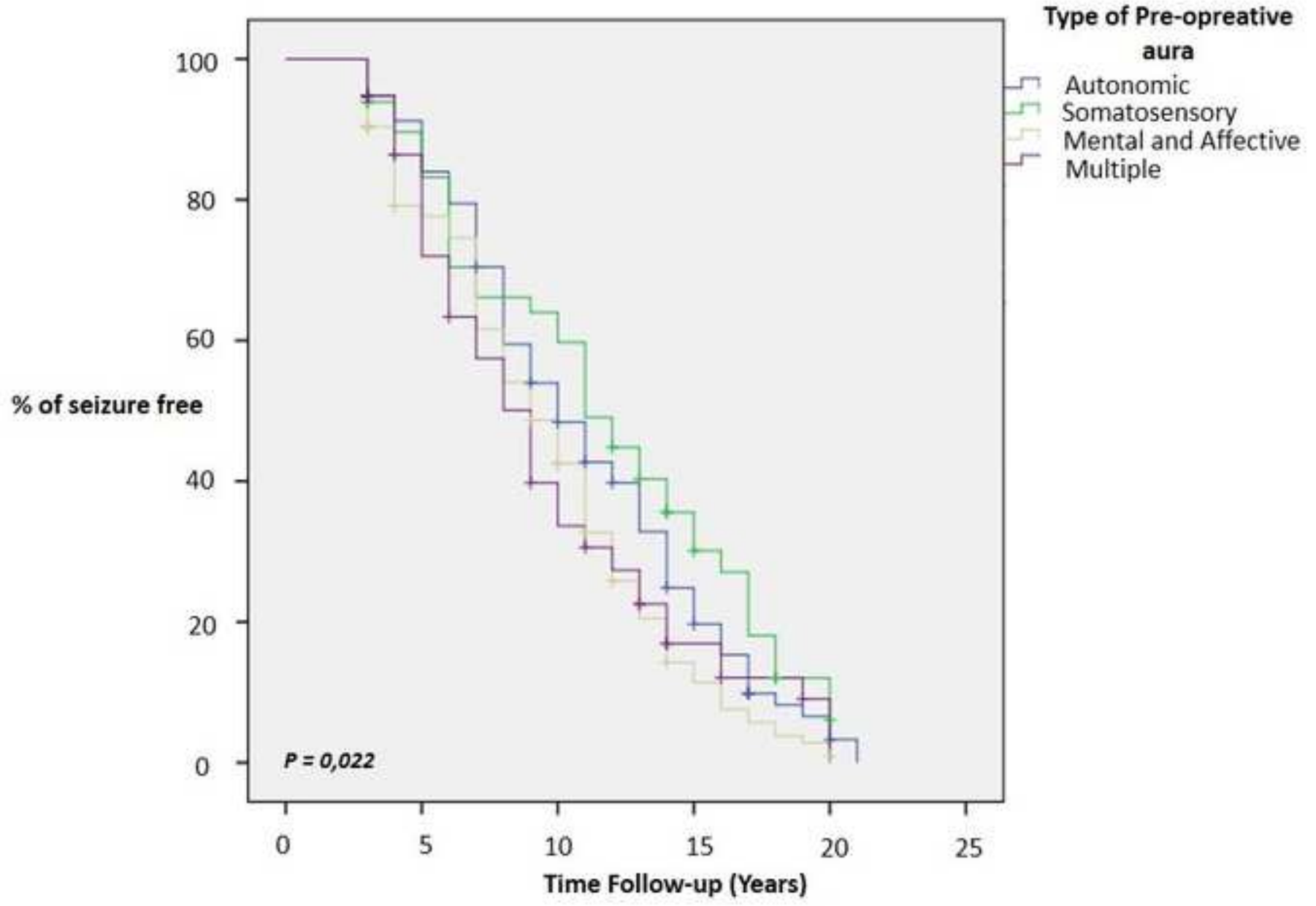
Author response

Thank you for your suggestion. In our study, most of our patients (275 patients, 55,22%) presented with Focal Impaired Awareness Seizure (FIAS) and Focal to Bilateral Tonic Clonic Seizure (183 patients, 36,74 %). Only 2 patients who developed focal aware seizure/simple partial seizure. As we mentioned before, our study focused to the correlation between pre-operative aura analysis to predict the outcome of surgery.

