fortune Journals

Research Article

ARCHIVES OF INTERNAL MEDICINE RESEARCH

ISSN: 2688-5654

Association of AgNOR and Ki-67 with Histopathological Grading in Patients Diagnosed with Gastric Carcinoma

Thanadar Ajmiree Flora[1]*, Thanadar Tamjeeda Tapu[2], Rezwana Rahman Khan[3], Tania Gaffar[4]

Abstract

Background: Gastric Carcinoma is the second most prevalent cause of death worldwide, characterized by diverse histopathological grading that reflects the tumor's differentiation and aggressiveness. This study aimed to investigate the correlations between the Ki-67 labeling index, AgNOR values, and histopathological grading in gastric carcinoma patients.

Methods: A total of sixty patients aged 35 years and older with gastric carcinoma who had received histopathological diagnoses of gastric carcinoma based on biopsies obtained through gastric endoscopy as well as resected tissue samples were included. Histopathologic grading distributions were categorized into well-differentiated, moderately differentiated, and poorly differentiated groups. Ki-67 labeling index and AgNOR values were measured, and ANOVA analysis revealed significant variations across grading. Bonferroni tests identified specific differences in means between grades. Scatter diagrams visually depict the correlation between markers and grading.

Results: Histopathological grading distributions comprised 13.33% well-differentiated, 50% moderately differentiated, and 36.67% poorly differentiated cases. Positive correlations were observed between the Ki-67 labeling index and histopathological grading ($r = 0.436$, $p = 0.001$) and between AgNOR values and grading ($r = 0.451$, $p = 0.001$).

Conclusion: This study highlights the significant correlations between histopathological grading, Ki-67 labeling index, and AgNOR values in gastric carcinoma. These correlations offer insights into tumor aggressiveness and cellular proliferation. These findings contribute to our understanding of gastric carcinoma's biological behavior and potential clinical implications.

Keywords: Gastric Carcinoma; Histopathological Grading; AgNOR, Ki-67; Tumor Differentiation

Introduction

Gastric carcinoma, also known as stomach cancer, is the second most common cause of death worldwide [1] and the fourth most commonly diagnosed malignancy worldwide, including in Japan and several regions of China and South America [2]. After observing the global distribution of the incidence of gastric cancer, many geographical factors have been associated with the incidence, mortality, and survival [3]. The Regional variations in stomach cancer partly reflect differences in dietary patterns.

Affiliation:

[1]Assistant Professor, Department of Pathology, Shahabuddin Medical College, Dhaka, Bangladesh

[2]Assistant Professor, Educational Sciences, Center for Medical Education, Dhaka, Bangladesh

[3]Assistant Professor, Department of Pathology, Dhaka Medical College Hospital, Dhaka, Bangladesh

[4]Associate Professor , Department of Pathology, Uttara Adhunic Medical College, Dhaka, Bangladesh

***Corresponding author:**

Thanadar Ajmiree Flora, Assistant Professor, Department of Pathology, Shahabuddin Medical College, Dhaka, Bangladesh.

Citation: Thanadar Ajmiree Flora, Thanadar Tamjeeda Tapu, Rezwana Rahman Khan, Tania Gaffar. Association of AgNOR and Ki-67 with Histopathological Grading in Patients Diagnosed with Gastric Carcinoma. Archives of Internal Medicine Research. 8 (2025): 65-72.

