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Usefulness of the Liverpool Adverse Events Profile for predicting a high risk of suicidality in people with drug-resistant epilepsy

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ABSTRACT

Purpose: Suicidality including suicidal ideation and attempt has been a critical issue in people with epilepsy, especially in people with drug-resistant epilepsy (PWDRE). Clinicians commonly ask about adverse effects of antiepileptic drugs (AEDs) using something like the Liverpool Adverse Events Profile (LAEP) at epilepsy clinics, but suicide is usually not of interest. A high risk of suicidality can increase mortality by committing suicide in PWDRE. This study aimed to investigate whether clinicians can discern a high risk of suicidality in PWDRE by referring to the LAEP.

Methods: We recruited PWDRE, aged from 19 to 68. They completed the 21-item LAEP, the suicidality module of the Mini International Neuropsychiatric Interview, and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E). Through receiver operating characteristic curve analysis, we tested the usefulness of LAEP to detect a high risk of suicide. By this, we determined each cutoff point of the total LAEP score and the number of severe LAEP items, for detecting the risk.

Results: A hundred forty-four PWDRE participated in this study. Among them, 36 PWDRE (25.0%) had a high risk of suicidality. Either > 45 of the total LAEP score or > 8 of the number of severe LAEP items was a suggested optimal cutoff point for discerning the high risk of suicidality. LAEP had a correlation with the suicidality item of the NDDI-E.

Conclusion: The LAEP may inform a high risk of suicidality in PWDRE. Referring to this, clinicians can discern suicidal problems in their epilepsy clinics.

1. Introduction

Suicidality encompasses suicidal ideation and suicide attempt. Epilepsy increases the risk of suicidality in people with epilepsy (PWE) [1–4]. In the PWE, the lifetime prevalence of suicidal ideation and the risk of suicide attempt are twice [1] and three times [2], respectively, compared to the people without epilepsy.

The Mini International Neuropsychiatric Interview (MINI) is a structured clinical interview and a gold standard test for detecting psychiatric disorders [5,6]. The Diagnosis and Statistical Manual of Mental Disorders-IV criteria is the base for diagnosing psychiatric disorders by the MINI. The MINI includes a suicide module that allows a relatively simple assessment of suicidality.

Factors related to seizures, such as high frequency and early onset, can be a risk factor for suicide in PWE [7]. Nonetheless, rather than seizure-related factors, depression and other psychiatric comorbidities have a more significant impact on the suicidality in PWE [4,8]. Among psychiatric diseases, affective disorders are most associated with the suicidality in PWE [2]. Major depression disorder in PWE increased the attempt of suicide [5]. Suicidal ideation occurs more frequently when there are depression symptoms in PWE [3]. If the degree of depressive symptoms in PWE is severe, their suicidal ideation is also severe [8].

Depression in PWE happens more often when their seizure controls are not proper [3]. Depression itself also disturbs seizure control of PWE [9]. Suicidality will be more of a problem in people with drug-resistant epilepsy (PWDRE) than in people with well-controlled epilepsy since depression is more common in the former than the latter and depression increases suicidality in PWE.

The first version of the Liverpool Adverse Events Profile (LAEP) is a self-report questionnaire having 19 items [10,11]. The 21-item version

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of the LAEP is also available now. In the 21-item version, "thinking unclearly" and "slurred speech" were added to the 19-item version [12]. High score of the LAEP has an associated with depression [13–18]. The association may be because depression may increase the adverse effects of antiepileptic drugs (AEDs), but there may be another reason. Because the LAEP includes items asking symptoms related to depression, depression may increase the LAEP score regardless of AEDs. The high score of LAEP also seems to correlate with suicidality because depression in PWE increases suicidality as we mentioned above.

Suicide victims with epilepsy are more than twice as likely to have depression as suicide victims without epilepsy [19]. Besides, depression is more potent as a risk factor for suicidality in PWE than in people without epilepsy [19]. A population-based study reported that the risk of suicide attempts was three times higher in PWE versus people without epilepsy [2]. The study also showed that the risk increased 32-fold in the presence of affective disorders in PWE.