Highlights

- few previous studies have investigated the epileptic aura, particularly with regard to its effect on surgical outcomes in patients with drug-resistant temporal lobe epilepsy.
- This study investigated the potential role of aura in predicting outcomes after surgery for TLE during the period from January 1999 to December 2017. Patients were followed at 3 and 12 months after surgery and at regular intervals thereafter.
- Auras were classified as autonomic, sensory, mental and affective, or multiple manifestations.
- Compared to those without persistent aura, those with positive pre-operative aura were 1.74-fold more likely to be seizure free after surgery for TLE
- Patients with a shorter duration of disease prior to TLE surgery were more likely to achieve seizure-free status postoperatively.
- Sensory aura was a good predictor that a patient would be seizure free during follow-up







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Table
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1 **Pre-operative Sensory aura predicts risk for seizure in temporal lobe epilepsy surgery**

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25

1 **Abstract**

2 **Background:** Patients with temporal lobe epilepsy (TLE) often report viscerosensory and
3 experiential auras, with substantial epilepsy localization. However, few previous studies have
4 investigated the epileptic pre-operative aura, particularly with regard to its effect on surgical
5 outcomes in patients with drug-resistant epilepsy.

6 **Objective:** This study investigated the potential role of pre-operative aura in predicting
7 outcomes after surgery for TLE.

8 **Material and methods:** This study included consecutive patients diagnosed with TLE who
9 underwent anterior temporal lobectomy (ATL) for drug-resistant TLE during the period from
10 January 1999 to December 2017. Data pertaining to patient age at the time of surgery, sex,
11 age at initial seizure onset, duration of epilepsy, presence of pre-operative aura,
12 comprehensive clinical semiology, side of surgery, and type of pathology were analyzed.
13 Pre-operative Auras were classified as autonomic, sensory, mental and affective, or Multiple
14 manifestations. Patients were followed at 3 and 12 months after surgery and at regular
15 intervals thereafter.

16 **Results and conclusions:** A total of 498 patients were included in the study. Positive pre-
17 operative aura was observed in 386 patients (77.51%). The correlation of each variable with
18 seizure outcomes was analyzed, and the only variable found to correlate with seizure outcome
19 was the presence of pre-operative aura. Compared to those with negative pre-operative aura,
20 those with positive pre-operative aura were 1.74-fold more likely to be seizure free after
21 surgery for TLE. The analysis of patient data suggested a later onset of initial seizure in those
22 with positive pre-operative aura, compared to those without ($p=0.04$, 95% CI 0.55–3.24).
23 Patients with a shorter duration of disease prior to TLE surgery were more likely to achieve
24 seizure-free status postoperatively. Pre-operative sensory aura was a good predictor that a
25 patient would be seizure free during follow-up ($p=0.022$).

1 Keywords: temporal lobe epilepsy, drug-resistant, aura, sensory aura

2

1 **1. Introduction**

2 Temporal lobe seizures often manifest as partial seizures. Approximately two-thirds
3 of people with intractable seizures require surgical treatment. Auras (from Latin for “wind”
4 and Greek for air) are, in general, important partial seizures that may appear in isolation but
5 occur in a large proportion of patients at the beginning of complex partial seizure (CPS). The
6 duration of an aura before the impairment of consciousness ranges from a few seconds to 2
7 minutes. Auras arise from the excitation of a functionally activated cortex near the ictal onset
8 zone and play a well-recognized role in localization and, under other circumstances,
9 lateralization of the ictal onset region. [1-5].

