ORIGINAL PAPER

Nagoya J. Med. Sci. **87**. 93–104, 2025
doi:10.18999/nagjms.87.1.93

# Mismatch repair deficiency and its relationship with histopathological features in gastric cancer patients

Thi Hong Chuyen Nguyen[1], Tran Bao Song Nguyen[2], Thanh Phuc Nguyen[3], Thi Minh Thi Ha[4], Nguyen Cuong Pham[5], Thi Thu Giang Nguyen[6], Minh Tri Phan[1], Thanh Huy Le[1], Thanh Thanh Ha[1], Tran Thuc Huan Nguyen[1] and Cong Thuan Dang[2]

[1]*Department of Oncology, University of Medicine and Pharmacy, Hue University, Hue, Vietnam*
[2]*Department of Histology, Embryology, Pathology, and Forensic Medicine, University of Medicine and Pharmacy, Hue University, Hue, Vietnam*
[3]*Department of Anatomy and Surgical Training, University of Medicine and Pharmacy, Hue University, Hue, Vietnam*
[4]*Department of Medical Genetics, University of Medicine and Pharmacy, Hue University, Hue, Vietnam*
[5]*Department of Pathology, Hue Central Hospital, Hue, Vietnam*
[6]*Oncology Center, Vinmec Central Park International Hospital, Ho Chi Minh City, Vietnam*

## ABSTRACT

Gastric cancer is a common malignancy disease with a poor prognosis. Deficient mismatch repair is a prognostic and predictive marker of response to systemic therapies. However, deficient mismatch repair frequency and the relationship between this status and microscopic characteristics are inconsistent across nations. We aimed to determine the rate of deficient mismatch repair and its association with histopathological features in gastric cancer patients. A cross-sectional study was conducted on 226 gastric cancer patients treated at Hue University of Medicine and Pharmacy Hospital and Hue Central Hospital from June 2020 to January 2024. Mismatch repair protein expression was evaluated using immunohistochemical staining, and any absence of mismatch repair proteins was regarded as deficient mismatch repair. The deficient mismatch repair rate was 12.8%. Deficient mismatch repair appeared to be more frequent in the intestinal subtype of Lauren classification odds ratio (OR) = 4.767 (95% confidence interval [CI], 1.086–20.921; p = 0.039), tubular/papillary adenocarcinoma (OR = 5.25; 95% CI, 1.185–23.251; p = 0.029), mucinous adenocarcinoma (OR = 6.19; 95% CI, 1.113–34.445; p = 0.037), and differentiated type (OR = 3.24; 95% CI, 1.324–7.931; p = 0.01). No statistically significant association was detected with histopathological features according to the Tumor Location-Modified Lauren classification and mucinous secreting morphology. Deficient mismatch repair status was unusual in gastric cancer. The degree of cell differentiation and microscopic characteristics based on the World Health Organization and Lauren classification could all impact the predictive power for microsatellite-instable status.

Keywords: gastric cancer, microsatellite instability, mismatch repair deficiency, histopathological features, immunohistochemical

Abbreviations:
GC: gastric cancer
MMR: mismatch repair

Received: June 18, 2024; Accepted: August 21, 2024
Corresponding Author: Cong Thuan Dang,
Department of Histology, Embryology, Pathology and Forensic Medicine, University of Medicine and Pharmacy, Hue University, 06 Ngo Quyen Street, Vinh Ninh Ward, Hue 530000, Vietnam
Tel: +84-913427196, E-mail: dcthuan@hueuni.edu.vn

MSI: microsatellite instability
MSM: mucinous-secreting morphology
SRC: signet ring cell
WHO: World Health Organization



## INTRODUCTION

Being one of the most common cancers, gastric cancer (GC) has the fourth-highest incidence and the third-highest mortality worldwide.[1] The global distribution of GCs shows geographic variation, with a 15- to 20-fold difference between regions with high and low incidence.[2] Vietnam is among the regions with the highest global rate of GC, with 16,277 new cases and 13,264 deaths, according to GLOBOCAN 2022 statistics.[3] Treatment strategies for resectable locally advanced stages are also different between continents; in Asia, adjuvant chemotherapy followed by radical surgery is preferred, whereas perioperative chemotherapy (possibly concurrent with radiotherapy) is chosen more often.[4] However, more than half of patients will relapse and die after treatment due to the disease. In contrast, some patients are cured by surgery alone and do not benefit from cytotoxic chemotherapy.[5] In metastatic cases, despite the use of targeted drugs, the outcome of treatment is modest, and the prognosis is still inferior.[6] Recent data indicate that the patient's prognosis depends not only on the stage of the disease but also on the molecular and histopathological features of the tumor.[7,8] Remarkably, the American Cancer Genome Atlas and the Asian Cancer Research Group regard GC as a complex, heterogeneous disease and recognize microsatellite instability (MSI) as a distinct subgroup associated with the prognosis.[8] MSI is characterized by increased microsatellite length, resulting from a mismatch repair (MMR) deficiency, usually MLH1, MSH2, PMS2, and MSH6.

