RESEARCH ARTICLE

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Is *GATA3* Useful for Differentiating between Classical Hodgkin Lymphoma and Nodular Lymphocyte-Predominant Hodgkin lymphoma? A Two-Center Study in Tehran, Iran during 2016 to 2022

Arezo Rahnavard[1], Farid Kosari[2], Fatemeh Nili[1], Salma Sefidbakht[2], Fereshteh Ameli[2]*

Abstract

Objective: Hodgkin's lymphoma (HL) has two main types; classic HL and nodular lymphocyte predominant HL (NLPHL) which should be differentiated due to the differences in treatment options and prognosis. While a reliable immune panel exists for the diagnosis of Hodgkin Lymphoma, there are instances where certain cases may not align perfectly with established categories. Hence, further research is required to discover more accurate and specific markers. The current study aimed to evaluate *GATA3* immunohistochemical expression pattern in classic HL and NLPHL. **Methods:** This retrospective cross-sectional study was conducted on patients with HL diagnosis who were referred to the Imam Khomeini and Dr. Shariati Hospitals, Tehran, Iran from 2016 to 2022. Clinical and demographic data were collected from medical records, while immunohistochemical staining and evaluation were performed on paraffin-embedded tissue blocks. *GATA3* expression was considered positive if nuclear staining was seen in neoplastic cells. The staining intensity was graded as weak (+1), medium (+2) and strong (+3). **Result:** Out of the 60 samples analyzed (30 classic HL and 30 NLPHL samples), the average age of NLPHL patients (36.7 ± 16.44) was significantly higher compared to classic HL patients (28.6 ± 13.88, p=0.031). *GATA3* nuclear expression was present in 63.3% of classic HL samples, while no expression was observed in NLPHL samples. Different levels of staining weak, medium, and strong were found in 20%, 26.7%, and 16.7% of the samples, respectively. There was no correlation between *GATA3* expression intensity and overall expression with gender, age group, or histologic subtypes (p>0.05). **Conclusion:** Differentiating between classic HL and NLPHL can be aided by the presence of *GATA3* expression, which favors cHL; however, its absence does not provide a diagnostic tool for classification of HL.

Keywords: Hodgkin's Disease- Classic Hodgkin's Lymphoma- Nodular Lymphocyte Predominant

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Introduction

Hodgkin's lymphoma (HL) is a malignant neoplasm originating from germinal center B-cells. HL is among the most common types of lymphomas, with a global incidence rate of three new cases per 1,000 population per year [1]. There are two age peaks for HL, one among young adults (third decade of life) and another peak seen among older adults (55 years) [2]. HL can be treated with chemotherapy and radiotherapy and is considered the first malignancy that can be treated with non-surgical methods [3]. HL is classified into two main categories, including classic HL and nodular lymphocyte predominant HL (NLPHL), based on pathologic and clinical characteristics [4]. The 5th Edition of the World Health Organization (WHO 2022) Classification of Hematolymphoid Tumors and the 2022 International Consensus Classification of Mature Lymphoid Neoplasms (ICC) maintains classic Hodgkin lymphoma (CHL) while using different terminologies for NLPHL. Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is now recognized as nodular lymphocyte predominant B cell lymphoma (NLPBL) in ICC to reflect its distinct pathological, biological, and clinical features [5]. The 2022 ICC emphasized that NLPHL is more closely associated with T-cell/histiocyte-rich large B cell lymphoma (THRLBCL) and should be classified as an (indolent) B cell lymphoma rather than a Hodgkin lymphoma [5]. Nonetheless, the 5th edition of the WHO continues to classify NLPHL as a member of the Hodgkin lymphoma family. The existing terminology

*[1]Department of Pathology, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Science, Iran. [2]Department of Pathology, School of Medicine, Tehran University of Medical Science, Iran. *For Correspondence: f-ameli@sina.tums.ac.ir*

for NLPHL (Hodgkin lymphoma) is maintained to prevent any disruption to ongoing clinical trials [5].

Classic HL comprises the majority of the HL (95%) cases [6]. While the age of onset varies in different subtypes of classic HL, the peak age of onset in NLPHL is the fourth and fifth decades of life [6]. Differentiating classic HL from NLPHL is critical, as these two types of HL have different clinical characteristics, prognosis, and treatment [4].

