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RESEARCH ARTICLE

Exploration of Histone H2B and Some Biochemical Markers in Sudanese Women with Breast Cancer

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Abstract

Background: H2B protein is associated with breast cancer and is thought to be an effective biomarker. This paper investigates the potential role of the H2B protein as a tumor marker and its association with some biochemical molecules in breast cancer patients.

Methods: This study was a retrospective hospital-based case-control study. A total of 121 Sudanese breast cancer patients with different stages of the disease and 31 healthy individuals as the control group were included in this study. A pretested structured questionnaire was used to collect participants' data, such as age, sex, district, type of therapy, and cancer stage. Blood samples were collected for laboratory investigation. H2B protein was measured by Enzyme-Linked Immunosorbent Assay (ELISA), and biochemical tests were measured by a spectrophotometer. The study data were analyzed by the GraphPad Prism software version 5.00.

Results: Most cases of breast cancer were prevalent in Khartoum, Darfur, Kordofan, and Gezira, respectively. They were commonly treated with surgery, chemotherapy, and radiation therapy. The diagnostic role of the H2B protein was investigated, and the mean value was found to be significantly different ($p < 0.05$) from the control group. Regarding the disease stages, the mean values in the late stages (stages II and III) showed significant differences ($p < 0.01$ and < 0.001, respectively) compared to the control group. However, there is no significant difference ($p > 0.05$) between the mean value in the early stage (stage I) and the control group. This result showed that the H2B protein can be used as a biomarker for breast cancer. Moreover, the H2B mean values were positively associated with cholesterol and lactate dehydrogenase (LDH), and negatively correlated with blood glucose and protein levels.

Conclusion: The results demonstrated a significant link between epigenetic (histone H2B levels) and metabolic changes (glucose, LDH, and cholesterol) in breast cancer patients, especially at the late stages.

Keywords: Breast cancer, Tumor marker, H2B protein, Blood glucose, Lactate dehydrogenase; Cholesterol

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Introduction

Breast cancer (BC) is a heterogeneous disease, comprised of various subtypes, which have different risk factors for incidence, therapeutic response, disease progression, and preferential organ sites of metastases [1]. BC is the primary causes of deaths among females and expected to reach around 3.2 million new cases worldwide by 2050 [2,3]. In Sudan, breast cancer was the most predominant malignancy among Sudanese female cancer patients [4]. Most cases were young-aged women; about 40% were below 45 years (mean age of 50) with late stages of the disease [4]. Therefore, the diagnosis and prediction of breast cancer are essential for the identification and control of the disease [5,6]. Although different breast cancer biomarkers are approved by the FDA as a diagnostic biomarkers, such as cancer antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA), they become less sensitive in the diagnosis of breast cancer progression and metastasis [7,8]. Additionally, other biomarkers like estrogen receptors (ERs), progesterone receptors (PRs), and human epidermal growth factor receptor 2 (HER2) are routinely used in breast cancer diagnosis [9]. However, their sensitivity and selectivity remain a challenge due to the presence of complex event that involves the mutation or deregulation of multiple genes [10].

It is well established that histone variants are associated

with the molecular and biological features of tumor cells [11]. Moreover, histone variants are conventional histones, comprising non-allelic isoforms (H2A, H2B, H3, and H4), that are encoded by independent genes and serve as diverse epigenetic marks by regulating the transcriptional outcomes [12]. For example, the H2B protein undergoes post-translational modifications (PTMs) and regulates fundamental processes in cancer development, including DNA damage response and expression of tumor-associated genes [13]. The incorporation of H2B into chromatin results in compact nucleosome configurations that change chromatin accessibility and trigger oncogenic and pro-inflammatory pathways [14]. In breast cancer, there are several deregulated H2B histone variations. In aggressive subtypes of breast cancer, such as triple-negative and HER2-enriched tumors, H2B overexpression is more common and is linked to a lower overall survival rate. Higher expression of the variation is seen in Asian, African American/Black populations, and in young female patients [15]. The available information comes solely from in vitro mechanistic investigations and tissue-based expression research [15], indicating a considerable gap in the translational potential of H2B as a blood biomarker. Moreover, blood-based H2B inquiry should be prioritized above traditional tissue analysis because of its non-invasive nature, demonstrated clinical effectiveness across a variety of disorders, capacity to capture systemic heterogeneity, and biological stability [16]. This strategy has revolutionary potential for real-time monitoring, early diagnosis, and tailored therapeutic interventions. However, to our knowledge, there is limited information on H2B blood levels as a diagnostic biomarker for breast cancer. Therefore, this study aims to investigate the diagnostic value of the H2B protein in the circulating blood of breast cancer patients and its possibility to be a biomarker. Furthermore, some biochemical parameters such as blood glucose, total protein, total cholesterol and LDH were measured to study their relation to H2B proteins and tumor stage progression.