Received: March 18, 2024
Accepted: March 30, 2024
Published: February 14, 2025

Flora TA, et al., Arch Intern Med Res 2025
DOI:10.26502/aimr.0197

Because patients with advanced stomach cancer have an average overall survival of less than 12 months, gastric carcinoma is a highly malignant condition [4]. Among the different types of gastric carcinoma, the incidence of primary gastric and oesophageal/gastroesophageal junction (GEJ) adenocarcinomas is increasing [5]. It is theorized to be the result of a combination of environmental factors and the accumulation of specific gene alterations and primarily affects older patients [6]. According to studies, foods that are salted, smoked, pickled, or preserved increase the risk of GC; however, a high intake of fresh fruits and vegetables, as well as antioxidants, is linked to a lower risk of GC [7]. Practically all gastric carcinomas begin in the generative cells of the foveolae or gastric pits, usually in the context of chronic atrophic gastritis with intestinal metaplasia, and can progress via dysplasia, carcinoma in the situation, or superficial carcinoma [8]. Many patients with gastroesophageal cancer present with advanced-stage or metastatic disease, and the prognosis of patients with these tumors is often very poor, with a median overall survival of less than 1 year and a 5-year survival rate ranging between 5% to 25% [5]. Medical advancements in the treatment of gastric carcinoma, including combination chemotherapy, have resulted in improved overall survival, compared to single-agent chemotherapy alone. Additional therapy aimed at specific targets in cancer has shown a survival benefit in certain tumors. Stomach cancer is often asymptomatic or causes only nonspecific symptoms. By the time symptoms manifest, the disease has often grown to an advanced stage and may have spread, which is one of the reasons for its poor prognosis. A biopsy with subsequent histology analysis is the only sure way to confirm the presence of cancer cells [9]. Constant efforts are being made to determine non-intrusive testing methods to diagnose stomach cancer. The AgNOR and Ki-67 are being tested as possible markers for stomach cancer. The Nucleolar organizer region (NOR) technique has recently been applied to several cancers. The nucleolar organizer region or NOR is a region in the chromosome around which the nucleolus forms. It contains genes for ribosomal RNA. The silver staining technique of NOR (AgNOR) is based on the argyrophilic of NOR-associated proteins and can be performed at room temperature on paraffin-embedded tissues [10]. Many studies have shown that increased AgNOR counts are frequently associated with malignancy and may have prognostic usefulness [10]. In individuals with histopathologically identified gastric cancer, the value of AgNOR rises with the gastric carcinoma grade [11]. Ki-67 is another possible predictor of Gastric Cancer (GC which has recently been identified as a predictor of cell proliferation, malignant potential, and cancer recurrence [12] However, there is controversy in Ki-67 expression in GC, as several retrospective articles have reported that a high level of Ki-67 is linked with poor prognosis in patients with GC, while some studies suggested that Ki-67 over-expression is prognostically irrelevant in GC patients [12]. Some previous studies have reported that In GC patients, high Ki-67 expression was linked to a low overall survival rate [13]. High Ki-67 expression was found to provide a prognostic value for the prognosis of GC patients in this pioneering research [14]. In our study, both Ki-67 and AgNOR count were used for the determination of therapeutic applications and further investigation on a sizable cohort of individuals with histopathologically confirmed gastric cancer. This study aimed to examine the relationship between the presence of AgNOR and Ki-67 expressions in individuals who had been diagnosed with gastric cancer through histopathological analysis.

Methods

A cross-sectional analytical study between July 2017 and June 2019 was conducted at the Department of Pathology in Sir Salimullah Medical College and Mitford Hospital, situated in Dhaka, Bangladesh. The study utilized a purposive sampling technique to gather data from participants aged 35 years and older, who had received histopathological diagnoses of gastric carcinoma via both gastric endoscopic biopsies and resected samples. Each participant provided both types of samples, which were duly collected and preserved and AgNOR dots were quantified within nuclei using oil immersion at a magnification of 1000x for them. The cumulative average AgNORs (referred to as mAgNOR) per nucleus was determined by tallying the AgNOR dots across 100 nuclei. To assess Ki-67 expression, a specific monoclonal antibody was employed for immunohistochemical staining. Based on an estimated gastric carcinoma proportion of 7.94% derived from a previous study in Bangladesh [15], and employing a significance level of 5% with 80% statistical power, a minimum sample size of around 57 was required. Followed by data collection, a dataset was cleaned and removed irrelevant data as well as computed basic descriptive statistics for each variable, including means, standard deviations, and distributions. Pearson correlation coefficient was conducted between histopathological grading and Ki-67 expressions within each age group and a one-way ANOVA test was also performed to examine when it was found statistically significant mean differences in AgNOR counts and Ki-67 expressions across the Histologic grading, We further performed Bonferroni post hoc tests to identify which specific pairs of gradings have significantly different means. Written informed consent was obtained from each participant before collecting any data, and ethical clearance was obtained from the Institutional Ethics Committee of SSMC, Dhaka, before commencing the research. Patients who had undergone radiotherapy or chemotherapy exhibited signs of mental instability, or presented with metastatic cancer were meticulously excluded from the study.