In epilepsy clinics, clinicians must meet a scheduled number of PWE during a limited-time session. Therefore, as the number of screening tests increases, time cannot be used effectively. To identify a risk of suicidality and common adverse effects of AEDs, clinicians should combine the suicidality module of MINI and the LAEP. However, it may be possible to identify both of them by examining only the LAEP if the high scores of LAEP have an association with the risk of suicidality. The purpose of this study was to evaluate the correlation of LAEP score with the high risk of suicidality in PWDRE.

2. Methods

2.1. Subjects

We had consecutively recruited PWDRE who had been treated with AEDs at the epilepsy clinic of the Kyungpook National University Hospital for more than one year. The age of them was limited to 18–70 years old. We diagnosed epilepsy according to the criteria of the International League Against Epilepsy (ILAE) for seizures and epileptic syndromes [20].

The definition of DRE was as follows: 1) Lack of seizure control, of more than two first-line AEDs, 2) In average, there was one seizure per month over the last 18 months; 3) The maximum seizure-free period was less than three months during that period [21,22]. We determined the seizure frequency of PWDRE by probing the electronic medical records.

We excluded the PWDRE with an intellectual disability or severe medical, neurological, or psychiatric disorder, or other diseases that prevented them from understanding the questionnaire and cooperating with the interviewer. Even when taking antidepressants, we did not exclude PWDRE if they did not have severe conditions and could collaborate with the interview. We also did not eliminate people with post-stroke epilepsy or history of stroke, if the stroke status was not severe and they could cooperate in testing the LAEP and the suicidal module of the MINI.

Initially, we recruited 170 consecutive PWDRE. Of these, 26 could not participate in the study because of the following reasons: the refusal of the study (n = 12), intellectual disability (n = 6), younger age (n = 5), and older age (n = 3). Finally, 144 people with PWDRE participated in this study.

2.2. Study design

The Institutional Review Board of Kyungpook National University Hospital approved this study. When enrolling PWDRE in this study, we provided all of them informed consent. We collected demographic and clinical information of patients through interviews in the clinic and reviews of electronic medical records and entered all of the obtained data into a computerized file. In the information, we divided the epilepsy syndrome into four categories: temporal lobe epilepsy; extra-temporal lobe epilepsy; generalized epilepsy; or unknown syndrome. We classified the AED regimen according to the number of AEDs PWDRE took: monotherapy or polytherapy. The recruited PWDRE filled up a self-report form of the LAEP, and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) and responded to an interview by a neuropsychologist using the suicidality module of the MINI-Plus Version 5.0.0.

2.3. Questionnaire and interview

2.3.1. LAEP

We used the LAEP with 21 items in this study. On the day PWDRE visited the clinic, the PWDRE filled up the LAEP as a self-report form before meeting a clinician. The LAEP has a constitution in which PWE report common adverse events during the last four weeks by themselves. Each item in the LAEP is a four-point Likert scale question as follows: 1, never a problem; 2, rarely a problem; 3, sometimes a problem; and 4, always or often a problem. Therefore, the total score of 21-item LAEP ranges from 21 to 84. For the test the usefulness of LAEP for detecting a high risk of suicidality, we looked at the optimal cutoff point of the total LAEP score and the number of severe LAEP items. We defined the number of severe LAEP items as the number of LAEP items reported as score 3 or 4 among four-point Likert scale scores.

2.3.2. The suicidal module of MINI

The MINI is a structured clinical interview for the diagnosis of psychiatric disorders and is a gold standard test for which the time spent is relatively short. We used the suicidality module included in the MINI to evaluate the risk of suicidality. After PWDRE visited the epilepsy clinic and filled the LAEP questionnaire, a clinical psychologist interviewed PWDRE with the suicidality module on the same day.

The suicidal module consists of six items. All six items are questions related to wish for death, and each item has a weight based on its severity. The first five questions ask patients what they experienced in the past month: Did you think you would be better off dead or wish you were dead? (weight of 1); Did you want to harm yourself? (weight of 2); Did you have suicidal thoughts? (weight of 6); Did you have a suicide plan? (weight of 10); Did you attempt suicide? (weight of 10). The sixth item is "Have you ever attempted suicide?" (Weight of 4). If a patient responds "yes" to any of these six items, we can assess that the patient has suicidality. If the sum of weight is $\geq$ 10, it means a high risk of suicidality. In that case, patients have a high risk of committing suicide.

