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Immunohistochemical Analysis of MDM2 Expression in Gastric Cancer and Correlation with Pathologic Stage and Grade

Paridokht Karimian[1], Issa Jahanzad[2], Aysan Nozheh[2], Morteza Koravi[1], Mohammadreza Mobayen[3], Elham Nazar[4], Fakhriyeh Kalavari[5]*

1. Department of Pathology, Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran
2. Department of Pathology, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
3. Burn and Regenerative Medicine Research Center, Guilan University of Medical Sciences, Rasht, Iran
4. Department of Pathology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran
5. Department of Pathology, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran

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ABSTRACT

Background & Objective: Gastric cancer ranks as the fifth most common cancer worldwide and involves multiple oncogenes and tumor suppressors. MDM2, a critical negative regulator of the tumor suppressor p53, has been implicated in cancer progression. This retrospective cross-sectional study aimed to evaluate MDM2 overexpression in relation to tumor grade and pathological stage in stomach cancer.

Methods: We examined paraffin-embedded tumor samples from 53 stomach cancer patients who underwent complete (R0) resection at Razi Hospital, Rasht, between 2013 and 2018. Tumor pathological features were evaluated histologically, and MDM2 protein expression was assessed using immunohistochemistry with a mouse monoclonal antibody (clone IF2).

Results: The patients' mean age was 68.4 years (SD = 11.2), with the majority being male (71.7%). Intestinal-type adenocarcinoma was the most common histological subtype (58.5%), and 58.5% of patients had received preoperative chemotherapy. Most tumors were grade 2 or 3, with pathological stage 3 being the most frequent (39.6%). MDM2 expression was predominantly weak (56.6%), with strong expression in 17.0% (9 individuals) of cases. No statistically significant association was found between MDM2 expression intensity and tumor grade (P = 0.395; Cramer's V = 0.16, 95% CI: 0.00–0.39) or pathological stage (P = 0.334; Cramer's V = 0.18, 95% CI: 0.00–0.42).

Conclusion: Although MDM2 is considered significant in cancer biology, our study did not find a correlation between its overexpression and stomach cancer grade or pathological stage. These findings suggest that MDM2 overexpression alone may not serve as a reliable prognostic marker in this patient population.

KEYWORDS Gastric Cancer, Stomach Neoplasms, Proto-Oncogene Proteins c-mdm2, Neoplasm Staging, Neoplasm Grading

Corresponding Information: Fakhriyeh Kalavari, Department of Pathology, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran, f.kalavari@gmail.com

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INTRODUCTION

Gastric cancer is a significant global health issue, with over one million new cases annually, and it ranks as the fifth most prevalent malignancy worldwide (1). The incidence of stomach cancer varies greatly by region and culture, with the highest rates in East and Central Asia and Latin America (2). Despite a general decline in incidence, it remains a lethal disease, accounting for 783,000 deaths per year and ranking as the third deadliest cancer among men globally (1, 3).

The molecular pathogenesis of gastric cancer involves numerous pathways. Vascular endothelial growth factor (VEGF)-targeted therapies show efficacy in metastatic disease but lack evidence for resectable tumors (4). Other factors, including the receptor ERBB2 (HER2), have also been successfully targeted or identified as prognostic factors (5).

This study focuses specifically on the MDM2 oncoprotein. MDM2 acts as a key inhibitory regulator of the p53 tumor suppressor (6–8). The p53 protein induces the expression of genes that inhibit cell growth and regulate apoptosis, and its loss of function is associated with a large portion of human cancers. MDM2 suppresses p53 through transcriptional blockade and ubiquitin-mediated proteolysis (9, 10). Furthermore, p53 negatively regulates the expression of the MDM2 gene in a self-regulatory cycle, and excessive expression of MDM2 can reduce intracellular levels of p53 (11). However, the predictive value of MDM2 for stomach cancer patients is controversial, and its role in primary gastric carcinogenesis has been disputed (12).