Immunohistochemistry is a diagnostic method used for differentiating classic from NLPHL. Classic HL is characterized by Hodgkin-Reed-Sternberg (HRS) cells, which express CD15 and CD30 and do not express or show variable expression of CD20 with weak expression of PAX5 [4]. In contrast, NLPHL is defined by the presence of scattered large neoplastic cells with multilobated nuclei (lymphocyte-predominant [LP] cells) exhibiting a GC B cell immunophenotype. These cells maintain a B cell program, expressing CD45, CD20, CD79a, PAX5, OCT2 (strong), BOB1, BCL6, and MEF2B, while lacking expression of CD30 and CD15 [4, 7]. Nevertheless, LP cells may exhibit CD30 expression in 10% of cases or CD15 expression in 6% of cases. It should be emphasized that these occurrences do not have any prognostic significance [8, 9]. However, differentiating classic HL from NLPHL might be challenging, especially in the case of needle biopsy. To our knowledge, there is currently no single reliable tissue marker that can differentiate classic HL from NLPHL; however, using a combination of markers can accomplish this distinction.

GATA3 is part of the GATA binding protein family [10] and serves as a transcription factor for T-cells, influencing cell maturation and internal signaling pathways, including the Notch-1 and NFκB pathways [11]. Additionally, *GATA3* is present in various non-hematopoietic tissues, such as fetal tissues, the adrenal glands, kidneys, the central nervous system, hair follicles, dermal tissue, and breast tissue [28-33]. While *GATA3* is typically absent in mature B-cells, it has been found to be expressed in neoplastic Hodgkin lymphoma (HL) cells [11-13]. Previous research has proposed that *GATA3* may help differentiate between classic HL and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) [11]. Therefore, the aim of this study was to evaluate the expression of *GATA3* in tumors of classic HL and NLPHL using immunostaining techniques.

Materials and Methods

Study design and population

This retrospective analytical cross-sectional study aimed to assess the expression of *GATA3* in classic Hodgkin Lymphoma (HL) and Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL) among patients admitted to Dr. Shariati and Imam Khomeini Hospitals in Tehran, Iran, between 2016 and 2022. Samples lacking adequate tissue for immunohistochemical staining and those with incomplete clinical records were excluded from the analysis. Sample size was calculated using the following equation:

$$N = \left(z_{1-\alpha/2} + z_{1-\beta}\right)^2 \Big/ C(r)^2$$

Considering the effect size of 0.5, type I error of 0.05, and 99% power, the sample size was 60 participants (30 participants with classic HL and 30 with NLPHL).

Study procedure

In order to conduct this study, the pathology database of the Imam Khomeini and Dr. Shariati Hospitals was searched, and all patients with a definitive histological diagnosis of classic HL or NLPHL based on immunohistochemical staining during the years 2016 to 2022 were identified. Then, the formalin-embedded paraffin blocks of these patients, as well as H&E-stained slides and immunohistochemistry-evaluated slides, were retrieved from the archives of the pathology department of the mentioned hospitals. The diagnosis was first confirmed by two hematopathologists and an assistant trainee pathologist. Then, the suitable paraffin blocks were selected to create tissue microarrays. Tumoral areas from each block were extracted with a 5 mm diameter and placed in a new block. The new microarray paraffin blocks were subjected to immunohistochemical staining with the *GATA3* marker. Furthermore, pathological and clinical information of the patients, including histological subgroup, age, and gender of patients, was extracted from the medical records of patients and the electronic pathology reporting system.

Immunohistochemical staining

To conduct the IHC study, 4-micrometer thick sections were prepared from the paraffin blocks. The sections were kept in an oven at 60 ˚C overnight. Immunohistochemical staining was performed according to the instructions by the *GATA3* kit manufacturer (Mouse anti-human *GATA3* monoclonal antibody (Clone L50-823) from Master Diagnóstica company with MAD-000632Q - 1:50 recommended dilution).