10 Patients with temporal lobe epilepsy (TLE) commonly report viscerosensory and
11 experiential auras, which have substantial epilepsy localization [6]. However, only a limited
12 number of previous studies have investigated the importance of the epileptic aura,
13 particularly with regard to its effect on surgical outcomes in patients with drug-resistant
14 epilepsy. Although recent studies have analyzed the significance of post-operative aura, few
15 of these reports have investigated the associated clinical variables, radiological and
16 pathological substrates, and electrophysiological characteristics in patients with aura. An
17 even smaller number of studies have classified such findings on the basis of aura subtype. In
18 this study, we sought to determine whether the presence of pre-operative aura could be used
19 to predict seizure outcomes in patients who had undergone surgery for drug-resistant TLE.

1 **2. Methods**

2 **2.1 Patient selection**

3 Consecutive patients who undertook a preliminary assessment and underwent temporal lobe
4 surgery for drug-resistant TLE were evaluated during the period from January 1999 to
5 December 2017. Patients were followed at 3 and 12 months postoperatively, then annually
6 thereafter. In all cases, the presurgical assessment included clinical examination, 1.5-T
7 magnetic resonance imaging (MRI), and routine electroencephalography (EEG). In some
8 cases, the preliminary assessment included long-term video EEG monitoring and a
9 neuropsychological evaluation. The surgery consisted of en-bloc standard ATL with lesion
10 resection when lesions other than temporal mesial sclerosis (MTS) were present and selective
11 amygdalohypocampectomy (SAH). The procedure was performed according to standard
12 protocols(7), and all surgeries were performed by the same team of neurosurgeons (Zainal
13 Muttaqin and Muhamad Thohar Arifin), who had expertise in epilepsy surgery. In this study,
14 ATL was performed as a 4–6 cm block resection of the lateral temporal cortex, followed by
15 microsurgical resection of the amygdala and full-block resection of the hippocampus and
16 parahippocampal gyrus. The transsylvian selective amygdalohippocampectomy was
17 performed for all cases. (8)

18 The All surgical specimens were submitted for histopathological examination. This
19 study was approved by the Joint Ethics Committee of the Kariadi Gerenal Hospital. Written
20 Informed consent was obtained from all patients for being included in the study, or a
21 parent/legal guardian of patients under the age of 18 years

22

23 **2.2 Assessment of variables and postoperative outcomes**

24 The variables analyzed included age at the time of surgery, sex, age at onset of the
25 first seizure, duration of epilepsy, presence of pre-operative aura, comprehensive clinical

1 semiology, side on which surgery was performed, and type of pathology. Patients were
2 assessed for the presence/absence of pre-operative aura, and aura was classified as
3 autonomic, sensory, mental and affective, or Multiple manifestations. Outcomes were
4 assessed at 3 and 12 months after surgery and at regular intervals thereafter. All patients were
5 examined in depth for the recurrence of seizures, and the date of any recurrence was
6 recorded. The cohort was divided into two broad categories: those who were "seizure-free
7 (Engel I)", with or without anti-epileptic drugs (AEDs) at any time during follow-up were
8 considered to have good outcomes; those who experienced seizures of any kind
9 postoperatively (Engel II,III,IV) were considered to have "poor outcomes".

10

11 **2.3 Statistical analysis**

12 Pearson's Chi-square test and Fisher's exact test were used to compare patients
13 positive vs. negative pre-operative aura in terms of baseline characteristics. Univariate
14 logistic regression analysis was used to assess the prognostic importance of aura subtype with
15 regard to seizure outcome. Variables significant at the 10% level in the preliminary analysis
16 were included in the Cox proportional hazards regression model. Kaplan-Meier plots were
17 used to analyze outcomes (likelihood of one year free of seizures) for each type of pre-
18 operative aura. A p-value of less than 0.05 was considered statistically significant. All
19 analyses were performed using a computerized statistical model.