The specific rationale for studying MDM2 in gastric cancer is that the TP53 gene is inactivated by mutations in only about 40-50% of cases (13). In wild-type TP53 cancers, the function of the gene is often suppressed by increased expression of oncogenes like MDM2 (14–16). Therefore, the overexpression of MDM2 is

suggested as a marker of poor prognosis in patients with gastric cancer (17).

Our study aims to evaluate the relationship between MDM2 overexpression and the histological grade and pathological stage of gastric cancer. Establishing this relationship is important for assessing its potential utility as a prognostic biomarker, which could aid in future therapy planning and patient stratification.

MATERIALS AND METHODS

Study Design and Population

This retrospective cross-sectional study utilized a convenience sampling method to select formalin-fixed, paraffin-embedded (FFPE) tissue blocks from 53 patients with gastric cancer who underwent surgical resection at Razi Hospital in Rasht between 2013 and 2018.

Inclusion Criteria:

Histologically confirmed primary gastric adenocarcinoma (intestinal or diffuse type).

Patients who underwent complete (R0) tumor resection with standard lymph node dissection.

Availability of well-documented clinical information and demographic data.

Exclusion Criteria:

Patients with recurrent gastric cancer or metastatic disease from a non-gastric primary site.

Patients with insufficient tumor tissue for analysis.

Grading and Staging Systems

Tumor grading was performed according to the WHO Classification of Tumours of the Digestive System (5th edition, 2019) (18). Pathological staging was performed according to the AJCC Cancer Staging Manual (8th edition) (19). For patients who received neoadjuvant chemotherapy, ypTNM staging was used.

Immunohistochemistry (IHC)

Primary Antibody: Mouse anti-human MDM2 monoclonal antibody, clone IF2 (Catalog #MABE340, Merck KGaA, Darmstadt, Germany), purified from ascites fluid by protein A chromatography and prepared in 10 mM PBS, pH 7.4, containing 0.2% BSA and 0.09% sodium azide, diluted 1:100.

For the immunohistochemical analysis of MDM2, both positive and negative controls were included in each staining batch.

Positive Control: A known MDM2-positive, well-differentiated liposarcoma (which carries MDM2 amplification) tissue section was used.

Negative Control: For each patient sample, a consecutive tissue section was processed identically but with the primary MDM2 antibody omitted and replaced with an antibody diluent or nonimmune serum.

Staining Protocol: Archival paraffin-embedded tissue blocks and the corresponding pathology reports were retrieved from the department's archive, and 4-µm sections were cut from each block. After deparaffinization, the sections were rehydrated through graded ethanol solutions and subjected to antigen retrieval using a microwave device with EDTA buffer (1 mM, pH 8.0) at 750W for 15 minutes. The slides were then incubated for 60 minutes at room temperature with the primary antibody; staining was performed on an automated platform (Autostainer Link 48, Agilent Technologies, Santa Clara, CA, USA) using an HRP–DAB detection system (EnVision FLEX, Agilent Technologies). After washing with PBS, the sections were incubated with an HRP-conjugated secondary antibody (EnVision FLEX/HRP, Agilent Technologies), developed with DAB, and counterstained with hematoxylin. Brown staining was considered positive for MDM2, and at least 500 cells were counted at ×400 magnification. Only nuclear staining was considered indicative of MDM2 positivity, as this is the biologically relevant localization of MDM2-mediated p53 inhibition in this context. Cytoplasmic and stromal signals were excluded during scoring.

Scoring System

Staining intensity was classified into four levels based on the intensity score (IS): 0 = no staining, 1 = weak, 2 = moderate, and 3 = strong.

Two experienced pathologists independently scored all cases while blinded to clinical data. Discrepant cases (difference ≥1 in PS or IS) were reviewed together and adjudicated by consensus. The inter-observer agreement for IS was substantial (weighted κ = 0.78, 95% CI: 0.65-0.91).

In this study, we used the intensity score (IS) as the primary analysis variable. The total immunostaining score (TIS), defined as the product of proportion score (PS) and IS, was calculated but not used as the primary outcome.

