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# Delirium in patients with acute ischemic stroke admitted to the non-intensive stroke unit: Incidence and association between clinical features and inflammatory markers

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ABSTRACT

*Background:* Stroke patients with development of delirium have unfavorable outcomes, higher mortality, longer hospitalizations, and a greater degree of dependence after discharge. Studies suggest that delirium is associated with abnormal immunological responses and a resultant increase in inflammatory markers.

*Objective:* Our aim was to determine whether there is an entity relationship between delirium, inflammation and acute ischemic stroke (AIS).

*Methods:* Sixty AIS patients admitted to the hospital were consecutively recruited. Delirium was diagnosed with the clinical assessment according to the Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum levels of Interleukin-1 beta (IL-1 beta), Interleukin 18 (IL-18), Tumor Necrosis Factor-alpha (TNF-alpha), Brain-Derived Neurotrophic Factor (BDNF), and Neuron Specific Enolase (NSE) at admission.

*Results:* Eleven (18.3%) of 60 patients were diagnosed with delirium, and the majority ($n = 8$, 72.7%) was the hypoactive type. Delirious and non-delirious patients had similar demographic and clinical features. Delirious patients had significantly higher lengths of hospital stay, National Institutes of Health Stroke Scale (NIHSS) at admission and discharge compared to non-delirious patients. In addition, there was no significant statistical difference between delirious and non-delirious patients with AIS in respect of levels of TNF-alpha, IL-1 beta, IL-18, BDNF and NSE. This study suggests that delirium is not scarce in patients with AIS admitted to the non-intensive stroke unit, and that delirium developing after AIS seems not to be associated with serum TNF-alpha, IL-1 beta, IL-18, BDNF and NSE but is associated with length of hospital stay and stroke severity.



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## 1. Introduction

Delirium is a common neuropsychiatric clinical syndrome characterized primarily by a disturbance of awareness, attention and additional cognitive functions such as memory, language and perception, and which can also affect sleep, psychomotor activity and emotions. Other main features of delirium are the development of disturbances usually lasting hours to days and a tendency to a fluctuation in the level of consciousness during the course of the day [1,2]. It may occur due to general medical conditions and their treatment, substance use or withdrawal, multiple etiologies or an unknown etiology [1,3]. Delirium is not only a manifestation of clinical syndromes but is also related to increased mortality [4], longer stays in hospital and poorer physical and social functioning in patients [5,6]. Therefore, delirium is an important clinical problem in hospitalized patients.

Its prevalence has been reported to be from 14% to 87% in critically ill patients [7]. Stroke is one of the recognized predisposing factors for delirium [8]. Although delirium affects 10–48% of patients with acute stroke [9], a meta-analysis indicated that, pre-stroke poor vision, impaired vision, pre-stroke dementia, metabolic disorders, Glasgow Coma Scale score less than 15 on admission, and inability to lift both arms on admission have been reported to be independent factors associated with delirium following stroke [8,10,11]. Similar to other general medical conditions, stroke patients with delirium have higher mortality, stay longer in hospital, and have high risk of institutionalization [11,12].

Pathophysiology of delirium remains unclear and poorly understood [13]. Because of the complex causation of delirium, a single cause or mechanism for this clinical condition will probably not be discovered [14]. It is possible to conclude that in most cases of delirium there is interaction of multiple biological precipitating and predisposing factors resulting in disruption of neuronal networks in the brain, associated with cognitive functions [13,14].

Many potential pathophysiological contributors to delirium have been studied. These studies include pro-inflammatory markers in addition to neurotransmitters, electrolytes, metabolic disturbances, and genetic factors [14]. Capri et al. reported that high levels of preoperative Interleukin 6 (IL-6) levels, Interleukin 8 (IL-8) and Interleukin 10 (IL-10) were independently associated with post-operative delirium [15]. Kazmierski et al. reported that patients with raised concentrations of Interleukin 2 (IL-2) and Tumor Necrosis Factor-alpha (TNF-α) measured the day after coronary-artery bypass graft surgery were more likely to develop delirium [16]. Moreover, some authors found significantly more IL-6 and IL-8 levels above the detection limit in patients with delirium who were acutely admitted to hospital compared to patients who did not have delirium [17]. In addition, it has been reported that at admission to an intensive care unit, Brain-Derived Neurotrophic Factor (BDNF) and Neuron Specific Enolase (NSE) levels were significantly higher in delirious patients than in nondelirious patients [18]. However, the role of proinflammatory cytokines, BDNF and NSE in delirium following acute stroke is unknown. Previous studies on this topic have been conducted in patients with other medical conditions. In this study, we aimed to investigate whether the occurrence of delirium in patients with acute ischemic stroke (AIS) is associated with serum TNF-alpha, Interleukin 1beta (IL-1 beta), Interleukin 18 (IL-18), BDNF and NSE on admission.