2.3.3. The 4th item of NDDI-E

The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is an epilepsy-specific inventory and is used to screen major depressive disorders in PWE. At the time of the development of the NDDI-E, the developers excluded all depressive symptoms that could be side effects of AEDs and remained only six items in the inventory [23]. Each of the six items is an item with a four-point Likert scale. The 4th item of the NDDI-E is "I'd better off dead" and is to probe the suicidal ideation of PWE.

2.4. Statistical analysis

2.4.1. Receiver operating characteristic analysis

For descriptive statistics, we used Statistical Package for the Social Sciences (SPSS) version 25.0 (SPSS, Inc., Chicago, IL, USA) software. We performed a receiver operating characteristic (ROC) analysis for LAEP. The purpose of ROC analysis was to test the LAEP as a screening tool for discerning a high risk of suicidality in PWDRE. For this, we used MedCalc Statistical Software version 18.10.2 (MedCalc Software bvba, Ostend, Belgium). ROC analysis of the LAEP was performed not only on the total LAEP score but also on the number of severe LAEP items. The significance level of statistical analysis was set at $p < 0.05$.

Table 1
Demographic and clinical characteristics of people with drug-resistant epilepsy participating in the study (n = 144).

Characteristics	Mean ± SD (range) or number (%)
Age, years	41.2 ± 11.3 (19-68)
Gender, male	86 (59.7)
Education, years	11.7 ± 3.0 (2-16)
Age at onset, years	20.3 ± 11.6 (1-61)
Duration of epilepsy, years	20.9 ± 12.6 (2-52)
Type of seizure, partial	137 (95.1)
Epilepsy syndrome	
Temporal lobe epilepsy	75 (52.1)
Extra-temporal lobe epilepsy	58 (40.37)
Generalized epilepsy	8 (5.6)
Unknown	3 (2.1)
Number of seizures during the last 3 months	2.1 ± 0.7 (1-3)
MRI, abnormal	78 (54.2)
History of febrile convulsion	38 (26.4)
Family history of epilepsy	5 (3.5)
Duration of AED intake, years	18.2 ± 12.3 (1.2-52.0)
Epilepsy surgery	13 (9.0)
Number of current AEDs	3.0 ± 1.1 (1-6)
Concurrent psychiatric medication	29 (20.1)
High suicidality by MINI	36 (25.0)
Total LAEP score	41.8 ± 14.7 (21-78)
Number of severe LAEP items*	6.5 ± 5.7 (0-21)
Score of 4th item of NDDI-E	1.80 ± 1.0 (1-4)

MRI: magnetic resonance imaging, AED: antiepileptic drug, MINI: Mini International Neuropsychiatric Interview—Plus Version 5.0.0, LAEP: Liverpool Adverse Event Profile, NDDI-E: Neurological Disorders Depression Inventory for Epilepsy, SD: standard deviation.

* The number of LAEP items reported as score 3 or 4 among four Likert scale scores.

2.4.2. Correlations between the two LAEP parameters and the 4th item of the NDDI-E

To see the association of the LAEP and suicidality, we analyzed the correlations between the score of the fourth item of the NDDI-E, the total LAEP score, and the number of severe LAEP items. For this analysis, we also used SPSS version 25.0 (SPSS, Inc., Chicago, IL, USA) software.

3. Results

3.1. Demographics and characteristics

Table 1 depicts the demographics and characteristics of the PWDRE participating in this study. The average age of PWDRE was 41.2 years, of whom 59.7% were male. For the epilepsy of the participants, the mean age of onset was 20.3 years, and the mean duration was 20.9 years. Of the 144 patients recruited in this study, 13 patients received epilepsy surgery, accounting for 9.0%. The average LAEP score was 41.8, and the average score of the 4th item of NDDI-E was 1.80. Thirty-six of 144 PWDRE had a high risk of suicidality, accounting for 25.0%.

3.2. Optimal cutoff point of the total LAEP score

The total LAEP score was 41.8 ± 14.7, ranged 21-78. Table 2 shows the results of the ROC curve analysis of the total LAEP score, and Fig. 1-A shows the ROC curve drawn by the analysis. The total LAEP score was suited for discerning the high risk of suicidality in PWDRE: area under the curve (AUC) = 0.862, SE = 0.0333, $p < 0.0001$, 95% CI [0.794, 0.914]. The optimal cutoff point was > 45. At the cutoff point of > 45, sensitivity and specificity were 83.3% and 74.1% respectively, with positive predictive values (PPVs) of 51.7% and negative predictive values (NPVs) of 93.0%.