The samples were deparaffinized and rehydrated by placing the samples in three xylol containers for 10 minutes and then three alcohol containers with the concentrations of 100%, 96% and 70%, respectively. The samples were kept in each container for 5 minutes until the tissue was ready for staining. Then, antigen retrieval was performed by placing the samples in 1 M citrate buffer with pH=6 at 95 ˚C for 20 minutes. The samples were gradually cooled down at room temperature for 20 minutes. In the next step, the endogenous peroxidase reaction was inhibited by applying 3% hydrogen peroxide solution for 10 minutes at room temperature, and then the slides were washed with PBS buffer. Then, *GATA3* monoclonal antibody was added to the samples. The samples were incubated for 60 minutes at room temperature.

Counterstaining was performed by adding two drops of hematoxylin solution to the slides. The slides were washed after 1 to 3 minutes and were then dehydrated in methanol solutions. After clarification of the slide with xylene solution, two drops of Histomount solution were added to the slides and a covering glass was placed on each slide. Tonsil and breast cancer tissues were used as

external positive controls.

Interpretation of immunohistochemical staining

The immunohistochemically stained slides were assessed by two hematopathologists using an Eye-rolling estimation technique under the Olympus CX43 microscope at high magnification. A positive result was defined by the nuclear expression of *GATA3* in tumor cells. The percentage of positive tumor cells in each sample was quantified (ranging from 0-100%), and the intensity of *GATA3* staining in positive samples was categorized as weak (+1), medium (+2), or strong (+3).

Statistical analysis

The statistical package for social sciences (SPSS) software version 22 was used for data analysis. Continuous variables were presented using mean ± standard deviation (SD) and qualitative variables were presented using frequency and percentage. The Kolmogorov-Smirnov test revealed that *GATA3* expression percentage was normally distributed. Comparison of continuous variables between study groups was performed using the Mann-Whitney or Kruskal-Wallis tests. Association between categorical variables and study groups was evaluated using the chi-square test. Level of statistical significance in all tests was $p<0.05$.

Ethical considerations

The current study was conducted on tissue samples obtained from therapeutic or diagnostic surgery in patients with HL; therefore, no invasive measures or additional costs were imposed on the patients. All personal information remained confidential. Furthermore, the principles of the Declaration of Helsinki regarding compliance with ethical standards in medical research were applied to patients. The current study was approved by the Ethics Committee of Tehran University of Medical Sciences (Code: IR.TUMS.MEDICINE.REC.1401.269). The necessary permissions to access the clinical files of the participants in Imam Khomeini Hospital Complex and Shariati Hospital, as well as the required permission for the implementation of the current study, were obtained from the relevant officials.

Results

A total of 60 participants (33, 55% males and 27, 45% females) including 30 participants with classic HL and 30 participants with NLPHL were included in the study. The mean age of the participants was 32.65 ± 15.63 years old (median age: 29.5 years) ranging from 10 to 76 years old. Comparison of the mean age and gender distribution between classic HL and NLPHL are shown in Table 1. The participants with NLPHL were significantly older compared to those with classic HL.

Nuclear expression of *GATA3* was detected in 19 out of 30 classic HL samples, accounting for 63.3%, while it was completely absent in all NLPHL samples (see Figure 1-2). The average percentage of *GATA3* expression was 32.17 ± 33.31, with a median of 15% and a range from 0% to 90%. Figure 3 illustrates the percentage intensity of *GATA3* expression in CHL.

Association between *GATA3* expression intensity and study variables are shown in Table 2. There was no significant association between *GATA3* expression intensity and gender (p=0.962), histologic subtype (p=0.450), and age groups (p=0.891).

Comparison of the mean *GATA3* expression percentage between study variables is shown in Table 3. There was

Table 1. Comparison of Gender Distribution and Age between Classic HL and NLPHL

Variable		Classic HL	NLPHL	p
Gender	Male	15 (50%)	18 (60%)	0.436†
	Female	15 (50%)	12 (40%)	
Age (years)		28.6 ± 13.88	36.7 ± 16.44	0.031*₸

HL, Hodgkin's lymphoma; NLPHL, Nodular Lymphocyte Predominant Hodgkin's Lymphoma; †, Frequency and percentage were reported and comparison was performed using chi square test; ₸, Mean and standard deviation were reported and comparison was performed using the Mann-Whitney test; *, Significant difference