## 2. Methods

### 2.1. Study population

Sixty patients with acute ischemic stroke admitted to our hospital within the first 24 h of stroke onset were prospectively included in the study. These patients were followed up in the non-intensive stroke unit. The inclusion criteria were clinical presentation of acute ischemic stroke, age 18 years or older. The study exclusion criteria included: (1) An admission to hospital after the first 24 h, (2) a diagnosis of transient ischemic attack (TIA), intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH), (3) the existence of impaired consciousness, severe aphasia or dysphasia, (4) a history of brain tumor with or without systemic malignancy, (5) a history of acute myocardial infarction, (6) the existence of renal dysfunction and symptomatic peripheral arterial disease, (7) a history of infection in the last three months, acquired infections after the application, autoimmune and immunosuppressive diseases or using immunosuppressive drugs, (8) a history of trauma or surgical history within one month, (9) the existence of acute/chronic inflammatory disease of the gastrointestinal tract, rheumatic disease, (10) a diagnosis of metabolic syndrome and (11) use of antidepressant or other psychotropic medication in the last month. Informed consent was obtained after providing verbal and written information to participants or nearest relatives when relevant. The study was performed in accordance with the Helsinki declaration and approved by the local ethics committee of the Necmettin Erbakan University, Meram Medical Faculty.

### 2.2. Stroke case ascertainment

Stroke was defined as the presence of rapidly developing focal neurological signs or symptoms of vascular origin that persisted for more than 24 h. All events were adjudicated by a panel of at least two neurologists. A general medical history was collected and physical and neurological examinations, standard laboratory tests, and 12-lead electrocardiogram were performed on all patients upon admission. The ischemic lesion and affected brain region were assessed and confirmed both by clinical examination and computed tomography (CT) and/or brain magnetic resonance imaging (MRI) during hospitalization for acute stroke. Stroke subtype was classified according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria [19]. Location of the infarct lesion was determined by radiological findings and the Oxfordshire classification criteria were used [20]. Stroke severity was evaluated by trained neurologists using the National Institutes of Health Stroke Scale (NIHSS) at admission and discharge [21].

### 2.3. Psychological measurement

The patients were assessed every day by the psychiatrist from the day of their hospitalization to their discharge from

the Department of Neurology. The diagnosis of delirium was determined by clinical evaluation according to the Statistical Manual of Mental Disorders, Fourth Edition [1] criteria and used the Delirium Rating Scale (DRS) developed by Trzepacz et al. [2]. This scale consists of 10 items ranging between 0 and 3. Delirium is defined when the score is 10 points or higher. Delirium subtypes were categorized as hyperactive, hypoactive, and mixed, which have been described by Liptzin and Levkoff and used in some previous studies [22,23].

### 2.4. *Blood collection and cytokine measurement*

Blood samples were taken at the first 24 h after stroke onset. A total of 8 ml of peripheral venous blood was drawn and centrifuged at 1000 × *g* for 10 min at room temperature to separate the blood components. Serum samples were kept at −80 °C until assay. TNF-alpha, IL-1 beta, IL-18, BDNF, NSE, and serum levels were measured with enzyme-linked immunosorbent assay (ELISA), using a commercial kit according to the manufacturer's instructions (BDNF, IL-1β and TNFα: Boster Biological Technology, California, USA; NSE: Yehua Biological Technology, Shanghai, China; IL-18: eBioscienceBender MedSystems, Vienna, Austria).