3.3. Optimal cutoff point of the number of severe LAEP items

The number of severe LAEP items was 6.5 ± 5.7, ranged 0-21. Table 3 shows the results of ROC analysis of the number of severe LAEP items, and Fig. 1-B shows the ROC curve drawn by the analysis. The number of sever LAEP items was also suited for discerning the high risk of suicidality in PWDRE: AUC = 0.858, SE = 0.033, $p < 0.0001$, 95% CI[0.790, 0.911]. The optimal cutoff point was > 8. At a cutoff point of > 8, sensitivity and specificity were 77.8% and 80.6% respectively, with PPV of 57.1% and NPV of 91.6%.

3.4. Correlations between the two LAEP parameters and the 4th item of the NDDI-E

The total LAEP score and the number of severe LAEP items had positive correlations with the score of the 4th item of the NDDI-E. Pearson correlation was 0.545 ($p < 0.001$) between the total LAEP score and the 4th item, and 0.543 ($p < 0.001$) between the number of severe LAEP items and the 4th item (Table 4).

4. Discussion

Prevalence of suicidality is higher among PWE than people without epilepsy. According to a Canadian community health survey, the lifetime prevalence of suicidal ideation was 25% in PWE, and the prevalence was two times higher than that of people without epilepsy [1]. A Danish survey using five nationwide longitudinal registries demonstrated that the odds ratio of suicide attempt was 3.17 between PWE and people without epilepsy [2].

In a Korean hospital-based study gathering PWE from two tertiary-care centers, the frequency of suicidal ideation of PWE was 3.6 times higher than that of healthy controls [3]. According to another Korean hospital-based multicenter study on PWE recruited from five secondary or tertiary care hospitals, 30.4% of PWE experienced suicidality. Of these, 14.6% reported suicidal ideation, and 15.8% reported both of suicidal ideation and suicide attempt. In the study, the frequency of suicidality of PWE was 4.6 times higher than that of people without epilepsy [4]. Suicidal attempt increases the frequency of completed suicide, and this leads to increased mortality of PWE [5].

PWE who had depression before the development of epilepsy have more possibility of drug resistance than those without the history of depression [9]. As the relationship between prior depression and subsequent drug resistance, depressive symptoms and disorders are more prevalent in PWE when their seizure controls are not proper [3,9]. Depression, like in the general population, is the causative factor of suicidality in PWEs [5,7,8]. Moreover, the impact of depression on suicidality is more potent in PWE than in the general population [19]. Drug resistance itself also increases suicidal ideation in PWE [3,4]. Taken together, the efforts to reduce suicidality may be more mandatory for PWDRE.

There are items associated with cognition and emotion in the LAEP: feelings of aggression, nervousness, restlessness, difficulty concentrating, depression, disturbed sleep, and memory problems [10,11]. The items can allow depression of PWE to increase the total score of the LAEP [13]. It is a drawback for the LAEP, as a screening tool for common adverse effects of AEDs, that depression may cause the high gaining of the total score. However, for the association between high LAEP score and depression, high LAEP score may suggest a possibility of having depression in PWE inversely.

The high LAEP score may also suggest a high risk of suicidality in PWE because depression is a potent risk factor for suicidality [4,8]. Through this study, we investigated the association between LAEP and a high risk of suicidality and revealed that LAEP could be useful for discerning a high risk of suicidality in PWDRE.

The U.S. Food and Drug Administration warned, through a meta-analysis of randomized trials, that the use of AEDs has an association

Table 2
ROC curve analysis of the total LAEP score for discerning a high risk of suicidality.