Flora TA, et al., Arch Intern Med Res 2025
DOI:10.26502/aimr.0197

Results

A total of sixty patients aged 35 years and older with Gastric carcinoma during the study period were considered in the analysis. Out of which over 56% (n=34) of patients were from the age group 60 years and above followed by more than 43% (n=26) of the patients belonging to the age group of 60 years or less. The mean age (±SD) of the patients was found to be 61.05 (±11.99) years, and the age range of the participants consisted from 40 to 82 years. Female patients were found predominant at 55% (n=33) and compared to males at 45% (n=27). Gastric carcinoma was identified in 63% (n=38) of patients in the pylorus region, 33% (n=20) elsewhere in the body, and 3.3% (n=2) in the cardiac endocardium [Table 1]. Based on the three tier of grading scheme, half of the study patients (n=30) were found to have moderately differentiated (G2- Intermediate grade) gastric carcinoma followed by close to 37% (n=22) poorly differentiated (G3- High grade) and 13% (n=8) Well-differentiated (G1- Low grade) gastric carcinoma [Table 1] [Figure 1].

Association between sites and Tumor with histopathological Grading of the study patients:

The association between tumor sites and histopathologic grading among the study patients (n=60) was examined. In terms of tumor sites, 38 cases in the pylorus region, there were 75% (6 cases of 8) with well-differentiated grading,

Table 1: Distribution patterns of Gastric carcinoma among the study patients (n=60).

Characteristics	Gastric carcinoma	
	Frequency	Percentage
Age (in years)		
Less than and equal to 60	26	43.33
Above 60	34	56.67
Sex		
Male	27	45
Female	33	55
Sites of GC		
Pylorus	38	63.33
Body site	20	33.33
Cardiac end	2	3.33
Histopatological Grading		
Well-differentiated (G1- Low grade)	8	13.33
Moderately differentiated (G2- Intermediate grade)	30	50
Poorly differentiated (G3- High grade)	22	36.67

followed by over 63% (14 cases of 22) with poorly differentiated and 60% (18 cases of 30) with moderately differentiated grading. Similarly, for the body site, 25% (2 cases of 8) were well-differentiated, over 33% (10 cases of 30) were moderately differentiated, and more than 36% (8 cases of 22) were poorly differentiated. Notably, in the cardiac end, only around 7% (2 cases of 30) (6.7%) were moderately differentiated, and Neither poorly differentiated nor well-differentiated cases were identified. The p-value for the comparison of tumor sites with histopathological grading was 0.652, indicating the insignificant association between these variables [Table 2].

Regarding the type of tumor, all 100% of cases (n=8) of the intestinal type of tumor were well-differentiated, 100% of cases (n=30) were moderately differentiated, and over 45% of cases (n=10) were poorly differentiated. Conversely, types of gastric carcinoma (Intestinal and diffuse) were evaluated with the grading, The study observed that all of the well-differentiated and moderately differentiated varieties belonged to the intestinal type of GC (n=38). Among the poorly differentiated cases (n=22), above 45% (n=10) were intestinal while the remaining close to 55% (n=12) were the diffuse type of tumor which was found statistically significant (p=0.001) association of tumor types with histopathological grading [Table 2].

A Bonferroni test followed by an ANOVA test was performed to compare the means of Ki-67 labelling index and AgNOR with the three respective Histopathological Gradings (G1, G2 and G3) of Gastric Carcinoma. The results of the ANOVA test, presented in Table 3 (A), revealed significant variations in the Ki-67 labelling index and AgNOR values across different histopathological gradings among the study participants (n = 60). For the well-differentiated group (G1), the mean±SD of the Ki-67 labelling index was found to be 36.75 ± 12.96, and the mean AgNOR value was found 2.34 ± 0.11. In contrast, the moderately differentiated group (G2) had a mean±SD Ki-67 index of 46.07 ± 10.21 and an AgNOR value of 2.63 ± 0.25. Finally, the poorly differentiated group (G3) exhibited the highest values with a mean±SD Ki-67 index of 53.05 ± 11.54 and an AgNOR value of 2.76 ± 0.27. The p-values associated with the Ki-67 index and AgNOR value indicated statistically significant differences across the three histopathological gradings (Ki-67: $p = 0.002$, AgNOR: $p = 0.005$) [Table 3 (A)].