Materials and Methods

Study population

The population consists of breast cancer patients and controls, healthy subjects matched to the case in terms of age. Breast cancer patients of any age who are taking different types of cancer treatment were included, based on their willingness. Breast cancer patients with diagnostic necrosis were excluded. In the context of the control group, healthy people of age relevant to cancer patients were included in this study. However, people taking medications before sample collection were excluded from being included in the control group.

The sample size was calculated using the following formula: n = N/1+ N (d)2; where n: sample size, N: Population, and d: degree of significance (0.05). The estimated study population (N) is 175 patients. Therefore, n= 175/(1+(175×0.0025)) = 122. The sample size of this study was about 122 patients.

Data collection and analysis

Secondary Data

A pretested structured data sheet containing closed questions, including age, gender, and district, has been used.

Assessment of H2B protein levels

Venous blood samples from 122 breast cancer patients and 31 healthy individuals were collected in test tubes containing EDTA as an anticoagulant, mixed for 10 min, and centrifuged at 1000 g (relative centrifugal force, RCF) for 5 min. Then, the H2B protein levels were measured by an ELISA Kit as described by Lodish et al. [17]. Briefly, the Kit components were equilibrated for 20 minutes at room temperature. Standards (9 ng/ml, 6 ng/ml, 3 ng/ml, 1.5 ng/ml, and 0.75 ng/ml) were added to designated wells, and a control diluent was added to the control well. Sample wells received 40µl of diluent buffer followed by 10µl of the sample. The plate was shaken, sealed, and incubated at 37°C for 30 minutes, then washed five times. HRP-conjugated anti-H2B antibody was added to wells (except control), followed by another incubation. TMB substrates A and B were added, mixed, and incubated in the dark at 37°C for 15 minutes, resulting in blue shades. After adding a stop solution, the color changed to yellow, and absorbance was read at 450 nm within 15 minutes.

Biochemical investigations

Venous blood samples from previously described individuals were taken in plain test tubes and centrifuged at 1000g (RCF) for 5 min. Then, the levels of blood glucose, total cholesterol, total protein, and lactate dehydrogenase (LDH) were investigated according to the corresponding manufacturer's instructions, using Biosystem commercial kits (Barcelona, Spain).

Data analysis

The study data were analyzed by the GraphPad Prism software version 5.00. Data are presented as the mean ± SEM. Student's t-test (two-tailed; Mann-Whitney) was used to compare the two independent groups (e.g., patients vs. control group). ANOVA with Tukey's post-hoc test was used to evaluate the pair-wise comparisons across groups. The two-sided probability level $p < 0.05$ was considered statistically significant. Differences with $p < 0.05$ are described as follows: $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

Ethical consideration

The ethical committee of the Ministry of Health, Khartoum State, approved this study in 2022. Consent was obtained from each patient, and permission from the Ministry of Health and from the general manager of the hospital was obtained.

Results

Demographic characteristics of breast cancer patients

A total of 121 breast cancer patients, selected randomly, were found to be females with a mean age of 47.5 ± 1.74 years. The most cases were prevalent in Khartoum state (29. 75%), followed by Darfur (15.70%), Kordofan (13.22%), Gezira (10.74%), Northern State (9.09 %), White Nile (8.26%), Sennar (4.96 %), the Nile River (4.15 %), the Blue Nile (2.48 %), and Gadarif (1.65 %), respectively.

Clinical characteristics of breast cancer patients.