Table 2. Association between *GATA3* Expression Intensity and Study Variables

Variable		No expression	Weak	Medium	Strong	p
		Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)	
Gender	Male	5 (33.3%)	3 (20%)	4 (26.7%)	3 (20%)	0.962
	Female	6 (40%)	3 (20%)	4 (26.7%)	2 (13.3%)	
Histologic subtype	Nodular sclerosis	6 (35.4%)	3 (17.6%)	5 (29.4%)	3 (17.6%)	0.45
	Mixed cellularity	1 (33.3%)	2 (66.7%)	0 (0%)	0 (0%)	
	Lymphocytic rich	1 (100%)	0 (0%)	0 (0%)	0 (0%)	
	Not specified	3 (33%)	1 (11%)	3 (33%)	2 (23%)	
Age	10-20 years	4 (40%)	2 (20%)	2 (20%)	2 (20%)	0.891
	21-30 years	4 (33.3%)	3 (25%)	3 (25%)	2 (16.7%)	
	31-40 years	0 (0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	
	41-50 years	1 (100%)	0 (0%)	0 (0%)	0 (0%)	
	51-60 years	1 (33.3%)	0 (0%)	2 (66.7%)	0 (0%)	
	61-70 years	1 (100%)	0 (0%)	0 (0%)	0 (0%)	

The chi square test was used for the analysis.

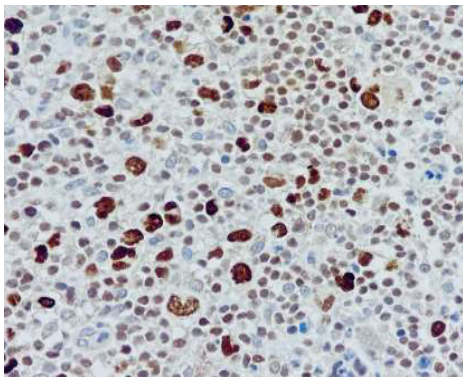

Figure 1. Strong *GATA3* Immune Expression in HRS Cells of Classic HL and Weak Positive Expression in Reactive T Lymphocytes in the Background (X400).

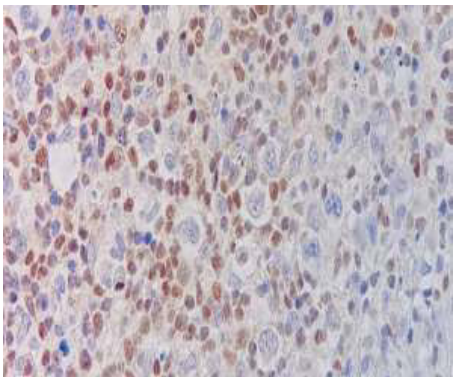

Figure 2. Negative Immunoreaction of *GATA3* in LP Cells of NLPHL and Positive Expression in Reactive T Lymphocytes in the Background (x400).

Table 3. Comparison of *GATA3* Expression Percentage between Study Variables

Variable		*GATA3* expression percentage Mean ± SD	p
Gender	Male	29.33 ± 31.72	0.650†
	Female	35 ± 35.7	
Histologic subtype	Nodular sclerosis	34.41 ± 35.78	0.40†
	Mixed cellularity	6.66 ± 5.77	
	Lymphocyte predominant	0	
Age	10-20 years	25.5 ± 35.93	0.540₸
	21-30 years	37.5 ± 34.14	
	31-40 years	50 ± 30	
	41-50 years	0	
	51-60 years	36.66 ± 32.14	
	61-70 years	0	

† The Mann-Whitney test was used for comparison; ₸ The Kruskal-Wallis was used for the comparison.

no significant difference in terms of *GATA3* expression percentage between genders (p=0.650), histologic subtypes (p=0.401), and age groups (p=0.540).

Discussion

The present study examined the expression of the immunohistochemical marker *GATA3* in samples of classic Hodgkin Lymphoma (HL) and Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL). Results indicated that *GATA3* was expressed in 63.3% of the HRS cells in classic HL cases, while no expression was detected in NLPHL samples. These results align with the majority of previous research. For example, Kezlarian et