In clinical settings, deficient mismatch repair (dMMR) can be identified at the genetic, protein, or functional levels. Typically, the dMMR assessment relies on MSI analysis by biomolecular experiments or immunohistochemistry, which assesses the expression of MMR proteins.[9] In GC, the prevalence of dMMR varies between countries and ranges from 8 to 25%. Although the correlation between dMMR status and pathological and clinical parameters has been documented, the findings still need clarification.[10] Remarkably, since there was a positive association between dMMR and PD-L1 expression, recent studies have postulated that dMMR may predict clinical benefits for immune checkpoint inhibitors.[10] A recent meta-analysis revealed that dMMR was the most significant predictor of immune checkpoint inhibitor effectiveness, outperforming PD-L1.[11] Additionally, neoadjuvant therapy with chemotherapy plus immune checkpoint inhibitors had encouraging outcomes in resectable GCs, with an overall response rate of up to 50% validated in the NEONIPIGA, INFINITY, and DANTE clinical trials.[11-13] Due to time and expense constraints, MSI fails to be performed for every patient despite its value in patient stratification for optimal treatment selection.[14]

As a result, highly successful artificial-intelligence-based models have been created to predict MSI/MMR using microscopic characteristics.[14] A systemic review of Alem et al indicates that these models could become an efficient and economical alternative to MSI prediction. However, significant drawbacks of research are the absence of big, multiracial data and external validation.[15] In light of these facts, we started this effort to gather additional information on MMR protein expression in GCs in Vietnam, an Asian nation, and to investigate the relationship between dMMR status and tumor microscopic features in this population.

## METHODS

*Study population*

We conducted a cross-sectional study on 226 patients newly diagnosed with GC by histopathological through endoscopy biopsies or resected specimens at the Hue University of Medicine and Pharmacy Hospital and Hue Central Hospital from June 2020 to January 2024. Clinical data, including patients' age and gender, were collected from the medical record system.

*Evaluation of pathological features*

Paraffin-block tissue sections with a 3–4 μm thickness were sliced and dyed with hematoxylin–eosin (H&E). The remaining sections will be heat treated to activate antigens, followed by staining with MLH1, PMS2, MSH2, and MSH6 antibodies. We evaluated tumor microscopic characteristics according to the Lauren and the World Health Organization (WHO) 2018 Classification, the Tumor Location-Modified Lauren Classification (MLC), mucinous-secreting morphology (MSM), and cell differentiation. Three subgroups were included in the MLC. Diffuse type is defined as a tumor located anywhere in the stomach, which can be diffuse or mixed, according to Lauren's classification. The remaining is named non-diffuse. When the gastric cardia region accounted for more than 80% of the tumor volume, the tumor was classified as non-diffuse/proximal. The non-diffuse/distal is named for the tumor in the distal part of the stomach, usually from the middle of the fundus to the end of the cardia. Based on the MSM, including mucinous adenocarcinoma and signet ring cell (SRC) carcinoma, we subcategorized this variable into four subtypes: MSM/non-diffuse, MSM/diffuse, non-MSM/non-diffuse and non-MSM/diffuse. Cell differentiation grade was divided into differentiated cancer: well-differentiated, moderately-differentiated tubular carcinoma, and papillary carcinoma. Undifferentiated tumors were made up of SRC carcinoma and mucinous and poorly differentiated adenocarcinoma.

*Immunohistochemistry*

We use the indirect enzyme immunoassay with Roche's ultraView diaminobenzidine color detection kit on the Ventana machine. All primary antibodies used in this study were Ventana monoclonal antibodies, including anti-MLH1 (Clone M1), anti-MSH2 (Clone G219-1129), anti-MSH6 (Clone SP93), and anti-PMS2 (Clone A16-4). Expressions of four MMR proteins (MLH1, MSH2, MSH6 and PMS2) were evaluated.