Cutoff point	Sensitivity (%)		Specificity (%)		PPV (%)	NPV (%)	AUC			
	Value	95% CI	Value	95% CI			Value	SE	95% CI	*p*-value
> 39	86.1	70.5 - 95.3	60.2	50.3 - 69.5	41.9	92.9				
> 40	83.3	67.2 - 93.6	62.0	52.2 - 71.2	42.3	91.8				
> 45*	83.3	67.2 - 93.6	74.1	64.8 - 82.0	51.7	93.0	0.862	0.0333	0.794 - 0.914	< 0.0001
> 46	77.8	60.8 - 89.9	75.9	66.7 - 83.6	51.9	91.1				
> 47	75.0	57.8 - 87.9	79.6	70.8 - 86.8	55.1	90.5				

ROC: receiver operating characteristic, LAEP: Liverpool Adverse Events Profile.
PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve.
SE: standard error, CI: confidence interval.
* Optimal cutoff point.

with suicidality in 2008. The odds ratio for suicidality in the meta-analysis was 1.80 comparing AEDs with placebo [24]. However, this data has several fundamental problems. They performed meta-analysis by collecting data from 11 different AEDs with different mechanisms, and adjunctive therapies among the trials included in the meta-analysis were heterogeneous. Also, between the primary studies included in this meta-analysis, the sources of outcome data were not uniform and statistical methodologies varied [25]. Past suicidal behaviors have a profound effect on current suicidality. However, it is also a significant limitation of the meta-analysis that most of the included studies did not consider past suicidal behaviors [26].

It is not yet clear whether AEDs are a risk of increasing suicidality. Some researchers have argued that the FDA's warning is too much. They argued that the degree to which AEDs increase suicidality in PWE is weak and hypothetical. And they warned that if we do not use AEDs or stop using AEDs, PWE will suffer more significant harm than suicidality [25,27,28]. In a study of suicidality in older veterans receiving new AED monotherapy, the most reliable predictor for suicidality was an affective disorder before the AED prescription [29]. Depression and anxiety that some AEDs may cause as side effects may have an association with suicidality in PWE. Although the LAEP does not have any query to ask for suicidality, a high score of the LAEP can reflect suicidality in PWE because the LAEP contains items related to depression and anxiety. Our study showed that the total LAEP score and the number of severe LAEP items correlated significantly with the 4th item of NDDI-E, asking for suicidal ideation. These results may be evidence that high score of LAEP may reflect suicidality in PWE.

The methodology of this study has limitations in determining the suicidality as a side effect of AEDs. A high score in a snapshot of the LAEP does not always mean high incidence of AED side effects in PWE. If PWE has comorbid depression and anxiety, the total score will increase. To identify the side effects of AEDs in PWE with psychiatric comorbidities, we need to compare the LAEP under the state of taking AEDs with the LAEP in the baseline condition without AEDs. Furthermore, since LAEP does not have suicidality items, it is difficult to directly know AED side effects associated with suicidality. Based on these, we investigated whether LAEP was helpful to discern a high risk of suicidality in PWDRE.

The time allocated for a session of epilepsy clinics is not sufficient for epileptologists to assess all aspects of PWE because an epileptologist must meet a relatively large number of PWE during the allotted time. We can screen depression and anxiety using quick inventories, such as the NDDI-E or the Hospital Anxiety and Depression Scale (HADS), to discern suicidality indirectly in PWE. While they are quick inventories, the time limitation of busy clinics does not allow all of the tests to be applied whenever examining LAEP in PWE. Also, if the physicians apply the inventories asking patients for mood disorders without any reason, PWE may feel another stigma in addition to the stigma for epilepsy. For these reasons, physicians need to select the appropriate ones according to the situation. When a physician has applied LAEP to PWE to assess adverse effects of AEDs, the high LAEP score may be a hint that the physician needs to evaluate the suicidality of the PWE. At this situation, the physician can use the suicidality module of MINI, the NDDI-E, or HADS.

Depending on the results of our study, if the total LAEP score exceeds 45 points or the number of items checked as score 3 or 4 exceeds eight, in the 21-item LAEP, the risk of suicidality may be high in PWDRE. In conclusion, the LAEP may be a multimodal inventory that not only screens common adverse effects of AEDs but also discerns a high risk of suicidality in PWDRE.