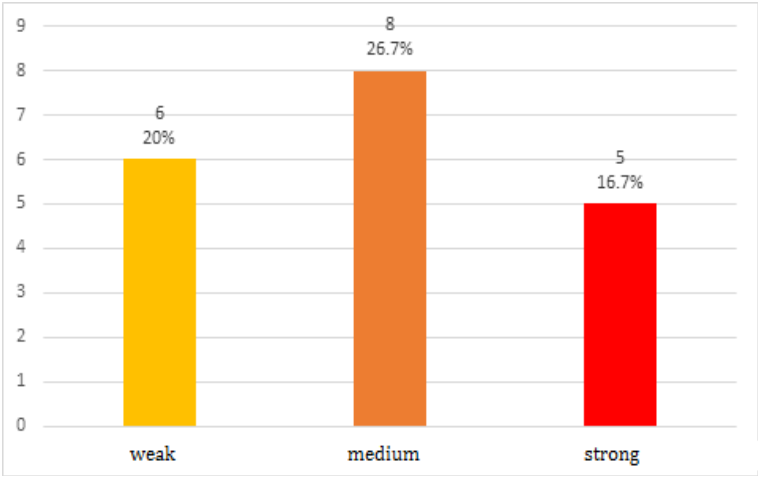

Figure 3. *GATA3* Expression Intensity in CHL

al. found that *GATA3* was expressed in 80% of classic HL cases, with no expression in NLPHL samples [11]. Similarly, Baber et al. reported *GATA3* expression in 95% of classic HL cases, noting that nuclear expression occurred in 75.9% of these cases, while 18.9% exhibited both nuclear and cytoplasmic staining, with no staining found in NLPHL cases [14].

Rashad et al. reported that *GATA3* was present in 81.6% of classic Hodgkin lymphoma (HL) cases, with no expression found in nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) cases [15]. Similarly, Kim et al. observed *GATA3* expression in 77% of classic HL cases [16], and Atayar et al. also found *GATA3* expression in classic HL, with none detected in NLPHL [12]. In the present study, *GATA3* expression was lower than previously documented. This difference may be due to variations in the antibody clones used, differences in the interpretation of immunohistochemical staining, or the specific subtypes examined. For instance, all classic HL cases in Kim et al.'s study were of the nodular sclerosis subtype [16], while other studies included a variety of classic HL subtypes.

The present study demonstrated that examining *GATA3* expression through immunohistochemical evaluation had a 100% positive predictive value in distinguishing classic HL from NLPHL. In simpler terms, if *GATA3* expression is positive in a questionable sample, it can be concluded that it is not NLPHL. However, if *GATA3* expression is negative, it does not necessarily mean that it is NLPHL. The study found that 36.7% of classic HL cases did not exhibit *GATA3* expression. All previous studies have also shown that *GATA3* expression is negative in some classic HL cases. Therefore, the absence of *GATA3* expression cannot definitively rule out classic HL.

In the current study, 31.5% of the classic HL cases that were positive for *GATA3* presented weak staining, while 68.5% presented medium to strong staining intensity. *GATA3* expression percentage ranged between zero and 90% in the current study. Kezlarian et al. reported that the staining intensity in classic HL cases ranged between 10 to 90% (weak to strong) [11]. Other studies did not report staining intensity.

The current study showed no significant association between *GATA3* expression percentage and classic HL subtypes. In the current study 64.7% of the nodular sclerosis HL cells and 66.7% of the mixed cellularity HL cells expressed *GATA3*, while expression was negative in the only sample of lymphocyte predominant HL. The current study included only three subtypes of classic HL. Among the two subtypes that expressed *GATA3*, weak staining was present in (6/60) 10% of the cases, while medium and strong staining was expressed in (8/60) 13.3% and (5/60) 8.3% of the cases, respectively. Kezlarian et al. reported that *GATA3* expression was present in 87% of nodular sclerosis, 70% in mixed cellularity, and 67% in lymphocyte predominant subtypes, which were significantly different [11]. Although the current study findings indicated higher tendency for nodular sclerosis subtype for strong staining compared to other subtypes, which was similar to the findings of previous studies, small sample size in the classic HL subtypes may have resulted in lack of significance in the current study. However, more studies with larger sample sizes are required in order to reach a conclusion.