The majority of patients in this study were in early disease stages, and they were treated with different therapeutic types. Regarding disease stages, out of 121 subjects who were diagnosed as breast cancer patients, 55 (45%) were at stage I, 37(31%) were at stage II, and 29 (24%) were at stage III, as shown in Table 1. In the context of treatment, 41 patients (22.3%) undergone surgery, 111 patients (60.3%) were treated with chemotherapy either alone or in combination with other therapy, 28 patients (15.2%) were treated with radiotherapy either alone or in combination with other therapy, and only 4 patients (2.2%) were treated with hormone therapy (Table 1).

Table 1. Clinical characteristics of breast cancer patients based on their disease stages and treatments

Patient Characteristics	Number of Patients	Percentage (%)
Cancer stage		
Stage I	55	45
Stage II	37	31
Stage III	29	24
Treatment*		
Surgery	41	33.88
Chemotherapy	111	91.74
Radiation therapy	28	23.14
Hormone therapy	4	3.31
*The percentages of this group are based on the patients who received each treatment.		

Blood biomarkers

H2B protein

H2B protein levels were investigated in breast cancer patients and the control group, and the results were presented in Table 2. The H2B protein levels were found to be higher in breast cancer patients compared with the control group. The mean value of H2B protein was significantly increased (P<0.05) in breast cancer patients, Figure 1.

The mean values of H2B protein were compared with the control group among the breast cancer stages (Table 3 and Figure 2). Patients in stage III showed the highest mean value, followed by stage II, while the patients in stage I and the control group showed the lowest mean value. Based on these results, it can be concluded that stages III and II tend to have high levels of H2B. Statistical tests confirmed that there are significant changes in the late stages (stages II and III, respectively, whereas there is no significant change (p> 0.62) in stage I compared to the control group.

Table 2. The mean value of H2B protein among breast cancer patients and the control group.

Parameters	Number of subjects	H2B protein levels (Mean ± SEM)
Patients	121	2.93 ± 0.07243
Control	30	2.51 ± 0.09194
p-value	-	< 0.05 (0.0007)

Table 3. The mean values of H2B protein among the stages of breast cancer patients and the control group.

Parameters	Control	Stages of breast cancer patients		
		T	N	M
H2B protein level (Mean ±SEM)	2.51± 0.092	2.57± 0.055	3.23± 0.152	3.79± 0.206
p-value	-	> 0.05*	< 0.01	< 0.001

Table 4. The mean levels of blood glucose, total protein, cholesterol, and LDH among breast cancer patients and the control group

Blood Biomarker	Control (No. 30)	Patients (No. 121)	p-value*
Blood glucose	91.87 ± 2.105	59.31 ± 2.990	<0.001
Total protein	7.18 ± 0.244	6.94 ± 0.086	>0.05
Total cholesterol	185 ± 6.364	244 ± 5.470	<0.001
LDH	347 ± 9.684	563 ± 18.93	<0.001
*Data presented as the mean ± SEM. p value computed by using two-tailed (Mann-Whitney)			

Table 5. Correlation of biochemical markers with H2B blood levels in breast cancer patients.

Biochemical Marker	Correlation Coefficient (Pearson's r)	p-value (two-tailed)
Cholesterol	0.1756	0.0310*
LDH	0.0834	0.3325
Glucose	-0.1291	0.1271
T. Protein	0.2455	0.0025**
*p < 0.05, **p < 0.01		

Considering the breast cancer stages, the mean values of biochemical markers were also compared with the control group (Figure 3). The patients in stage II showed the lowest glucose mean levels followed by stages III and I, respectively. Statistical analysis demonstrated that there is a significant reduction in the blood glucose levels (Figure 3A) in all tumor stages (I, II and III) when compared to the control group. However, there are no significant differences in total protein levels among all stages (Figure 3B).

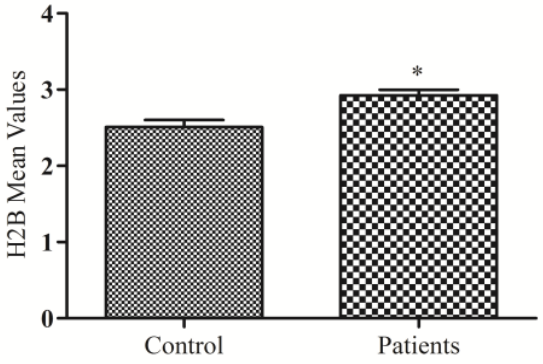

Figure 1. Comparing the H2B mean levels in control and breast cancer patients. Graph bars represent the mean ± SEM. *, P < 0.05; Two-tailed (Mann-Whitney) test.