20

1 **3. Results**

2 **3.1 Correlation between pre-operative aura and surgical outcomes in TLE patients**

3 The patient population included 498 patients diagnosed with TLE who underwent
4 surgery for TLE during the period from January 1999 to December 2017. Among this group,
5 196 (39.35%) were male. Median age, age at onset of the first seizure, and duration with TLE
6 prior to surgery were 23 years (2–62 years), 11 years (0.16–40 years), and 10 years (1–62
7 years). Positive pre-operative aura was reported by 386 patients (77.51%); 112 (22.48%) did
8 have negative pre-operative aura. The most common etiologies were focal impaired
9 awareness seizure (FIAS) 275 (55.22%) and focal to bilateral tonic-clonic seizure (FBTCS
10)183 (36.74%), followed by “other” (n=35, 7.02%), Generalized tonic-clonic seizure (GTCS)
11 3 (0.60%), and focal awareness seizure (FAS) 2 (0.40%). ATL was the most common type of
12 surgery performed (n=417, 83.73%), followed by SAH (n=55, 11.04%), lesionectomy (n=20,
13 4.01%), and “other” (n=6, 1.20%) (Table 1). Over years of follow-up, we evaluated the
14 outcomes of epilepsy surgery using the Engel classification and stratified patients into a
15 seizure-free group and a seizure group. Flow-chart of this study was presented in Figure 1.

16 Using the Pearson Chi-Square test, we analyzed the correlation of each variable with
17 seizure outcomes. The only variable found to correlate with seizure outcome was the
18 presence of aura (Table 2) We analyzed the correlation between aura and seizure-free status
19 after TLE surgery. The results showed that patients with positive pre-operative aura were
20 1.74-fold more likely to be seizure free after TLE surgery (p=0.03, OR 1.74) (Table 3).

21 We compared patients with positive vs. negative pre-operative aura in terms of mean
22 age at the time of initial seizure onset. Mean age at the time of initial seizure onset was 12.35
23 + 7.01 years in those with positive pre-operative aura and 10.70 + 7.22 years in those with
24 negative pre-operative aura (p=0.04, 95% CI 0.55–3.24). These results indicate that patients

1 with positive pre-operative aura have a later onset of epilepsy, compared to those with
2 negative pre-operative aura (Table 4).

3 Between-group comparisons revealed that those with a longer duration of disease
4 were less likely to be seizure free after TLE surgery, compared to those with a shorter
5 duration of disease [12.018.00 years in the seizure-free group vs. 13.959.29 years in the
6 seizure group; $p=0.04$, 95% CI -3.85–(-0.02)] (Table 5).

7

8 **3.2 Correlation between pre-operative aura subtype and outcomes after TLE surgery**

9 We stratified the 386 patients included in the study based on pre-operative aura
10 subtype: autonomic, sensory, mental and affective, or Multiple manifestations. A total of 118
11 patients (30.6%) were classified as having pre-operative autonomic aura. Among this group,
12 palpitation was reported by 41, GI issues by 65, and suffocation by 12. A total of 47 patients
13 (12.2%) were classified as having pre-operative sensory aura. Among this group, visual aura
14 was reported by 16 patients, olfactory aura by 1 patient, gustatory aura by 0 patients, auditory
15 aura by 2 patients, and general somatosensory aura by 28 patients. A total of 145 patients
16 (37.6%) were classified as having pre-operative mental and affective aura. Among this group,
17 feelings of fear were reported by 22 patients, depressed mood by 2 patients, experimental
18 sensory (déjà vu) by 55 patients, vertigo by 1 patient, cognitive aura by 9 patients, and
19 unspeakable feeling/malaise (odd feeling) by 54 patients. Pre-operative Multiple aura
20 manifestations were reported by 76 patients (19.7%) (Table 6).