### 2.5. *Statistical analysis*

Statistical analyses were performed with SPSS 16.0 for Windows (Statistical Package for the Social Sciences, Chicago, IL). For comparisons between the study groups t test (for normally distributed variables) and Mann–Whitney *U* test (for abnormally distributed variables) were used for continuous variables and $\chi^2$ test (for 3 or more × 2 variables) or Fisher's exact test (for 2 × 2 variables) for categorical variables. All significant levels were 2-tailed and set at the level of 0.05.

## 3. Results

The mean age of the study sample (*n*: 60) was 66.15 ± 12.53 (range: 31–89) years. Thirty-one of the patients in the study population (51.7%) were female and twenty-nine (48.3%) were male. Thirty-six of the patients in the study group (60%) were living in the city center, and 21 (35%) were living in rural areas, 54 (90%) were living with family and 54 (90%) belonged to the normal income group. In the study group, Hypertension (HT) (*n*: 45, 75%), Diabetes Mellitus (DM) (*n*: 23, 38.3%), Coronary Artery Disease (CAD) (*n*: 18, 30%) and Hyperlipidemia (HL) (*n*: 16, 26.7%) were the most common diseases. The average NIHSS

**Table 1 – Sociodemographic data, medical history, length of hospital stay and functional scores of the patients.**

| | Patient with AIS *n* = 49 | Patient with AIS and delirium *n* = 11 | *p* |
|---|---|---|---|
| **Sociodemographic data** | | | |
| Age (mean ± SD) | 64.63 ± 13.18 | 72.91 ± 5.61 | 0.002 |
| Sex, Male *n* (%) | 24 (49) | 5 (45.5) | 1.000 |
| Sex, Female *n* (%) | 25 (51) | 6 (54.5) | 1.000 |
| Habitation *n* (%) | | | |
| City center | 29 (59.2) | 7 (63.6) | 0.701 |
| Rural area | 17 (34.7) | 4 (36.4) | 0.701 |
| Village | 3 (6.1) | 0(0) | 0.701 |
| Income status *n* (%) | | | |
| High income | 4 (8.2) | 2 (18.2) | 0.302 |
| Ordinary income | 45 (91.8) | 9 (81.8) | 0.302 |
| Living condition *n* (%) | | | |
| Live with family | 45 (91.8) | 4 (8.2) | 0.302 |
| Live alone | 9 (81.8) | 2 (18.2) | 0.302 |
| **Medical history** | | | |
| HT *n* (%) | 36 (73.5) | 9 (81.8) | 0.714 |
| DM *n* (%) | 18 (36.7) | 5 (45.5) | 0.734 |
| CAD *n* (%) | 12 (24.5) | 6 (54.5) | 0.710 |
| HL *n* (%) | 11 (22.4) | 5 (45.5) | 0.120 |
| CHF *n* (%) | 4 (8.2) | 3 (27.3) | 0.108 |
| AF *n* (%) | 10 (20.4) | 4 (36.4) | 0.264 |
| Smoking *n* (%) | 11 (22.4) | 3 (27.3) | 0.707 |
| ASA *n* (%) | 17 (34.7) | 5 (45.5) | 0.511 |
| Anticoagulant *n* (%) | 2(4.1) | 1 (9.1) | 0.462 |
| Antihypertensive *n* (%) | 33 (67.3) | 7 (63.6) | 1.000 |
| OAD *n* (%) | 13 (26.5) | 1 (9.1) | 0.430 |
| İnsülin *n* (%) | 11 (22.4) | 3 (27.3) | 0.707 |
| **Length of hospital stay** (mean ± SD) | 11.08 ± 5.63 | 16 ± 5.17 | **0.010** |
| **Functional scores** | | | |
| NIHSS at admission (mean ± SD) | 6.10 ± 3.80 | 10.36 ± 5.88 | **0.021** |
| NIHSS at discharge (mean ± SD) | 2.92 ± 2.57 | 5.73 ± 3.87 | **0.014** |

Note: Significant *p* values are boldfaced.