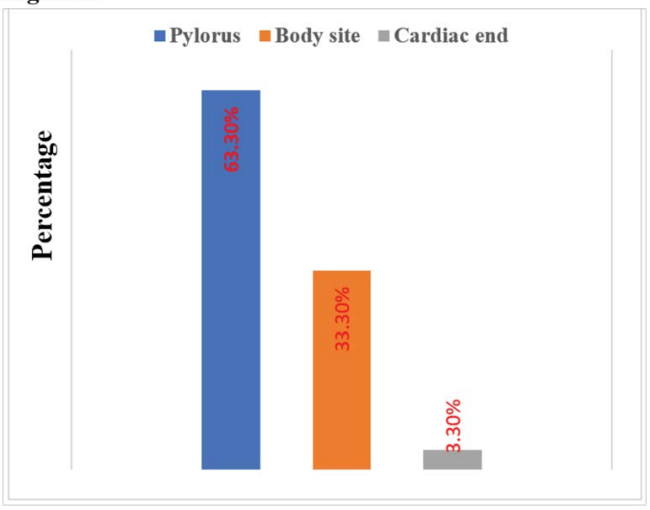
Since the ANOVA indicates a significant difference for both the Ki-67 labelling index and AgNOR, we further performed Bonferroni post hoc tests to identify which specific pairs of gradings have significantly different means, as shown in Table 3 (B). Bonferroni test unveiled specific variations between histopathological gradings and their impact on Ki-67 and AgNOR values. Comparing well-differentiated (A) and moderately differentiated (B) groups, a statistically

Flora TA, et al., Arch Intern Med Res 2025
DOI:10.26502/aimr.0197

Table 2: Association between tumor sites and types with the histopathological gradings of the study patients.

Malignancies	Histopathological Grading						p-value
	Well-differentiated		Moderately differentiated		Poorly differentiated		
	n=8	*%*	*n=30*	*%*	*n=22*	*%*	
Sites of GC							
Pylorus site (38)	6	75	18	60	14	63.6	0.652
Body site (20)	2	25	10	33.3	8	36.4	
Cardiac end (2)	0	0	2	6.7	0	0	
Type of Tumor							
Intestinal	8	100	30	100	10	45.5	0.001
Diffuse	0	0	0		12	54.5	

Figure 1:



significant difference was observed in both Ki-67 (p = 0.037) and AgNOR values (p = 0.003). Similarly, well-differentiated (G1) and poorly differentiated (G3) groups exhibited significant differences in both Ki-67 (p = 0.002) and AgNOR values (p = 0.001). However, the comparison between moderately differentiated (G2) and poorly differentiated (G3) groups indicated a significant difference in Ki-67 (p = 0.025), while the AgNOR values did not reach statistical significance (p = 0.079).

Graphical presentation:

The following scatter diagrams showed the correlation of the Ki-67 labeling Index and AgNOR with Histopathological Grading of Gastric Carcinoma. In the following scatter diagrams [Figure 2 (A) and Figure 2 (B)], the Ki-67 labeling Index and AgNOR, respectively, demonstrated a significant positive correlation (r = 0.436; p = 0.001 and r = 0.451; p = 0.001, respectively) with Histopathological Gradings of Gastric cancer.

Discussion

The study aimed to investigate the correlation between AgNOR and Ki-67 expressions with histopathological grading in patients diagnosed with gastric carcinoma. The results shed light on the intricate relationships between these biomarkers and tumor differentiation, providing valuable insights into the potential clinical significance of these associations.

The demographic characteristics of the study population revealed that the majority of patients were aged 60 years and above, comprising over 56% of the sample. This trend aligns with the known increased incidence of gastric carcinoma in the elderly population [16]. The mean age of 61.05 years, alongside the age range of 40 to 82 years, underscores the diverse age distribution within the study cohort. Additionally, a higher proportion of female patients (55%) was observed compared to males (45%), indicating potential gender-related differences in the occurrence of gastric carcinoma. This is consistent with the findings of another study [17].