21 We used Kaplan-Meier analysis to predict median overall survival time and to
22 compare outcomes among aura subgroups. The results showed that median time without a
23 seizure after TLE surgery was 10 years for those with pre-operative autonomic aura (95% CI
24 8.327–11.673 years), 11 years for those with pre-operative sensory aura (95% CI 9.086–
25 12.914 years), 9 years for those with pre-operative mental and affective aura (95% CI 7.667–

1 10.333 years), and 9 years for those with pre-operative Multiple aura manifestations (95% CI
2 7.692–10.887 years) ($p=0.022$) (Table 7).

3 In the pre-operative autonomic aura group, the likelihood of being seizure free after 3,
4 5, 10, and 15 years of follow-up was 94.8%, 84.0%, 48.4%, and 19.7%, respectively. In the
5 pre-operative sensory aura group, the likelihood of being seizure free after 3, 5, 10, and 15
6 years of follow-up was 93.9%, 83.2%, 59.7%, and 30.1%, respectively. In the pre-operative
7 mental and affective aura group, the likelihood of being seizure free after 3, 5, 10, and 15
8 years of follow-up was 90.3%, 77.6%, 42.5%, and 11.4%, respectively. In the pre-operative
9 Multiple aura manifestations group, the likelihood of being seizure free after 3, 5, 10, and 15
10 years of follow-up was 94.7%, 72.0%, 33.7% and 12.1%, respectively (Table 8).

11 The results of Kaplan-Meier analysis showed significantly different outcomes among
12 groups ($p=0.022$). Pre-operative sensory aura was associated with the greatest likelihood of
13 seizure-free status after surgery for TLE, followed by the pre-operative autonomic aura
14 group, pre-operative Multiple auras groups, and pre-operative mental and affective aura
15 group (Figure 2).

16

1 **4. Discussion**

2 The correlation between type of pre-operative aura and surgical outcomes was
3 examined in patients with TLE. The results showed that patients with positive pre-operative
4 aura who underwent TLE surgery had a 1.74-fold increase in the likelihood of seizure-free
5 status. Patients with positive pre-operative aura had a later onset of epilepsy than patients
6 without pre-operative aura. These results support those in previous studies, which showed
7 that patients with medically refractory TLE-MTS who reported abdominal auras prior to
8 seizures had better postoperative seizure control than those who did not report auras [6,9,10].
9 Seizure-free status is more common among patients with a shorter period of TLE disease, as
10 reported previously [11-12]. People with shorter epilepsy duration are more likely to have
11 seizure-free follow-up. In addition, there is a favorable correlation among shorter duration of
12 disease and freedom from seizures among patients with relatively long durations of epilepsy.
13 Patients who can benefit from epilepsy surgery should also be recommended for preliminary
14 examination without further delay, regardless of the duration since the epilepsy diagnosis [6].

15 Patients with pre-operative sensory auras had greater likelihood of remaining seizure
16 free during the follow-up period, followed by those with pre-operative autonomic auras, pre-
17 operative Multiple auras, and pre-operative mental and affective auras. Similar findings were
18 reported previously in a study that described favorable surgical outcomes in TLE patients
19 with somatosensory auras [13]. We conclude that pre-operative sensory aura is a good
20 indicator for seizure-free status postoperatively. .Possible mechanism for the production of
21 somatosensory aura is the spread of seizure activity from the temporal lobe to the perisylvian
22 region by stimulation of the insular cortex or the second sensory area. The insular cortex has
23 extensive connections to temporal lobe structures, and temporal lobe seizures tend to enter
24 the insular cortex. After seizure in the temporal lobe, several anatomical regions can generate
25 somatosensory phenomena. First, somatosensory auras may emerge directly from seizure