Proportion Score (PS): Indicates the extent and percentage of positive cells relative to the total cells, divided into five grades:

Grade 0: 0%

Grade 1: 1-25%

Grade 2: 26-50%

Grade 3: 51-75%

Grade 4: >75%

Intensity Score (IS): Indicates the intensity of staining of positive cells, divided into four grades: (Fig 1-3)

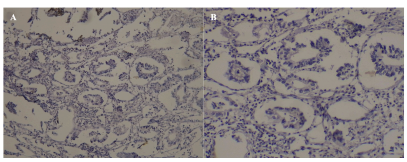

Fig 1. Intensity Score (IS) of MDM2 IHC staining of positive cells; grade 0, no nuclear staining. (For each panel, the left image (A) is at ×100 magnification (scale bar = 50 µm) and the right image (B) was captured at ×400 magnification (scale bar = 10 µm))

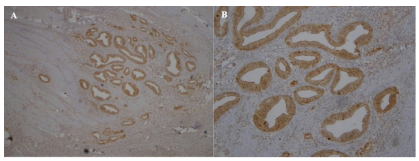

Fig 2. Intensity Score (IS) of MDM2 IHC nuclear staining of positive cells; grade 2, moderate. (For each panel, the left image (A) is at ×100 magnification (scale bar = 50 µm) and the right image (B) was captured at ×400 magnification (scale bar = 10 µm))

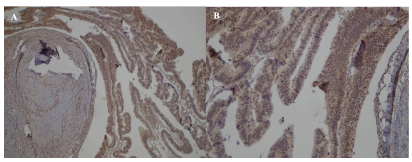

Fig 3. Intensity Score (IS) of MDM2 IHC nuclear staining of positive cells; grade 3, strong. (For each panel, the left image (A) is at ×100 magnification (scale bar = 50 µm) and the right image (B) was captured at ×400 magnification (scale bar = 10 µm))

Grade 0: Negative, no staining
Grade 1: Weak
Grade 2: Moderate
Grade 3: Strong

Statistical Analysis

The data obtained from the research were analyzed using descriptive and inferential statistics. In the descriptive statistics section, quantitative variables were described using appropriate measures of central tendency and dispersion (mean and standard deviation), while qualitative variables were described based on frequencies and percentages.

For the association between MDM2 expression (IS categories) and tumor grade/stage, the Fisher-Freeman-Halton exact test was used due to the small expected cell counts (<5 in >20% of cells). Cramer's V was calculated as a measure of effect size. The 95% confidence intervals for Cramer's V were estimated using a bootstrap method with 1000 replicates.

All statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant. All data analyses were conducted using IBM SPSS Statistics software version 24 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics

The study included 53 patients who underwent surgical resection for gastric adenocarcinoma. The mean age of the patients was 68.4 years (SD = 11.2), with an age range from 41 to 84 years. The cohort was predominantly male, comprising 71.7% (38 individuals) of the study population. The most common histologic subtype was intestinal adenocarcinoma, identified in 58.5% (31 individuals) of the samples. A total of 58.5% (31 individuals) of the patients had received neoadjuvant chemotherapy before their surgery (Table 1).

Table 1. Baseline Demographic, Clinical, and Pathological Characteristics

Characteristic	N (%)
Total Patients	53 (100)
Age (years), mean ± SD	68.4 ± 11.2
Age Range (years)	41 – 84
Sex	
Male	38 (71.7)
Female	15 (28.3)
Histological Subtype	
Intestinal	31 (58.5)
Diffuse	22 (41.5)
Neoadjuvant Chemotherapy	
Yes	31 (58.5)
No	22 (41.5)
Tumor Grade	
Grade 1	9 (17.0)
Grade 2	21 (39.6)
Grade 3	20 (37.7)
Grade 4	3 (5.7)
Pathological Stage	
Stage 1	5 (9.4)
Stage 2	8 (15.1)
Stage 3	21 (39.6)
Stage 4	19 (35.8)

Tumor Pathology

Regarding tumor pathology, the distribution of disease grades was as follows: grade 1 in 9 individuals (17.0%), grade 2 in 21 individuals (39.6%), grade 3 in 20 individuals (37.7%), and grade 4 in 3 individuals (5.7%), totaling 53 patients. The most common pathological stage at presentation was stage 3, which accounted for 39.6% (21 individuals) of the patient cohort (Table 1).