**Table 2 – Etiological classification and stroke location of the patients.**

| | Patient with AIS $n = 49$ | Patient with AIS and delirium $n = 11$ | $p$ |
|---|---|---|---|
| **TOAST classification** | | | |
| Large artery $n$ (%) | 10 (20.4) | 5 (45.5) | 0.086 |
| Cardio embolism $n$ (%) | 11 (22.4) | 4 (36.4) | 0.340 |
| Small vessel disease $n$ (%) | 7 (14.3) | 0 (0) | 0.186 |
| Undetermined $n$ (%) | 19 (38.8) | 2 (18.2) | 0.199 |
| Other $n$ (%) | 2 (4.1) | 0 (0) | 0.499 |
| **Stroke location** | | | |
| TACI $n$ (%) | 1 (2) | 3 (27.3) | **0.017** |
| PACI $n$ (%) | 27 (55.1) | 6 (54.6) | 1.000 |
| POCI $n$ (%) | 14 (28.6) | 2 (18.2) | 0.710 |
| LACI $n$ (%) | 7 (14.3) | 0 (0) | 0.330 |

Note: Significant $p$ value is boldfaced.

**Table 3 – Biological parameters of the patients.**

| | Patient with AIS $n = 49$ | Patient with AIS and Delirium $n = 11$ | $p$ |
|---|---|---|---|
| **Biological parameters** | | | |
| BGL (mean ± SD) | 144.69 ± 74.27 | 155.36 ± 71.40 | 0.666 |
| Urea (mean ± SD) | 39.36 ± 15.63 | 44.00 ± 16.49 | 0.383 |
| Creatine (mean ± SD) | 0.30 ± 0.46 | 0.36 ± 0.50 | 0.717 |
| Hemoglobin (mean ± SD) | 12.83 ± 2.11 | 12.81 ± 1.77 | 0.909 |
| WBC (mean ± SD) | 8283.67 ± 1983.93 | 8627.27 ± 1884.72 | 0.603 |
| CRP (mean ± SD) | 4.46 ± 3.36 | 5.90 ± 4.03 | 0.221 |
| Uric acid (mean ± SD) | 5.16 ± 1.72 | 5.45 ± 2.01 | 0.625 |
| TNF-alfa-pg/ml (mean ± SD) | 30.86 ± 36.88 | 33.82 ± 19.61 | 0.221 |
| IL-1beta-pg/ml (mean ± SD) | 3.71 ± 4.06 | 3.27 ± 0.90 | 0.483 |
| IL-18-pg/ml (mean ± SD) | 165.82 ± 114.82 | 181.55 ± 77.19 | 0.668 |
| NSE-ng/ml (mean ± SD) | 5.39 ± 5.53 | 5.18 ± 3.51 | 1.000 |
| BDNF-pg/ml (mean ± SD) | 1035.33 ± 761.07 | 905.73 ± 653.89 | 0.603 |

on admission and discharge of the study group were found to be 6.88 ± 4.52 and 3.43 ± 3.02, respectively (Table 1). There was no significant difference between the delirious and nondelirious in terms of sociodemographic characteristics or medical histories.

In the study group, 11 (18.3%) of 60 patients were diagnosed with delirium. The majority of delirium observed in the study group ($n$: 8, 72.7%) was the hypoactive type. The hyperactive delirium and mixed type delirium were diagnosed as ($n$: 2, 18.2%) and ($n$: 1, 9.1%), respectively. Delirium started in the first three days in 90% of patients and the average was 2.18 ± 0.98 days (range: 1–4 days). Delirium resolved within seven days in 80% of patients and the average recovery time of patients was 5.50 ± 2.63 days (range: 3–11).

The average length of stay of the patient group diagnosed with delirium was 16 ± 5.17 days, and the average length of stay in the non-delirious patients group was 11.08 ± 5.63 days ($p$: 0.010). The average NIHSS on admission of the patient group diagnosed with delirium and non-delirious patients group were 10.36 ± 5.88 and 6.10 ± 3.80, respectively ($p$: 0.021). The average NIHSS on discharge of the patient group diagnosed with delirium and non-delirious patients group were 5.73 ± 3.87 and 2.92 ± 2.57, respectively ($p$: 0.014). There was a significant difference between the delirious and non-delirious in terms of length of hospital stay (from hospitalization to discharge from the neurology department), NIHSS at admission, and NIHSS at discharge (Table 1).