*Evaluate staining results*

Two independent, experienced pathologists evaluated the results. Nuclear staining of normal epithelial cells, lymphocytes, and stromal cells in the immediate vicinity or tumor infiltration was considered an internal positive control. Loss of MMR protein expression was designated when none of the cancerous epithelial cells displayed nuclear staining in the presence of acceptable internal positive controls, irrespective of the proportion or intensity.[10] Tumor cells expressing all four proteins to any degree and intensity were considered proficient MMR. Loss of expression of at least one of the four proteins was considered dMMR (Fig. 1 and Fig. 2).

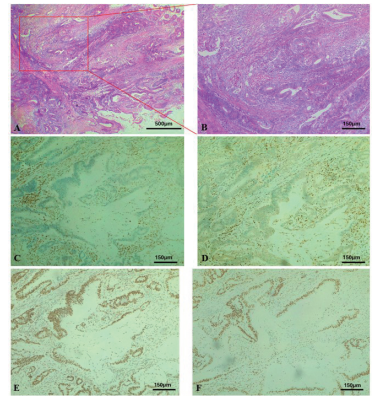

**Fig. 1** Sample pictures from a case of dMMR differentiated tubular adenocarcinoma

**Fig. 1A:** Hematoxylin-eosin stain (40×): Gastric Adenocarcinoma with irregular malignant glands invading mesenchymal tissue.

**Fig. 1B:** Hematoxylin-eosin stain (100×): Gastric Adenocarcinoma with irregular malignant glands invading mesenchymal tissue.

**Fig. 1C–F:** Immunohistochemistry stainings. (C) (100×): deficient expression of MLH1. (D) (100×): deficient expression of PMS2. (E) (100×): intact expression of MSH2. (F) (100×): intact expression of MSH6.

dMMR: deficient mismatch repair

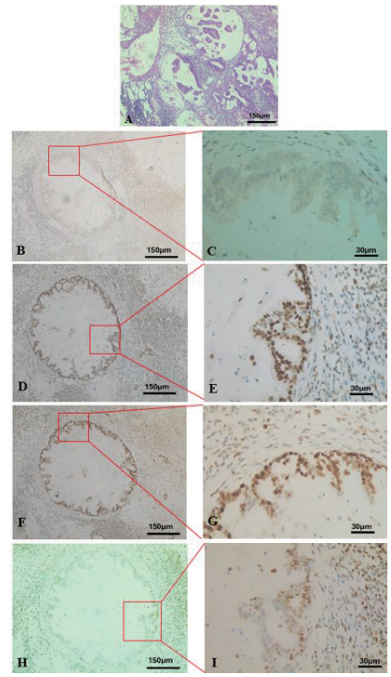

**Fig. 2** Sample pictures from a case of dMMR mucinous adenocarcinoma

**Fig. 2A:** Hematoxylin-eosin stain (100×): Mucinous adenocarcinoma with malignant cells in mucinous pool.

**Fig. 2B–I:** Immunohistochemistry stainings. (B) (100×): deficient expression of PMS2. (C) (400×): deficient expression of PMS2. (D) (100×): intact expression of MSH2. (E) (400×): intact expression of MSH2. (F) (100×): intact expression of MSH6. (G) (400×): intact expression of MSH6. (H) (100×): intact expression of MLH1. (I) (400×): intact expression of MLH1.

dMMR: deficient mismatch repair

*Statistical analyses*

The values of variables are encoded and processed using SPSS 21.0 software. Statistical algorithms included descriptive analysis and comparative testing. Descriptive analysis calculated mean, standard deviation, max, min, percentage values. In regard to comparative testing, we used the chi-squared test to analyze the association between MMR expression and tumor microscopic features, statistically significant comparisons with $p < 0.05$. Fisher's exact test was chosen if the sample is less than 5. The Binary Logistic Regression test was employed to estimate the probability of dMMR in correlated subgroups.

## RESULTS

*Clinicopathological features of the cohort patients*

Two hundred twenty-six patients satisfied the study criteria. The patient's mean age was 64.4±12.8. Of the 226 tissue samples analyzed, 84 (37.2%) were biopsied, and 142 (62.8%) were surgical tissue samples. The oldest age was 97; the youngest was 22 years old. Males constitute a majority (70%). Of the 226 GC patients, 29 were dMMR, accounting for 12.8% (Table 1).