1 activity in the temporal medial lobe. The electrical stimulation of discrete mesial temporal
2 structures in patients undergoing brain surgery may induce somatosensory aura or numbness.
3 Induced somatosensory anomalies may be positive or negative and may occur unilaterally or
4 bilaterally [14, 15,16]. Somatosensory phenomena associated with temporal lobe seizures are
5 considered by some investigators to be a proxy for neocortical or lateral lobe seizures [17].
6 The most important clinical consequences of this research are that pre-operative auras with
7 somatosensory signs do not necessarily imply extratemporal seizure onset. We found that
8 patients with pre-operative somatosensory aura associated with TLE had a favorable
9 prognosis for seizure remission after partial temporal lobe resection. Thus, the frequency of
10 pre-operative somatosensory aura, whether bilateral or unilateral, should not serve as a barrier
11 to temporal lobe resection in patients with refractory epilepsy in whom etiology and/or
12 electrophysiological and imaging findings support a unilateral temporal lobe seizure focus.

13 There were several limitations to our report. First, this was a single-center analysis. A
14 multicenter study with a wider group of patients from different institutions or areas is
15 required to further analyze aura subtype and its association with epilepsy outcomes. Second,
16 all of our patients were tested by scalp EEG, not intracranial EEG, which renders our
17 conclusion less reliable.

18

1 **5. Conclusion**

2 Patients who underwent TLE surgery with positive pre-operative aura had a 1.74-fold
3 increase in the likelihood of seizure-free status postoperatively, compared with patients who
4 had seizures during the postoperative period. Patients who had positive pre-operative aura
5 also had later onset of epilepsy than patients without pre-operative aura. In the case of TLE
6 patients with positive pre-operative aura who are candidates for surgery, the greatest
7 likelihood of seizure-free status postoperatively is observed in those with pre-operative
8 sensory aura, followed by those with pre-operative autonomic aura, those with pre-operative
9 Multiple auras, and those with pre-operative mental and affective auras. Pre-operative
10 sensory auras are a good predictor of seizure-free status and better outcomes after TLE
11 surgery.

12

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15 epilepsy surgery program and Dr. Sopiudin Dahlan, who helped with statistical analysis.

16 **Disclosure of Conflicts of Interest**

17 No relevant conflict of interest was reported by the authors for this study. We confirm
18 that we have read the Journal's position on issues involved in ethical publication and affirm
19 that this report is consistent with those guidelines.

20 **Author contributions**

21 Muhamad Thohar Arifin: conception and design of the study, data analysis, preparation of the
22 manuscript, final drafting/proofing.

23 Ryosuke Hanaya : collection of data, critical revision, manuscript editing

24 Yuriz Bakhtiar: collection of data, re-analysis of statistical results, graphics

1 Aris Catur Bintoro, Koji Iida, Kaoru Kurisu, Kazunori Arita Zainal Muttaqin: critical revision,
2 final manuscript editing

3 Jacob Bunyamin Rofat Askoro, Surya P Brilliantika : statistical analysis, data analysis, analysis
4 of surgical outcomes, editing the manuscript

5

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9

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1 **Figure legend**

2

3 Figure 1. Flow-chart study

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5 Figure 2. Kaplan-Meier Plot for survival free of seizures, according to aura type.

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7

8 **Tables**

9 Table 1. Demographic characteristics of patients who underwent TLE surgery

10

Variable	N(%)	Median (min-max)
Sex	Male	196 (39.35)
	Female	302 (60.64)
Age	Age	23 (2–62)
	Age at onset	11 (0.16–40)
	Duration of Disease	10 (1–62)
Pre-operative Aura	Positive Aura	386 (77.51)
	Negative Aura	112 (22.48)
Seizure semiology	FAS	2 (0.40)
	FIAS	275 (55.22)
	FBTCS	183 (36.74)
	GTCS	3 (0.60)
	Others	35 (7.02)
	ATL	417 (83.73)
Type of Surgery	SAH	55 (11.04)
	Lesionectomy	20 (4.01)
	Others	6 (1.20)

11

12

1 Table 2. Correlations with seizure outcome in TLE patients

2

	<i>p</i>
Type of Seizure	0.529
Pre-operative Aura	0.030*
Type of Operation	0.195
Duration of Epilepsy	0.299
Sex	0.104

3 *Significant difference, $p < 0.05$.