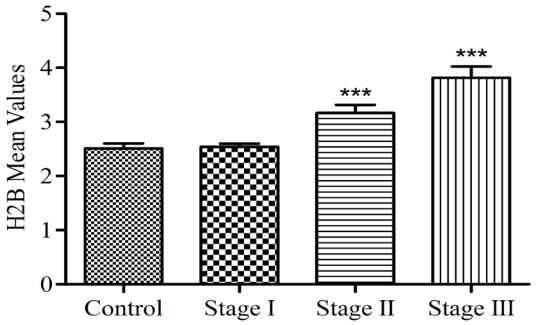

Figure 2. The H2B mean levels in control and breast cancer stages. Graph bars represent the mean ± SEM. **, P< 0.01; ***, P < 0.001, One way ANOVA (Tukey's Multiple Comparison Test).

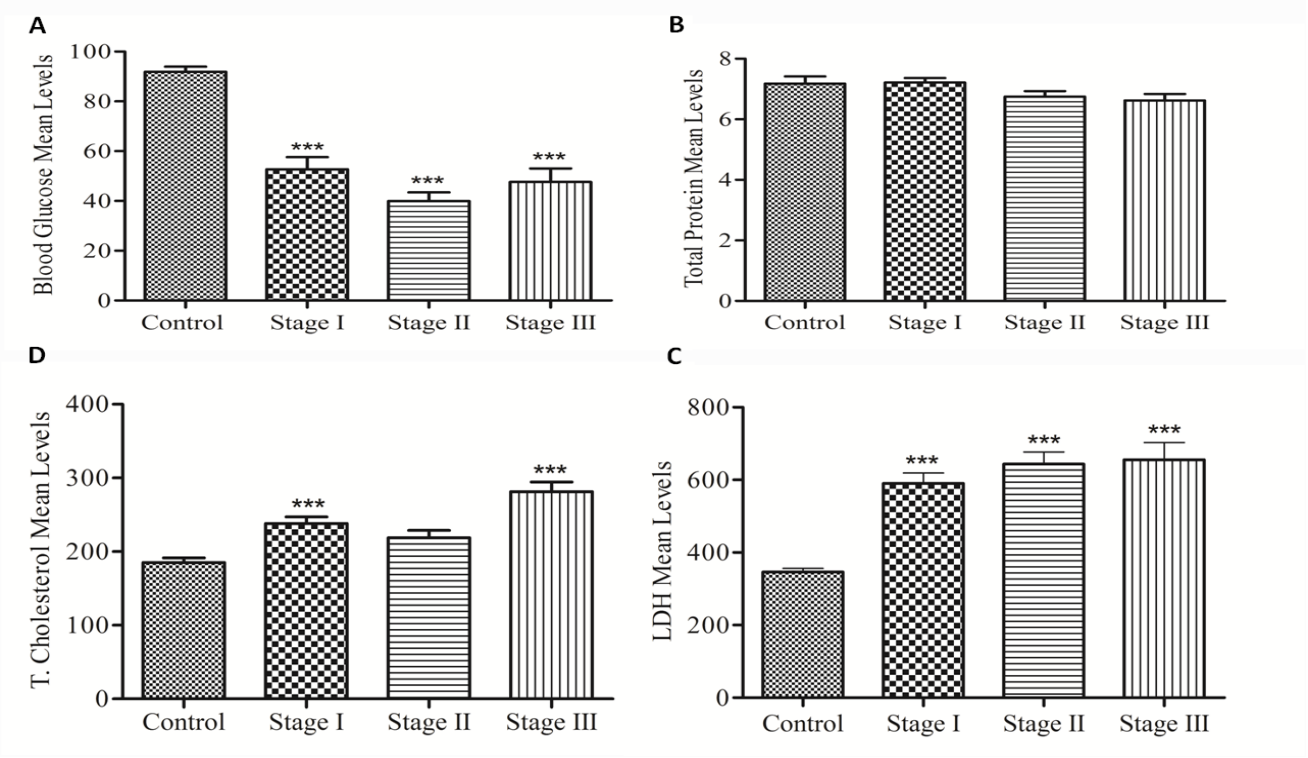

Figure 3: The biochemical marker mean levels in control and breast cancer stages. Graph bars represent the mean ± SEM. One-way ANOVA (Tukey's Multiple Comparison Test) is used to compute the significant changes (p-value) between the control and all tumor stages I, II, and III.