The distribution of gastric carcinoma across tumor sites indicated a predominant presence in the pylorus region, accounting for 63% of cases. This distribution pattern is consistent with existing literature highlighting the pylorus as a common site for gastric carcinoma. Conversely, the cardiac endocardium exhibited the lowest incidence of gastric carcinoma (3.3%), which could be attributed to the limited tissue accessibility of this region [18]. Another recent study conducted in 2015 showed that the most common anatomic site of gastric cancer was the antrum in 47.5% of the participants, 38.8% had cancer in the body and only 13.7% had carcinoma in the cardiac end [19]. However, a few studies showed different results where the most common site of GC was the body of the stomach and the cardiac end [20,21]. This difference might be due to global and cultural differences, along with dietary differences.

Flora TA, et al., Arch Intern Med Res 2025
DOI:10.26502/aimr.0197

Table 3 (A): ANOVA test for Correlation of Ki-67 proliferation index and AgNOR with histopathological grading

Histopathological Grading		Ki-67 labelling Index		AgNOR	
	n	*Mean±SD*	*p-value*	*Mean±SD*	*p-value*
Well-differentiated (G1)	8	36.75±12.96	0.002	2.34±0.11	0.005
Moderately differentiated (G2)	30	46.07±10.21		2.63±0.25	
Poorly differentiated (G3)	22	53.05±11.54		2.76±0.27	

Table 3 (B): Bonferroni test followed by ANOVA test: to compare the means of Ki-67 labelling index and AgNOR with the three respective Histopathological Gradings (G1, G2 and G3) of Gastric Carcinoma

Comparison between Histopathological Gradings	*p-value*	
	Ki-67 labelling Index	AgNOR
G1 vs G2	0.037	0.003
G1 vs G3	0.002	0.001
G2 vs G3	0.025	0.079

Figure 2 (A): Correlation between Ki-67 proliferation index and histopathologic grading

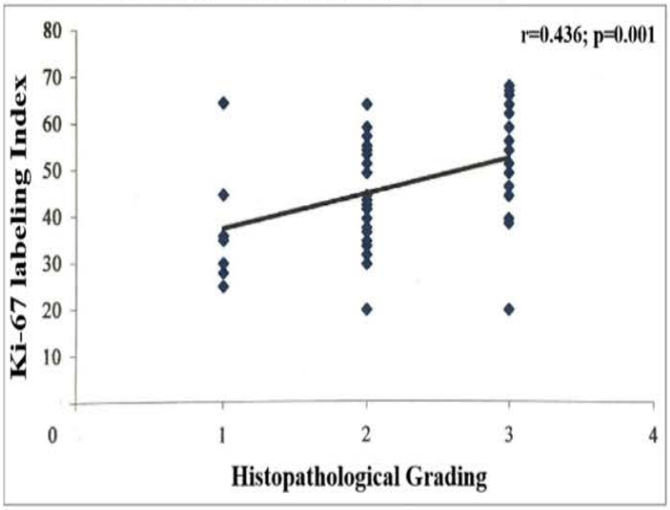
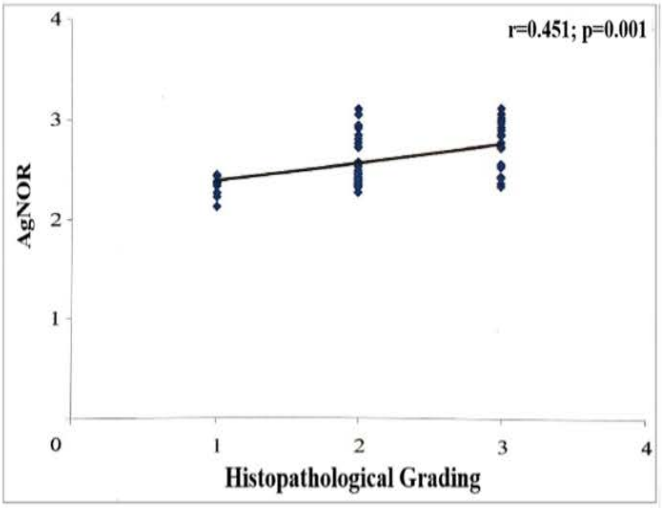