Analysis of MDM2 Expression

Immunohistochemical analysis of MDM2 protein levels revealed that the majority of tumor samples exhibited some degree of expression. The most frequent level of expression was weak intensity, which was present in 56.6% (30 individuals) of the samples. Moderate expression was observed in 7.5% (4 individuals), while strong MDM2 expression was identified in 17.0% (9 individuals) of the cases. The remaining 18.9% (10 individuals) showed no detectable MDM2 expression.

Association Between MDM2 Expression and Pathological Stage

The association between the intensity of MDM2 expression, categorized as none, weak, moderate, or strong, and the pathological stage of the disease, stages 1–4, was analyzed using the Fisher-Freeman-Halton exact test. The analysis demonstrated that there was no statistically significant association between these two variables (P = 0.334; Cramer's V = 0.18, 95% CI: 0.00–0.42). This indicates that the intensity of MDM2 expression was not significantly associated with the pathological stage of gastric cancer in this patient population.

Association Between MDM2 Expression and Histological Grade

We next evaluated the relationship between MDM2 expression intensity and the histological grade of the tumors using the Fisher-Freeman-Halton exact test. The statistical analysis showed no significant association between these two factors (P = 0.395; Cramer's V = 0.16, 95% CI: 0.00–0.39). This finding suggests that MDM2 expression levels were not significantly associated with the tumor grade in gastric adenocarcinoma.

Stratified Analysis by Neoadjuvant Therapy Status

To explore potential confounding effects, we stratified the analysis based on a history of neoadjuvant therapy.

MDM2 and Grade (Stratified): The distribution of MDM2 staining intensity across tumor grades was examined separately for patients with and without neoadjuvant chemotherapy. Among the 22 patients without pre-surgery treatment, strong staining intensity (IS = 3) was observed in 4 of 6 patients (66.7%) with grade 3 tumors. In the treated group (31 patients), strong staining intensity was observed in 3 of 8 patients (37.5%) with grade 3 tumors and in 2 of 3 patients (66.7%) with grade 4 tumors. The remaining patients showed no strong staining (IS < 3). Statistical analysis revealed no significant association between MDM2 intensity score 3 and tumor grade in either subgroup. However, due to the small number of cases with strong staining intensity, these subgroup analyses are underpowered, and the results should be interpreted with caution (Table 2).

Table 2. MDM2 Expression Intensity (IS=3) by Tumor Grade and Neoadjuvant Status

Tumor Grade	No Neoadjuvant (n=22)	Neoadjuvant (n=31)	Total (N=53)
Grade 1	0	0	0
Grade 2	0	0	0
Grade 3	4	3	7
Grade 4	0	2	2
Total IS=3	4	5	9

Table 3. MDM2 Expression Intensity (IS=3) by Pathological Stage and Neoadjuvant Status

Pathological Stage	No Neoadjuvant (n=22)	Neoadjuvant (n=31)	Total (N=53)
Stage 1	0	ND	ND
Stage 2	0	ND	ND
Stage 3	ND	ND	ND
Stage 4	1	0	1
Total IS=3	1	ND	ND

ND: not determined.

MDM2 and Stage (Stratified): Similarly, the relationship between MDM2 and pathological stage was analyzed within the same subgroups. In the group without pre-surgery treatment, one case with strong MDM2 expression (IS = 3) was observed at stage 4. In the treatment group, strong expression was observed in stages 1 and 2. Despite these observed patterns, no statistically significant relationship between MDM2 expression and pathological stage was found in either subgroup (Table 3).