**Table 1** Clinicopathological features of the cohort patients (n = 226)

| | n | % | Mean ± SD |
|---|---|---|---|
| Age | | | 64.4 ± 12.8 |
| Sex | | | |
| Male | 158 | 69.9 | |
| Female | 68 | 30.1 | |
| Tissue sample | | | |
| Biopsied | 84 | 37.2 | |
| Resected | 142 | 62.8 | |
| Microscopic features according to WHO classification | | | |
| Tubular | 121 | 53.5 | |
| Papillary | 4 | 1.8 | |
| Mucinous | 26 | 11.5 | |
| Poorly differentiated | 41 | 18.1 | |
| Signet ring cell | 21 | 9.3 | |
| Poor adhesive | 5 | 2.2 | |
| Specific | 8 | 3.5 | |
| Microscopic features according to Lauren classification | | | |
| Intestinal | 146 | 64.6 | |
| Difffuse | 34 | 15.0 | |
| Unidentified | 46 | 20.4 | |
| MSM | | | |
| MSM/non-diffuse | 22 | 9.7 | |
| MSM/diffuse | 26 | 11.5 | |
| Non-MSM/non-diffuse | 167 | 73.9 | |
| Non-MSM/diffuse | 11 | 4.9 | |

| | | |
|---|---|---|
| MLC | | |
| Non-diffuse/proximal | 12 | 5.3 |
| Non-diffuse/distal | 174 | 77.0 |
| Diffuse | 40 | 17.7 |
| Differentiated grade | | |
| Differentiated | 119 | 52.7 |
| Undifferentiated | 107 | 47.3 |

WHO: World Health Organization
MSM: mucinous-secreting morphology
MLC: Tumor Location-Modified Lauren classification

*The detailed patterns of dMMR cases*

The most frequent pattern is the simultaneous loss of PMS2 and MLH1 expression, followed by the single loss of PMS2 expression (Table 2).

**Table 2** Detailed patterns of dMMR cases

| | | | | | n = 29 | % |
|---|---|---|---|---|---|---|
| MMR proteins | MLH1 | PMS2 | MSH2 | MSH6 | | |
| | – | – | + | + | 16 | 55.2 |
| | + | + | – | – | 4 | 13.8 |
| | + | + | + | – | 0 | 0.0 |
| | + | – | + | + | 9 | 31.0 |

dMMR: deficient mismatch repair
MMR: mismatch repair
$^{+}$ Intact expression
$^{-}$ Loss of expression

*The association between MMR and microscopic traits*

According to our research, there were correlations between MMR status and cell differentiation ($p = 0.007$), as well as histological subgroups categorized by the WHO ($p = 0.034$) and Lauren ($p = 0.01$). We failed to find any correlation when examining the association between MMR status and other histological features, including mucinous secreting morphology and the MLC (Table 3).

**Table 3** Association between MMR and microscopic traits

| Microscopic feature | dMMR | | pMMR | | |
|---|---|---|---|---|---|
| | n | % | n | % | p |
| Lauren | | | | | |
| Intestinal | 26 | 17.8 | 120 | 82.2 | |
| Diffuse | 1 | 2.9 | 33 | 97.1 | 0.010 |
| Unidentified | 2 | 4.3 | 44 | 95.7 | |

| | | | | | |
|---|---|---|---|---|---|
| WHO | | | | | |
| Tubular, papillary | 21 | 16.8 | 104 | 83.2 | 0.034 |
| Mucinous | 5 | 19.2 | 21 | 80.8 | |
| SRC | 1 | 4.8 | 20 | 95.2 | |
| Poorly differentiated, poorly adhesive, specifics | 2 | 3.0 | 65 | 97.0 | |
| MSM | | | | | |
| MSM/non-diffuse | 4 | 18.2 | 18 | 81.8 | $p_1 = 0.244$ |
| MSM/diffuse | 1 | 3.8 | 25 | 96.2 | $p_2 = 0.573$ |
| Non-MSM/non-diffuse | 24 | 14.4 | 143 | 85.6 | $p_3 = 0.165$ |
| Non-MSM/diffuse | 0 | 0 | 11 | 100 | |
| Differentiated grade | | | | | |
| Differentiated | 22 | 18.5 | 97 | 81.5 | 0.007 |
| Undifferentiated | 7 | 6.5 | 100 | 93.5 | |
| MLC | | | | | |
| Non-diffuse/proximal | 3 | 25.0 | 9 | 75.0 | 0.056 |
| Non-diffuse/distal | 25 | 14.4 | 149 | 85.6 | |
| Diffuse | 1 | 2.5 | 39 | 97.5 | |