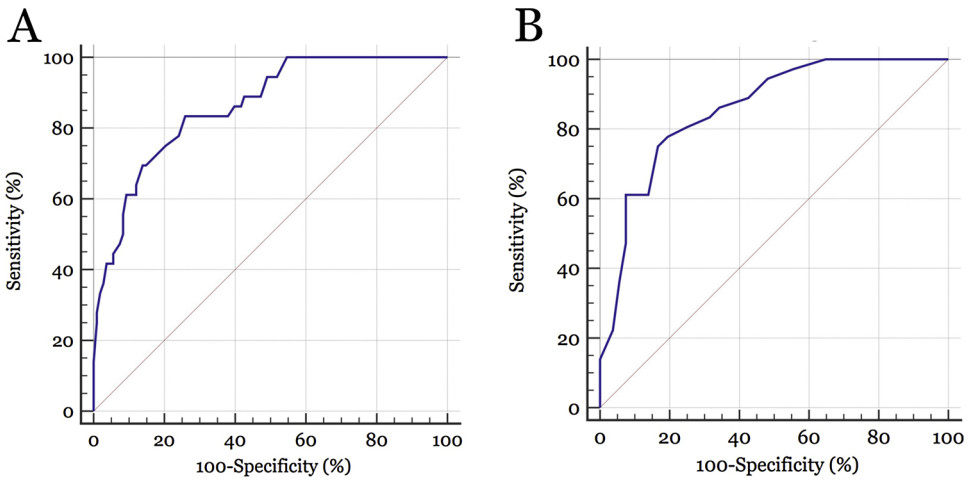

Fig. 1. The Receiver Operating Characteristics (ROC) curve for the Liverpool Adverse Events Profile (LAEP) to discern a high risk of suicidal ideation in people with drug-resistant epilepsy. (A) The area under the curve (AUC) was 0.862 as a result of ROC curve analysis for the total LAEP score. Sensitivity and specificity for the cutoff point of > 45 were 83.3% and 74.1%, respectively. (B) The ROC curve analysis of the number of severe LAEP items revealed an AUC of 0.858. Sensitivity and specificity were 77.8% and 80.6% for the cutoff point of > 8, respectively. We defined the number of severe LAEP items as the number of LAEP items reported as score 3 or 4 among four-point Likert scale scores.

Table 3
ROC curve analysis of the number of severe LAEP items for discerning a high risk of suicidality.

Cutoff point	Sensitivity (%)		Specificity (%)		PPV (%)	NPV (%)	AUC			
	Value	95% CI	Value	95% CI			Value	SE	95% CI	*p*-value
> 6	83.3	67.2 - 93.6	68.5	58.9 - 77.1	46.9	92.5				
> 7	80.6	64.0 - 91.8	75.0	65.7 - 82.8	51.8	92.0				
> 8*	77.8	60.8 - 89.9	80.6	71.8 - 87.5	57.1	91.6	0.858	0.033	0.790 - 0.911	< 0.0001
> 9	75.0	57.8 - 87.9	83.3	74.9 - 89.8	60.0	90.9				
> 10	61.1	43.5 - 76.9	86.1	78.1 - 92.0	59.5	86.9				

ROC: receiver operating characteristic, LAEP: Liverpool Adverse Events Profile.
PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, SE: standard error, CI: confidence interval.
* Optimal cutoff point.

Table 4
Correlation between the total LAEP score, the number of severe LAEP items, and the 4th item score of the NDDI-E.

		Total LAEP score	Number of severe LAEP items	4th item score of NDDI-E
Total LAEP score	Pearson correlation	1.000	0.967*	0.546*
	p (2-tailed)	–	0.000	0.000
	Number of PWE	144	144	144
Number of severe LAEP items	Pearson correlation	0.967*	1.000	0.543*
	p (2-tailed)	0.000	–	0.000
	Number of PWE	144	144	144
4th item score of NDDI-E	Pearson correlation	0.546*	0.543*	1.000
	p (2-tailed)	0.000	0.000	–
	Number of PWE	144	144	144

LAEP: Liverpool Adverser Event Profile, NDDI-E: Neurological Disorders Depression Inventory for Epilepsy, PWE: people with epilepsy.
* Correlation is significant at the 0.01 level (2-tailed).

Conflict of interest

The authors have no financial or other potential conflicts of interest related to the present study to report.

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Authors' contributions

SPP took part in the design of the study and contributed to the data collection. OYK participated in writing the manuscript and was responsible for data statistics. All authors agreed to accept equal responsibility for the accuracy of the content of the paper. Both authors read and approved the final manuscript.

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