As shown in Table 2, patients with AIS, ($n$: 15, 25%) were classified as large artery disease, ($n$: 15, 25%) cardio embolic, ($n$: 21, 35%) undetermined, ($n$: 7, 11.7%) small vessel disease and other etiology ($n$: 2, 3.3%). There was no significant difference between the delirious and nondelirious in terms of TOAST classification. Total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), posterior circulation infarcts (POCI) and lacunar infarcts (LACI) were found in ($n$: 4, 6.7%), ($n$: 33, 55%), ($n$: 16, 26.7%) and ($n$: 7, 11.7%) patients, respectively. There was a significant difference between the delirious and non-delirious in terms of TACI.

The serum samples were taken at 11.58 ± 3.04/hours after the onset of AIS symptoms on average from the delirious patient group, and at 12.02 ± 2.58/hours after the onset of AIS symptoms on average from the non-delirious patient group ($p$: 0.587). As shown in Table 3, there was no significant difference between the delirious and non-delirious patients in terms of hematologic and biochemical variables. In addition, serum baseline levels of TNF-alpha, IL-1 beta, IL-18, NSE, and BDNF were similar in the two groups.

## 4. Discussion

Delirium prevalence has been reported to be from 14% to 87% in critically ill patients [7]. In this study the incidence of delirium was 18.3%. A meta-analysis suggests that the

incidence of delirium in stroke patients is 10–30% [8,12] and 10–25% in patients admitted to general internal medicine wards [24], which is similar to the value detected in our study.

The relationship between the increase in serum TNF-alpha, IL-1beta and IL-18 and NSE measured in patients diagnosed with AIS, and infarct volume, severity of neurological deficit and neuronal death has been determined in studies [25–27]. In addition to this, elevated blood levels of inflammatory markers are associated with unfavorable functional outcome and increased mortality after stroke [28]. Berretta A. et al. have suggested that BDNF plays a key role in functional improvement after AIS [29].

In our sample, we found that there was no significant relationship between delirium developed after AIS and pro-inflammatory cytokines (TNF-alpha, IL-1beta, IL-18), BDNF and NSE. As we know, our study is the first investigating the relationship between delirium developing in the patient group followed in the non-intensive stroke unit due to AIS and pro-inflammatory cytokines (TNF-alpha, IL-1beta, IL-18), BDNF and NSE. The present studies investigating delirium after AIS have not investigated biological factors, such as pro-inflammatory cytokines, BDNF and NSE during AIS, and the development of delirium. These studies examined mainly cerebral ischemic and hemorrhagic events together rather than just ischemic stroke and usually focused on delirium incidence, clinical features, related clinical or demographic characteristics and clinical outcomes [8,30–32]. Previous studies that examined the relationship between delirium and inflammatory markers were mostly conducted in patient groups that were followed because of medical and surgical diseases in medical and surgical intensive care units [15–18].

When the results of previous studies on patient groups excepting cerebrovascular diseases were analyzed, high basal pro-inflammatory cytokines, NSE and BDNF can be expected to be related to the development of delirium in patients undergoing AIS. However, our findings do not support this hypothesis. This may include possible reasons such as: First, our expectations prior to studies about the parameters of this study stem from findings obtained from studies conducted in patients diagnosed with delirium during medical and surgical clinical follow-up. The studies on the parameters mentioned did not include the patient group with AIS. Second, the serum samples were taken within the first 24 h and this shows relatively basal values of these parameters. However, the serum levels of these parameters in patients may have the potential to undergo a partial change in the period starting from the cerebrovascular event until the time that serum samples were taken. Therefore, the resulting serum levels may not fully reflect the value at the moment of the development of the cerebrovascular event. Third, that we have a study group consisting of patients with mild to moderate stroke may have influenced our findings about pro-inflammatory cytokines, BDNF and NSE.

Our study is particularly distinguished from earlier studies and carries originality with two aspects: First, it aimed to examine delirium developed following AIS within the plane of basal pro-inflammatory cytokines, BDNF and NSE. A previous study designed in this manner has not been found in the literature. Second, most of the previous studies related to delirium have been carried out in the intensive care unit. Our study offers a new contribution to the literature on the subject because it provides data regarding the patient group followed in the non-intensive stroke unit and the patient exclusion criteria of the study were designed taking into account many situations that could affect the inflammatory response.