MMR: mismatch repair
dMMR: deficient mismatch repair
pMMR: proficient mismatch repair
SRC: signet ring cell
WHO: World Health Organization
MSM: mucinous-secreting morphology
MLC: Tumor Location-Modified Lauren classification
[p1] Comparison between 4 categories in mucinous secreting morphology
[p2] Comparison between MSM and non-MSM
[p3] Comparison between MSM/intestinal and MSM/diffuse

*The logistic regression model forecasts the probability of dMMR expression in subgroups based on microscopic characteristics*

We further examined the binary logistic regression test using variables connected to MMR expression status through chi-square analysis to estimate the likelihood of dMMR emerging in these subgroups. As demonstrated by odds ratio (OR) = 4.767 (95% CI, 1.086–20.921; $p = 0.039 < 0.05$), the intestinal subtype was more likely to exhibit loss of MMR protein expression compared to the unidentified subtype. Tubular/papillary and mucinous adenocarcinoma presented dMMR more frequently than the poorly differentiated, poorly adhesive, and specific subgroups, with an OR of 5.250 (95% CI, 1.185–23.251; $p = 0.029 < 0.05$) and 6.190 (95% CI, 1.113–34.445; $p = 0.037 < 0.05$), respectively. Differentiated carcinoma increased the chance of dMMR status by 3.240 times compared to the undifferentiated subgroup (95% CI, 1.324–7.931; $p = 0.010 < 0.05$; Table 4).

**Table 4** The logistic regression model forecasts the probability of dMMR expression in subgroups based on microscopic characteristics

| Microscopic feature | dMMR | |
|---|---|---|
| | OR (95% CI) | p |
| Lauren | | |
| Unidentified | 1 | |
| Intestinal | 4.767 (1.086–20.921) | 0.039 |
| Diffuse | 0.667 (0.058–7.668) | 0.745 |
| WHO | | |
| Poorly differentiated, poorly adhesive, specific | 1 | |
| Tubular, papillary | 5.250 (1.185–23.251) | 0.029 |
| Mucinous | 6.190 (1.113–34.445) | 0.037 |
| SRC | 1.300 (0.112–15.144) | 0.834 |
| Differentiated grade | | |
| Undifferentiated | 1 | |
| Differentiated | 3.240 (1.324–7.931) | 0.010 |

dMMR: deficient mismatch repair protein
SRC: signet ring cell
WHO: World Health Organization
OR: odds ratio

## DISCUSSION

GC ranked third in terms of dMMR frequency among 39 cancer types in an analysis of 11,139 tumors with dMMR/MSI-H.[11,16] In our investigation, the dMMR rate was 12.8%. While our result was lower than that of research conducted in the West, it was consistent with reports on the same continent. According to earlier research, the dMMR/MSI-H ratio ranged from 8% to 25%; in Asian nations, it varied from 8% to 17%, while in Western nations, it exceeded 20%.[17] The wide range of dMMR proportions could be because of examining cohorts from different geographic locations, the variability in the stages of the sample populations, variations in patient selection criteria during clinical trials, and distinctions in the markers employed in various research.[17-20]

The most prevalent pattern was the loss of MLH1 and PMS2 protein expression, which occurred at a rate of 50% to 90% in the majority of studies.[10,21,22] The results of our investigation supported this conclusion as well, showing that MLH1 and PMS2, with a rate of 55.2%, are the most prevalent patterns. The primary cause of dMMR is epigenetic silencing of hMLH1 through increased promoter methylation, whereas hMLH1 and hMLH2 mutations are relatively infrequent (15% and 12%, respectively).[18]

Pathologists are searching for morphological characteristics on H&E-stained specimens that indicate dMMR gastric cancer, but it is still unknown how they are related.[15,23] Gastric cancer has a distinct variety in cell morphology and architecture histopathologically. Lauren's histological classification is divided into two primary subgroups: diffuse and intestinal.[24] The intestinal subgroup often comprises dMMR GCs, accounting for over 90%.[22] The connection between intestinal subtypes and the dMMR phenotype has been demonstrated in numerous studies; alternatively, diffuse and poorly adhesive subtypes are not frequently associated with this subgroup.[21,25-27] Our findings supported this trend, showing a statistically significant correlation ($p = 0.01$) between

Lauren's histological subgroup and MMR status. Our analysis revealed that the intestinal subtype was more likely than the unidentified subtype to lose MMR protein expression with an OR of 4.767 (95% CI, 1.086–20.921; $p = 0.039 < 0.05$). Meanwhile, no correlation was seen between tumor phenotype and dMMR in a specific report. This contrasting result was probably due to the dMMR rate in the diffuse subgroup in our study being much lower than in this study (2.9% vs 17%, respectively).[20]