Association Between MDM2 Expression and Neoadjuvant Therapy

We directly investigated whether MDM2 expression levels were associated with the administration of neoadjuvant therapy. The analysis showed that there was no significant difference in MDM2 expression intensity between patients who received pre-surgery chemotherapy and those who did not (Fisher-Freeman-Halton exact test, P = 0.348). The proportion of patients with any MDM2 expression (IS ≥ 1) was 80.6% (25/31) in the treated group and 81.8% (18/22) in the untreated group (difference = -1.2%, 95% CI: -0.21 to 0.29).

DISCUSSION

Studies indicate variable prognostic roles of MDM2 across different cancers, but consensus on its association with p53 in gastric cancer remains limited (17). Understanding how this protein functions in tumors with wild-type p53 is crucial for refining prognostic assessments. Analysis of cancer genomics data from cBioPortal reveals that MDM2 overexpression occurs frequently in multiple cancers—including lung, breast, liver, esophageal, gastric, and colorectal cancers—with lung cancer showing the highest frequency (20). Elevated MDM2 levels are also found in tumors resistant to EGFR inhibitors, suggesting their involvement in therapeutic failure (21, 22).

As the principal negative regulator of p53, MDM2 maintains p53 at low cellular levels by binding its N-terminal domain, inhibiting transcriptional activity, and promoting ubiquitin-mediated degradation through its E3 ligase activity (23). Since 1995, MDM2 has been implicated in chemoresistance, notably by suppressing cisplatin-induced apoptosis (24). Hayashi et al. (25) demonstrated that the p53-MDM2 feedback loop contributes to cisplatin resistance in epidermoid carcinoma: phosphorylated p53 induced by cisplatin reduces resistance, whereas increased MDM2 and unphosphorylated p53 expression associate with resistant tumor cells, modulated in part by cofactors regulating p53.

MDM2 overexpression thus plays a pivotal role in cisplatin resistance by directly lowering cellular sensitivity to the drug and diminishing p53 function. Breast cancer cells with MDM2 amplification exhibit reduced chemosensitivity linked specifically to wild-type p53 suppression, not mutant forms. The p53-MDM2 loop's role in chemoresistance was further confirmed in studies showing that treatment with gemcitabine and cisplatin activates MDM2 and p53 expression, with Musashi-2 (MSI2) enhancing MDM2 ligase activity to accelerate ubiquitination of wild-type p53. MSI2 silencing reduces MDM2 and increases p53, enhancing tumor cell sensitivity to gemcitabine and decreasing invasiveness. This highlights MSI2 as a critical regulator of the p53-MDM2 feedback contributing to drug resistance. Other proteins like HOXA13 also modulate p53-MDM2 to confer resistance to fluorouracil (5-FU) in tumors.

Beyond chemotherapy resistance, MDM2 overexpression associates with radioresistance. Gene therapy targeting p53 can disrupt the p53-MDM2 interaction, stabilizing p53 and sensitizing tumor cells to radiotherapy, especially in tumors overexpressing MDM2 (26).

Tyrosine kinase inhibitors (TKIs), such as EGFR inhibitors used in advanced non-small cell lung cancer (NSCLC), face challenges due to primary and secondary drug resistance (27, 28). Notably, combining MDM2 inhibitors with TKIs shows synergistic effects, addressing resistance mechanisms (29). Clinically, MDM2 overexpression correlates with resistance to trastuzumab in HER2-positive breast cancer and poor progression-free survival in NSCLC with EGFR-sensitive mutations. However, the detailed mechanisms of MDM2-related TKI resistance require further study.

Overall, increased MDM2 expression is observed across multiple human cancers and associates with poor prognosis, tumor invasion, metastasis, and resistance to chemotherapy and targeted therapies, marking it as a promising therapeutic target.

Recent investigations have further elucidated the role of MDM2 in gastric carcinogenesis. For instance, a comprehensive analysis by Abdullazade et al. (30) demonstrated that MDM2 gene amplification is a relatively rare event in gastric cancer, finding no significant correlation between MDM2 amplification, protein expression, and patient survival outcomes. Our findings

align with this evidence, reinforcing the conclusion that MDM2 expression may not function as an independent prognostic marker in our cohort.