Figure 2 (B): Correlation between AgNOR and histopathologic grading



Histopathological grading, a crucial prognostic indicator, demonstrated a varying distribution among the study participants. The majority of patients were diagnosed with moderately differentiated (G2) gastric carcinoma (50%), followed by poorly differentiated (G3) (37%) and well-differentiated (G1) (13%) types. These findings suggest that the majority of cases in this study population tend to be of intermediate to high-grade malignancy. The distribution of histopathological gradings underscores the heterogeneity of gastric carcinoma, ranging from less aggressive to more aggressive forms. These findings provide a foundation for further investigations into correlations between histopathological grading and other variables, such as molecular markers and clinical outcomes, ultimately contributing to improved diagnostic and therapeutic strategies for patients with gastric carcinoma.

The association analysis between tumor sites and histopathological grading unveiled interesting trends. While a higher proportion of well-differentiated cases were observed in the pylorus region (75%), poorly differentiated cases were more prevalent in both the pylorus (63.6%) and body sites (36.4%). Although there were no cases of well-differentiated carcinoma in the cardiac end, the small sample size limits definitive conclusions for this region. The lack of

Flora TA, et al., Arch Intern Med Res 2025
DOI:10.26502/aimr.0197

significant association (p = 0.652) between tumor sites and histopathological grading implies that tumor location might not be a primary determinant of differentiation in gastric carcinoma.

The correlation between tumor types and histopathological grading, on the other hand, exhibited a significant association (p < 0.001). Specifically, well-differentiated and moderately differentiated cases were predominantly of the intestinal type, while poorly differentiated cases demonstrated a notable presence of both intestinal and diffuse types. These findings emphasize the potential impact of tumor type on differentiation patterns, further highlighting the intricate nature of gastric carcinoma subtypes.

In examining the specific grading, the well-differentiated group (G1) exhibited a mean Ki-67 labelling index of 36.75 ± 12.96 and an AgNOR value of 2.34 ± 0.11. The moderately differentiated group (G2), on the other hand, demonstrated a higher mean Ki-67 index of 46.07 ± 10.21 and a slightly elevated AgNOR value of 2.63 ± 0.25. Interestingly, the poorly differentiated group (G3) displayed the highest values, both in terms of Ki-67 labelling index (53.05 ± 11.54) and AgNOR value (2.76 ± 0.27). These findings suggest a progressive increase in both proliferation index (Ki-67) and nucleolar organizer region (AgNOR) counts with a decline in tumor differentiation. The statistical significance of the results was reaffirmed by the associated p-values for Ki-67 (p = 0.002) and AgNOR values (p = 0.005), indicating significant differences in these markers across the three histopathological gradings [Table 3 (A)]. This underscores the potential of both Ki-67 and AgNOR as indicative markers of the tumor's aggressiveness and differentiation level. Subsequent Bonferroni post hoc test investigated the specific differences between grading and their impact on Ki-67 and AgNOR values. The comparisons provided a more clear understanding of the relationships. For instance, the significant differences observed in both Ki-67 and AgNOR values between well-differentiated (G1) and moderately differentiated (G2) groups (Ki-67: p = 0.037, AgNOR: p = 0.003) highlight a shift in the proliferation index and nucleolar organizer regions as the tumor progresses from well to moderately differentiated. Similarly, the differences in both Ki-67 and AgNOR values between well-differentiated (G1) and poorly differentiated (G3) groups (Ki-67: p = 0.002, AgNOR: p = 0.001) emphasize the substantial changes that occur in these markers during tumor differentiation. Conversely, the comparison between moderately differentiated (G2) and poorly differentiated (G3) groups indicated significant differences in Ki-67 values (p = 0.025), while AgNOR values did not reach statistical significance (p = 0.079). This suggests that while the proliferation index (Ki-67) still exhibits variations, the nucleolar organizer regions (AgNOR) might not contribute significantly to this specific differentiation shift. A previous study reported different Ki-67 scores associated with gastric carcinomas. Gastric carcinomas were divided into two categories for accurate grouping of the results; those with a high Ki-67 (on or above 45%) and those with a low Ki-67 (less than and equal to 45%) [22].