An association between MMR status was observed not only with Lauren's subtypes but also with the ductal and papillary structures based on the WHO classification.[22] According to our research, which was partly consistent with this finding, dMMR is more common in tubular/papillary and mucinous adenocarcinomas than in the others, with OR of 5.25, (95% CI, 1.185–23.251; $p = 0.029 < 0.05$) and 6.19 (95% CI, 1.113–34.445; $p = 0.037 < 0.05$) respectively. Moderately differentiated tubular GCs showed the highest dMMR rate (43.3%) of all the categories in a Japanese study. Nevertheless, no dMMR instances were discovered in the papillary GCs. This result may be because of their study's low papillary GC frequency.[28]

At a rate of 4.8%, our study demonstrated that dMMR is less common in SRC. According to the WHO 2018 classification, SRC is histologically identified based on microscopic imaging, presenting over 90% of SRCs.[29] While there are numerous findings of MMR expression in SRC patients, the prevalence of dMMR varies from 0% to 33% across research. Our findings support the conclusions of previous studies indicating that this group has a low dMMR rate, which ranged from 0% to 3.7%.[30,31] A study conducted on 89 patients with advanced-stage GCs showed that the dMMR prevalence in this patient population was 32.6%.[32] Although the exact reason for this ratio dispersion was unknown, it could be brought about by disparities in the cutoff points for interpreting positive or negative immunohistochemistry results.[33]

We further examined the connection between MMR protein expression and the mucinous secreting morphological trait, a unique histological type of GCs. MSM is a rare subset of GC exhibiting considerable differences in appearance, cellular features, and protein expression.[34] dMMR was more common in intestinal mucinous GCs than diffuse non-mucinous GCs but was not distinct from intestinal non-mucinous GCs.[35] Conversely, neither our results nor the Korean findings indicated a difference in the MMR expression status between the subgroups that secreted mucinous matter and those that did not.[36] Furthermore, our investigation observed no correlation between MMR status and subgroups based on MLC. Contrary to an Italian study, dMMR GC was more common in the distal/non-diffuse subgroup.[20]

GC is classified as differentiated or undifferentiated under the microscope, depending on the frequency at which ductal structures form.[23] It was demonstrated that dMMR was prevalent in well-differentiated groups.[17] This statement perfectly aligned with the findings of our investigation. Our results indicated that dMMR expression is higher in differentiated gastric adenocarcinoma compared to the undifferentiated group (OR = 3.24; 95% CI, 1.324–7.931; $p = 0.01 < 0.05$).

Our research attempts to provide additional information on dMMR status as well as the correlation between dMMR status and microscopic histological characteristics of GC patients in Vietnam. However, one disadvantage of the study that makes it challenging for statistical algorithms to obtain significance is the limited sample size coupled with the low dMMR rate.

## CONCLUSIONS

The Vietnamese GC patient population displayed a comparatively low dMMR rate. Our findings demonstrated statistically significant correlations between MMR expression status and H&E-stained features, particularly within cell differentiation subgroups defined by WHO and Lauren

classification. These correlations highlight the potential of tumor microscopic characteristics to inform artificial intelligence models for predicting MSI.

## ACKNOWLEDGMENT

*Statement of ethics*

The study conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee in biomedical research of the University of Medicine and Pharmacy, Hue University (Ethics Approval Number: H2021/441).

*Author contributions*

THC Nguyen carried out and analyzed the immunoassays, conceived, designed the study and wrote the manuscript. TBS Nguyen, NC Pham, and CT Dang conducted pathological diagnosis, provided histological information, and carried out and analyzed the immunoassays. TTG Nguyen, TP Nguyen, TH Le, TT Ha, TTH Nguyen supplied the clinical information, collected samples and designed the figures. TP Nguyen, MT Phan analyzed and interpreted the data, CT Dang and TMT Ha participated in the sequence alignment and reviewed and edited the manuscript content. All authors contributed to discussions and approved on the final version of the submitted manuscript.

*Conflict of interest statement*

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

*Funding sources*

There is no funding to report.

*Data availability statement*

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

*Miscellaneous acknowledgment*

We would like to thank the patients for joining the study and gratefully acknowledge the support for equipment and techniques from the Department of Pathology, Hue University of Medicine and Pharmacy Hospital in Vietnam.

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