4

5

1 Table 3. Correlation between pre-operative aura and seizure-free status after TLE surgery
 2

		Event of seizure after TLE Surgery		<i>P</i>-value	OR
		Seizure Free	Seizure		
Pre-operative aura	Positive	324 (80.19)	62 (15.34)	0.03*	1.74
	Negative	84 (75)	28 (25)		

3 *Significant difference, $p < 0.05$.
 4
 5

1 Table 4. Mean age at onset of initial seizure in patients with positive vs. negative pre-
 2 operative aura after TLE surgery

		N(Mean \pm SD)	P Value	95% CI
Pre-operative aura	Positive	372 (12.35 \pm 7.01)	0.04*	0.55–3.24
	Negative	95 (10.70 \pm 7.22)		

4 *Significant difference, $p < 0.05$.

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1 Table 5. Correlation between duration of disease and seizure-free status after TLE surgery

2

		N (Mean \pm SD)	P-value	95% CI
Outcome	Seizure Free	397 (12.01 \pm 8.00)	0.04*	-3.85 -(-0.02)
	Seizure	87 (13.95 \pm 9.29)		

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1 Table 6. Pre-operative aura types among patients who underwent TLE surgery

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Manifestations	Number of patients	Percentage	Areas with abnormal electroencephalography					Non-lesional findings
			Frontal	Central	Parietal	Temporal	Occipital	
Autonomic auras								
• Palpitation	41	10.6%	6	1	2	37	0	1
• GI	65	16.8%	5	1	0	64	0	0
• Suffocation	12	3.1%	1	0	0	11	0	0
Total	118	30.6%	12	2	2	112	0	1
Sensory auras								
• Visual	16	4.1%	0	0	0	16	0	0
• Olfactory	1	0.3%	0	0	0	1	0	0
• Gustatory	0	0.0%	0	0	0	0	0	0
• Auditory	2	0.5%	0	0	0	2	0	0
• General somatosensory	28	7.3%	5	0	0	27	0	0
Total	47	12.2%	5	0	0	46	0	0
Mental and affective auras								
• Feeling of fear	22	5.7%	4	0	0	21	0	0
• Depressed mood	4	1.0%	0	0	0	4	0	0
• Experiential sensory	55	14.2%	6	0	0	55	1	0
• Vertigo	1	0.3%	0	0	0	1	0	0
• Cognitive auras	9	2.3%	0	0	0	9	0	0
• Unspeakable feeling/malaise	54	14.0%	7	2	1	51	1	0
Total	145	37.6%	17	2	1	141	2	0
Multiple symptoms	76	19.7%	10	2	1	74	1	0
Total	386	100.0%	44	6	4	373	3	1

3

1 Table 7. Seizure-free status among patients with different pre-operative aura subtypes

2

Type of Pre-operative Aura	Median Survival Time (95% CI)	p-value
Autonomic	10 (8.327–11.673)	0.022*
Sensory	11 (9.086–12.914)	
Mental and Affective	9 (7.667–10.333)	
Multiple	9 (7.692–10.887)	

3 *Significant difference, $p < 0.05$.

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Table 8. Likelihood of seizure-free status after TLE surgery

Pre-operative Aura type	Likelihood of Seizure-Free Status (%)			
	3 years	5 years	10 years	15 years
Autonomic	94.8	84.0	48.4	19.7
Sensory	93.9	83.2	59.7	30.1

Mental and Affective	90.3	77.6	42.5	11.4
Multiple	94.7	72.0	33.7	12.1

Pre-operative Sensory aura predicts risk for seizure in temporal lobe epilepsy surgery

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