Finally, upon scrutiny of both scatter diagrams, it becomes evident that both the Ki-67 labelling Index and AgNOR values exhibit a significant positive correlation with the Histopathological Grading of Gastric Carcinoma. The strength of this correlation is indicated by the Pearson correlation coefficient (r), which is 0.436 for Ki-67 (p = 0.001) and 0.451 for AgNOR (p = 0.001). These results suggest that as the histopathological grading advances from well-differentiated to poorly differentiated tumors, there is an upward trend in both the Ki-67 labelling Index and AgNOR values. The implications of these findings are profound, offering potential insights into tumor behavior and aiding in risk stratification and treatment decisions. Our study underlines the complex interplay between Ki-67 labelling index, AgNOR values, and histopathological gradings, highlighting their clinical significance and potential roles as prognostic indicators in gastric carcinoma. Further research with larger cohorts could refine and extend these observations, contributing to improved patient management strategies.

Limitations

Despite the valuable insights garnered, this study had several limitations. The relatively small sample size and single-centre design could potentially limit the generalizability of the findings to broader populations. Additionally, the study's cross-sectional nature restricts the establishment of causal relationships. Further longitudinal studies with larger and more diverse cohorts are essential to validate these correlations and elucidate their clinical relevance in a more comprehensive context.

Conclusion

In this study, the examination of histopathological grading distributions among patients diagnosed with gastric carcinoma revealed a diverse spectrum of tumor differentiation, ranging from well-differentiated to poorly differentiated forms. The analysis of the Ki-67 labeling index and AgNOR values across these gradings highlighted significant variations, underscoring their potential as indicators of tumor aggressiveness and cellular proliferation. The positive correlations observed between these markers and histopathological gradings were further supported by strong statistical significance. These findings enhance our understanding of the intricate relationships between these markers and the biological behavior of gastric carcinoma, paving the way for potential clinical implications in prognosis and management. Further research is warranted to elucidate the underlying molecular mechanisms driving these correlations and their broader clinical utility.

Citation: Thanadar Ajmiree Flora, Thanadar Tamjeeda Tapu, Rezwana Rahman Khan, Tania Gaffar. Association of AgNOR and Ki-67 with Histopathological Grading in Patients Diagnosed with Gastric Carcinoma. Archives of Internal Medicine Research. 8 (2025): 65-72.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee, SSMC

Authors' contributions:

The manuscript was reviewed and accepted by all contributors.