Then, the mean values of total cholesterol and LDH, in all cancer stages, were compared with the control group (Figure 3C and 3D). The mean values of total cholesterol and LDH in breast cancer stages (stages I, II and III) were found to be higher than the healthy control group. Figure 3D confirmed that there are significant differences in cholesterol levels between cancer stages I and III. However, there are no significant changes between patients in stage II and the control group. Similarly, the mean values of LDH in breast cancer stages (stages I, II and III) were found to be significantly higher than the control group (Figure 3C).

Discussion

Factors associated with breast cancer patients

This study was a case-control-based hospital study; it was conducted in the Radio Isotope Center in Khartoum (RICK), which is a reference hospital for Sudanese cancer patients. A total of 121 patients with breast cancer were included and selected randomly in the study. All patients were found to be females. Breast cancer in Sudanese males is considered rare; it constitutes 3.5-4%, as reported by Amani et al. [18].

In this study, the median age in Sudanese patients with breast cancer was found to be 48 years; this result is considered to be in line with previous results reported by Elhoweris [19]. Most cases in this study were prevalent in Khartoum state, Darfur, Kordofan, Gezira, the Northern, White Nile, Sennar, Nile River, Blue Nile, and Gadarif, respectively. This result is in agreement with those previously reported by Ali and Saeed [20,21]. These differences in prevalence may be due to several factors, such as the different rates of screening and diagnosis, poverty, a lack of primary health care in some states, and traditional mineralization, as well as genetic and environmental factors.

The majority of patients in this study were in early disease stages; this may support the successful screening and early detection programs or rapid death without diagnosis. Or due to relatively indolent growth rates in breast cancer patients, which can be detected by early symptoms or screening, allowing a long pre-clinical window [22].

According to this study, the most common treatments for patients with breast cancer in Sudan are chemotherapy, surgery, radiation therapy, or combined therapy, depending on the patient's status and the stages of the disease. There is also hormone therapy, but until now it's been rare.

H2B protein as a predictive biomarker for breast cancer

An elevation of histone H2B most directly associates with increased cellular proliferation and turnover in the tumors. However, its release into blood circulations is a complex biomarker that can be influenced by greater tumor burden, necrotic cell death and active secretion [16]. Therefore, it is a complicated mechanism of dynamic tumor biology [16]. The results showed that the concentration of H2B protein increases when the disease progresses to the late stages (stages II and III). This result is in line with the result of a study conducted by Kang and his colleagues [23]. They measured H2B gene expression in normal and tumor tissues; their study showed that H2B genes were differentially expressed in cholangiocarcinoma, esophageal carcinoma, glioblastoma multiforme, head and neck squamous cell carcinoma, and cutaneous melanoma. Although their study applied to other tumors on a genetic level, the result supports our result based on the fact that the proteins are the products of expressed genes. Moreover, the data from the HPA database showed that the protein expression of H2B genes was more highly expressed in glioma than in normal tissues; this result is also in line with our result regardless of the type of cancer. Besides that, a high frequency of H2B gene alteration was shown in mature B-cell tumors and ovarian epithelial cancer; this H2B gene alteration may lead to mutations that are subsequently associated with different types of cancer, including breast cancer. An explanation for the expression of the H2B protein in breast cancer may be the epigenetic role of histone variants in cancer development. Jia and colleagues [24] reported the importance of these variants in cancer progression and development. Together, these results may support our finding that there is an increase in H2B levels, particularly in the late stages. Therefore, high expression of the H2B protein level can be used as a diagnostic biomarker for breast cancer.