LIMITATIONS

This study has several limitations. First, the sample size (n=53) is relatively small, which limits the statistical power to detect small effect sizes and makes subgroup analyses underpowered. Second, this was a single-center study with convenience sampling, which may limit the generalizability of our findings. Third, the use of archival FFPE tissue and a single antibody clone (IF2) may have affected the sensitivity of MDM2 detection. Fourth, the mixed population of patients with and without neoadjuvant chemotherapy (pTNM vs. ypTNM) complicates the interpretation of grade and stage associations. Fifth, TP53 mutational status was not assessed, which is an important confounder as MDM2's effects depend on p53 status. Finally, the absence of survival data prevented us from evaluating the prognostic value of MDM2 for patient outcomes.

Discrepancies in the literature likely arise from context-dependent factors, such as TP53 mutational status and the heterogeneity of immunohistochemical protocols (e.g., variation in antibody clones and scoring systems). Future prospective research, utilizing standardized scoring criteria and larger cohorts, is essential to definitively establish the clinical utility of MDM2 as a standalone biomarker in gastric cancer.

CONCLUSION

In conclusion, no significant association was found between MDM2 protein expression and tumor grade or pathological stage in this retrospective cross-sectional study. These findings suggest that MDM2 overexpression alone may not be a reliable marker for tumor grade or stage in this patient population. These findings contribute to the ongoing discussion on the role of MDM2 in gastric cancer and highlight the need for further research into alternative molecular pathways influencing tumor behavior. Future studies with larger sample sizes and genetic analyses could provide deeper insights into MDM2's functional significance in stomach cancer pathogenesis.

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Conflict of interest

The authors declared no conflict of interest.

Data Availability

The data that support the findings of this study are available from the corresponding author upon request.

Ethics Approval

This retrospective study was conducted on archival FFPE tissue specimens and corresponding records from Guilan University of Medical Sciences. No prospective recruitment or intervention involving patients took place. The study protocol was reviewed and approved by the Ethics Committee of Guilan University of Medical Sciences (approval code IR.GUMS.REC.1401.376) and was carried out in accordance with the ethical principles of the Declaration of Helsinki. Given the use of anonymized archival material, the ethics committee granted a waiver of obtaining new written informed consent from the individuals whose samples were included.

Authors' Contributions

Conceptualization: P.K., I.J.; Methodology: P.K., I.J.; Formal analysis: M.K.; Investigation: A.N., M.M.; Resources: M.K., M.M., E.N.; Data curation: A.N., M.K., E.N., F.K.; Validation: A.N., M.M., E.N.; Writing – Original Draft Preparation: P.K., I.J., A.N., F.K.; Writing – Review & Editing: A.N., M.K., M.M., E.N., F.K.; Supervision: P.K., I.J., F.K.; Project administration: P.K., I.J. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

Not applicable.

Declaration of AI Use

During the preparation of this work, the authors used Grammarly to improve the readability and language quality of the document. The authors thoroughly reviewed and edited the content as needed and take full responsibility for the final publication. Abbreviations: IHC: Immunohistochemistry MDM2: Murine double minute 2 (MDM2 proto-oncogene, E3 ubiquitin protein ligase) FFPE: Formalin-fixed, paraffin-embedded DAB: 3,3'-Diaminobenzidine HRP: Horseradish peroxidase PBS: Phosphate-buffered saline BSA: Bovine serum albumin EDTA: Ethylenediaminetetraacetic acid NSCLC: Non-small cell lung cancer HER2/ERBB2: Human epidermal growth factor receptor 2 (ERBB2) PECAM-1: Platelet endothelial cell adhesion molecule-1 MSI2: Musashi RNA binding protein 2 SPSS: Statistical Package for the Social Sciences CI: Confidence interval TKIs: Tyrosine Kinase Inhibitors EGFR: Epidermal Growth Factor Receptor VEGF: Vascular endothelial growth factor TIS: Total immunostaining score PS: Proportion score IS: Intensity score

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