In the present study, there was a significant difference between the delirious and nondelirious in terms of age and these results were similar to previous studies performed on patients with AIS [10,12,30]. Older age is a predisposing factor for the development of post-stroke delirium. It is known that older age is a low-level inflammatory condition caused by increased activity of natural immunity and neuroinflammation increases the cholinergic deficit in patients with delirium [33,34]. Although our study results showing that older age but not baseline levels of serum proinflammatory cytokines predict occurrence of delirium after AIS do not support this hypothesis, further studies should be conducted on this topic.

It is known that delirium after AIS lengthens the duration of hospitalization and this condition is associated with the severity of the patients' neurological deficit and hence hospitalization functional status [10,11]. There was a significant difference between the delirious and non-delirious in terms of the NIHSS of patients on admission and discharge and length of stay in hospital. When our patient group was evaluated for NIHSS, it could include patients with mild to moderate stroke severity. The studies conducted until now were performed by categorizing the severity of the stroke of patients and the absence of large-scale studies planned in the framework of delirium-inflammation relationship reduce the strength of the reviews that we made on this issue. However, the findings of this study suggest that delirium developing after AIS is associated with stroke severity during hospitalization and the development of delirium has a negative impact on duration of hospital stay and functional recovery. It has been demonstrated in many studies performed previously that delirium had a negative effect on length of stay in hospital and the disease course [10–12,32].

Previous studies have reported that stroke location is associated with a greater risk of delirium. For example, it has been reported with strokes within the anterior or dorsomedial thalamus, the posterior cerebral artery territory, the bilateral anterior cerebral artery territories, the inferior part of the genu of the internal capsule, the caudate nucleus, and the middle cerebral artery territory, particularly in the frontostriatal region and middle temporal gyrus [35]. In the current study, the Oxfordshire classification criteria of cerebral infarction were used [20] and it was found that delirium was more likely to occur in patients with a TACI. Sheng et al. have revealed a similar result [10].

Three clinical subtypes of delirium (hyperactive, hypoactive, and mixed subtypes) have been defined [22,23]. The hypoactive type can often be undetected or misdiagnosed as depression. Potentially, this means that delirium in acute stroke may be missed, particularly the hypoactive type [11]. Results of the current study indicated that the most common type of delirium following AIS was hypoactive. We found no study regarding types of delirium in patients with AIS in the literature. The levels of cytokine have been found to be higher in the patient group with hyperactive delirium compared to the patient group with hypoactive delirium in the studies conducted by Munster et al. and it has been suggested that

there was a linear correlation between hyperactive delirium and the levels of cytokine [36]. Most of the patients with delirium in our sample were the hypoactive type. This may be another reason why we have not reached a conclusion with statistical significance between delirious and non-delirious patient groups in terms of proinflammatory cytokines, BDNF and NSE measurements

Some limitations should be considered when interpreting our study findings. First, the study has a relatively small sample size. Concerns that neuroinflammatory responses may affect the study results led to rigidity of study exclusion criteria and therefore the exclusion of a significant portion of the patients who could have been included in the study. In addition, we think that to study the biological parameters by creating groups that will need a high number of patients in a single center would be pretty hard in the presence of the exclusion criteria mentioned. Second, the study has a cross-sectional but not prospective observational design. Serum samples from the patient group were taken in the first twelve hours after AIS on average as we have expressed in the earlier parts of the discussion. Ideally, taking blood samples according to the temporal course of neuroinflammatory response can provide more robust data on the relationship between delirium and inflammatory biological parameters in patient groups without diseases that can cause neuroinflammatory response. Delirium after AIS was diagnosed by a psychiatrist as a result of an assessment held with the psychiatric interview instruments and the patients were followed during current conditions. Despite all these limitations, there are major strengths in our study.

## 5. Conclusion

Despite the limitations, our study findings show that delirium in patients undergoing AIS was not associated with basal serum pro-inflammatory cytokines (TNF-alpha, IL-1 beta, IL-18), BDNF and NSE. Cross-sectional, multicenter, and prospective controlled studies in large samples are needed in order to obtain more precise data and more accurate reviews.

## Conflict of interest

None declared.

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## Ethics

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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