Other associated biochemical markers for breast cancer

Cancer cells consume more glucose than normal cells to fulfill their energy needs for rapid growth and proliferation. The finding indicates that tumor cells in breast cancer patients can reprogram the glucose metabolism by increasing the rate of glycolysis, the Warburg effect, which can lead to hypoglycemia [25]. Based on these facts, our results showed that the mean values of the blood glucose in all tumor stages (stages I, II, and III) were less than the mean value of the control group. However, in the context of total protein levels, our results showed that there is no significant difference between the control group and patients in all stages of the tumors. This result disagrees with the finding that the mean values of the protein concentration in serum of breast cancer patients were significantly higher than those in healthy individuals with a statistical significance ($P<0.05$) [26]. This controversial maybe due to the genetic and metabolic conditions that differ from one population to another.

Furthermore, nutritional behavior is another factor that may affect the ratio of protein levels. It is known that the concentration of the plasma total protein depends on the balance between the rate of synthesis and the rate of loss, and this balance is controlled by the metabolic genes [27]. However, metabolic reprogramming is a feature of cancer cells, and it includes reprogramming of protein metabolism as well as amino acids. Glutamine is an important amino acid for cancer metabolism, and a source of this amino acid is protein catabolism. Theoretically, this means that cancer cells may degrade protein more than in normal conditions, and this study did not prove this assumption.

In addition to protein, the cholesterol level is sought to be higher in breast cancer [28]. As well, the current results showed that the mean values of cholesterol were found to be higher in breast cancer patients than in the control group. These results are similar to a finding reported by Ehmsen et al. [29], who concluded that the increased de novo synthesis of cholesterol is a feature of breast cancer cells and inhibiting the cholesterol synthesis decreases the growth of cancer stem cells. In addition, a study conducted by Wang et al. [30] concluded that many cancer cells overexpress low-density lipoprotein receptor (LDLR) compared to normal cells; the enhancement of cholesterol uptake by cancer cells leads to their rapid proliferation and progression. This finding also falls in line with our results. Although we did not find significant increases in cancer stage II, we can conclude that breast cancer cells may share the same feature of de novo synthesis of cholesterol.

To this end, LDH is one of the most important enzymes, which converts pyruvate into lactate in the hypoxic tumor microenvironment and leads to its acidification. The result of this study showed that there are significant increases in LDH levels among the cancer stages I, II, and III. Of note, this change is noted when the disease goes into the late stages, indicating the potential role of LDH in breast cancer. Moreover, the high levels of LDH enzyme may effectively convert glucose into lactate, explaining the decreased levels of glucose in breast cancer patients. These findings are in line with those of Ratnikov et al. [31], who reported that tumor cells convert 60% to 80% of glucose to lactate; the rate may rise up to 90% in a hypoxic tumor microenvironment. Previous findings [32] also reported

the high levels of LDH and its potential role in different cancer types, including breast cancer. Overall, excessive accumulation of lactate in breast cancer plays a significant role in tumor drug resistance [33].

Conclusion and Perspective

Among all types of cancers in Sudan, breast cancer is the most prevalent. The results demonstrated that the H2B protein is increased in the late stages of breast cancer, confirming its value as a tumor marker. Moreover, the hypoglycemia is considered a normal result in breast cancer patients because tumor cells consume more glucose. The study did not find significant changes in the total protein. However, the elevated level of cholesterol in this study was found to play a role in breast cancer development and proliferation. Moreover, the increased levels of LDH as a result of metabolic reprogramming can be used as a significant tumor marker in breast cancers. Collectively, there was a positive association between H2B, T. cholesterol, and LDH mean levels in breast cancer patients and tumor stages. In contrast, the blood glucose levels were negatively associated with the H2B levels and tumor stages. Moreover, there were no changes in the total protein levels among the tested groups.

Despite these promising results, a large sample size is recommended to confirm the potential role of H2B protein in breast cancer patients. In addition, more clinical and molecular investigations are required to know the mechanisms and the risks behind breast cancer and other cancer types in Sudan. Although some biochemical tests, such as glucose and total protein, are investigated, their exact relation with H2B in cancer is not clear.

Author contributions

Dr. Ahmed M. E. Abdalla and Ahmed I. M. Ahmed designed the primary concept, idea, and wrote the first draft. Dr. Yasir A. Taha contributed to the data analysis, draft revision, and interpretation of the topic. Dr. Ahmed M. E. Abdalla and Dr. Yasir A. Taha approved the final version and decided for all aspects of the work integrity.

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Data Availability Statement

No data were used to support this study.

Conflict of interest statement

All the authors declare no conflicts of interest.

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