Conceptualization and design: TAF, TG

Data collection: TG, RRH

Data curation: TAF, MI

Data analysis: MI, RRK

Draft manuscript preparation: TAF, MI

Review and editing: MI, TAF

Critical review: MI

Acknowledgement: Author acknowledged to the staff of the hospital

References

1. Shan L, Ying J, Lu N. HER2 expression and relevant clinicopathological features in gastric and gastroesophageal junction adenocarcinoma in a Chinese population. Diagnostic Pathology [Internet], 8 (2013): 76.
2. Latest world cancer statistics – GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 – IARC [Internet]. [cited 2023 Jan 25]. Available from: https://www.iarc.who.int/news-events/latest-world-cancer-statistics-globocan-2012-estimated-cancer-incidence-mortality-and-prevalence-worldwide-in-2012/
3. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer [Internet], 127 (2023): 2893-917.
4. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012: Globocan 2012. Int J Cancer [Internet]. 136 (2023): E359–386.
5. Jeung J, Patel R, Vila L, et al. Quantitation of HER2/neu Expression in Primary Gastroesophageal Adenocarcinomas Using Conventional Light Microscopy and Quantitative Image Analysis. Archives of Pathology & Laboratory Medicine [Internet]. 2012 Jun 1 [cited 2023 Jan 25]; 136 (2012): 610-617.
6. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA: A Cancer Journal for Clinicians [Internet]. 2011 [cited 2023 Jan 25]; 61 (2023): 69-90.
7. EBSCOhost | 18222740 | Epidemiology of gastric cancer: an evaluation of available evidence. [Internet]. [cited 2023 Jan 25]. Available from: https://web.p.ebscohost.com/t?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=09441174&AN=18222740&h=HhqSLDbGiTNHuPI15izhPAzKubzMS4P5ZqpIkVzTfcSEcQyya9zG95SOfncZC7f9zHKZvChbpT335RldOpkIJQ%3d%3d&crl=c&resultNs=AdminWebAuth&resultLocal=ErrCrlNotAuth&crlhashurl=login.aspx%3fdirect%3dtrue%26profile%3dehost%26scope%3dsite%26authtype%3dcrawler%26jrnl%3d09441174%26AN%3d18222740
8. Rosai J. Rosai and Ackerman's Surgical Pathology E-Book. Elsevier Health Sciences (2011): 2767p.
9. Thrumurthy SG, Chaudry MA, Hochhauser D, et al. The diagnosis and management of gastric cancer. BMJ [Internet]. 2013 Nov 4 [cited 2023 Jan 25]; 347 (2023): f6367.
10. Crocker J, Nar P. Nucleolar organizer regions in lymphomas. The Journal of Pathology [Internet]. 1987 [cited 2023 Jan 25]; 151 (2023): 111–118.
11. Gosh S, Ghosh TK, Dewasi N, et al. Prognostic information of gastric carcinoma using Goseki system in relation to nuclear organizer region (AgNOR) and proliferating cell nuclear antigen (PCNA) expression. Bangladesh Journal of Medical Science [Internet]. 2010 Aug 4 [cited 2023 Jan 25]; 9 (2010): 76-86.
12. Liu G, Xiong D, Zeng J, et al. Clinicopathological and prognostic significance of Ki-67 immunohistochemical expression in gastric cancer: a systematic review and meta-analysis. Onco Targets Ther [Internet]. 2017 Sep 1 [cited 2023 Jan 25];10: 4321–4328.
13. Tsamandas AC, Kardamakis D, Tsiamalos P, et al. The Potential Role of Bcl-2 Expression, Apoptosis and Cell Proliferation (Ki-67 Expression) in Cases of Gastric Carcinoma and Correlation with Classic Prognostic Factors and Patient Outcome. Anticancer Research [Internet]. 2009 Feb 1 [cited 2023 Jan 25]; 29 (2023): 703–709.
14. Luo G, Hu Y, Zhang Z, et al. Clinicopathologic significance and prognostic value of Ki-67 expression in patients with gastric cancer: a meta-analysis. Oncotarget [Internet]. 2017 Apr 20 [cited 2023 Jan 25]; 8 (2023): 50273–50283.
15. Histopathologic Pattern Of Gastric Cancer In Bangladesh.
16. Okada E, Ukawa S, Nakamura K, et al. Demographic and lifestyle factors and survival among patients with

esophageal and gastric cancer: The Biobank Japan Project. Journal of Epidemiology 27 (2017): S29–35.

17. Sitarz R, Skierucha M, Mielko J, et al. Gastric cancer: epidemiology, prevention, classification, and treatment. Cancer Management and Research 10 (2018): 239.

18. Kim K, Cho Y, Sohn JH, et al. Clinicopathologic characteristics of early gastric cancer according to specific intragastric location. BMC Gastroenterology 19 (2019): 24.

19. Tiwari E, Pallipady A, Misra R, et al. P53 and ki67 Immunostaining in Gastric Biopsies: A Histopathological Study. INTERNATIONAL JOURNAL OF SCIENTIFIC STUDY. 2 (2015): 96–101.

20. Sanaat Z, Halimi M, Ghojezadeh M, et al. Immunohistochemical Analysis of p53, Ki-67, CD44, HER-2/neu Expression Patterns in Gastric Cancer, and Their Association with One Year Survival in North-West of Iran. Int J Hematol Oncol Stem Cell Res [Internet]. 2013 [cited 2023 Jan 25]; 7 (2023): 15–20.

21. Ahadi M, Moradi A, Musavinejad L, et al. The Expression of p53, CD44, Ki-67, and HER-2/neu Markers in Gastric Cancer and Its Association with Histopathological Indicators: A Retrospective Study. Asian Pac J Cancer Prev [Internet]. 2020 Jun [cited 2023 Jan 25]; 21 (2020): 1607-1614.

22. Lazăr D, Tăban S, Sporea I, et al. Ki-67 expression in gastric cancer. Results from a prospective study with long-term follow-up. Rom J Morphol Embryol 51 (2010): 655-661.