GATA3 is a transcription factor in T-cells that is required for the primary development of these cells. While HRS cells are mostly derived from B-cells, they lose the expression of the specific markers of the B-cell lineages and only preserve some markers of B-cells [17]. The underlying mechanism of *GATA3* expression in B-cells is not understood. Laboratory studies have shown that disorders in the regulation of NFκB and Notch-1 pathways that cooperate in the expression of *GATA3* might be the underlying cause of *GATA3* expression, which in part results in the activation of specific cytokines that regulate the classic HL cell environment [13]. No genetic change has yet been reported for *GATA3*; therefore, *GATA3* expression is not of great value in determining the prognosis of classic HL [16]. Considering the heterogeneity in *GATA3* expression in classic HL cases, the aberrant *GATA3* expression in HRS cells may be attributed more to the microscopic environment than to genetic changes [16].

The most common subtype of classic HL in the current study was nodular sclerosis (56.6%), while the frequency of the mixed cellularity subtype was 10%. Large epidemiological studies in Western countries have also reported that the most common subtype of classic HL was nodular sclerosis (70%) followed by mixed cellularity (20-25%) [4]. A study conducted in Taiwan reported that the prevalence of nodular sclerosis and mixed cellularity subtypes were 45% and 29%, respectively [18]. In a study conducted in Iran in 2007, the prevalence of nodular sclerosis and mixed cellularity subtypes were reported to be 48% and 30%, respectively [19]. In another study conducted in the United States, the prevalence of nodular sclerosis and mixed cellularity subtypes of classic HL were 55% and 30%, respectively [11]. In contrast to the findings of the mentioned studies, a study conducted in Ethiopia reported that mixed cellularity subtype accounted for 50% of the classic HL subtypes [20].

The median age of the participants in the current study was 29.5 years, and the majority of the patients were within the 21-30 years age group. Similarly, in another study conducted in Iran, the mean age of HL was reported to be 30.5 years [19]. The findings of the current study also showed a peak in HL frequency at 51-60 years. Previous studies have also reported two peaks in the prevalence of HL: one at the third decade of life and another in later adulthood, around the age of 55 years [4]. In the current study, the NLPHL patients were significantly older than the patients with classic HL. Previous studies have also shown that NLPHL is expected to be diagnosed at an older age compared to classic HL. For instance, a study reported that the mean age of patients with classic HL and NLPHL was 38 and 44 years, respectively [21]. Another study reported the mean age of patients with classic HL and NLPHL as 35 and 38 years, respectively [22]. The current study showed that the overall male: female ratio in HL was 1.22:1, while this ratio was 1:1 in classic HL and 1.5:1 in NLPHL. The current study also showed that nodular sclerosis subtype of classic HL was 2.4 times

more frequent among women compared to men. While majority of previous studies indicated a higher prevalence of HLs among men compared to women (male: female ratio of 1.15:1 to 2.2:1), some studies reported female predominance in nodular sclerosis subtype (male: female ratio of 1:1.85 to 1:2.25) [16, 18-20]. Although some studies reported higher prevalence of nodular sclerosis subtype among men compared to women, it is mostly reported to be slightly more predominant among women [23-25].

The strength of the current study lies in its evaluation of *GATA3* staining intensity in relation to its expression in classic Hodgkin Lymphoma (HL) and Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL). However, a notable limitation is the small sample size for the HL subtypes, which may limit the applicability of the statistical analyses to the wider population. Therefore, it is advisable to conduct additional longitudinal studies on HLs, specifically examining *GATA3* expression and intensity in the rarer subtypes of classic HL using a stratified sampling method. The findings of this study suggest that *GATA3* expression could potentially help differentiate other types of B-cell lymphomas that contain large neoplastic cells resembling Reed-Sternberg (HRS) cells. Thus, further investigation is warranted to explore this hypothesis.

Author Contribution Statement

Study concept and design: F. K , and F. A ; analysis and interpretation of data: A. R , and F. A; drafting of the manuscript: A. R , and S. S; critical revision of the manuscript for important intellectual content: F. N. All authors reviewed the manuscript

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Approval

The study was approved by the Ethics Committee of the Tehran University of Medical Sciences (Code: IR.TUMS.MEDICINE.REC.1401.269). The study was conducted on the archived samples and data of the patients; therefore, no written consent was obtained from the patients for this study. However, based on the regulations of teaching hospitals, general written informed consent is obtained from patients at the time of admission.

Ethical Declaration

The study was approved by the Ethics Committee of the Tehran University of Medical Sciences (Code: IR.TUMS.MEDICINE.REC.1401.269).

Data Availability

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that they have no competing interests

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