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Article

Gastric Cancer Risk in Patients with Intestinal Metaplasia: Long-Term Outcomes from a Large Single-Center Cohort

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Abstract

Background/Objectives: Gastric intestinal metaplasia (GIM) is a recognized premalignant condition for gastric cancer (GC), but long-term outcomes and predictors of progression remain incompletely understood. This study aimed to evaluate the progression of GIM and identify factors associated with malignant transformation. **Methods:** In this retrospective single-center study, 1,454 adult patients with histologically confirmed GIM and at least 12 months of follow-up after esophagogastroduodenoscopy (EGD) were analyzed. Clinical and pathological variables, including GIM extent, *Helicobacter pylori* status, family history of GC, demographic factors, and residence in endemic regions, were assessed. Patients were stratified into high- and low-risk groups according to established criteria, and progression to GC or other neoplasms was recorded. **Results:** During a mean follow-up of 38.5 months, 47.2% of patients showed regression of GIM, 49.2% remained stable, and 3.5% progressed. Among progressed cases, adenocarcinoma accounted for 41.3%, neuroendocrine tumors for 31.4%, and dysplasia for 19.6%. Older age, male sex, enterochromaffin-like cell hyperplasia, and *H. pylori* negativity were significantly associated with progression. The overall progression rate to adenocarcinoma was 0.01%. No significant difference in progression or survival was observed between high- and low-risk groups. **Conclusions:** The long-term malignant transformation rate of GIM is very low. Age, sex, ECL hyperplasia, and absence of *H. pylori* are associated with progression, whereas conventional risk stratification did not predict outcomes. These findings support individualized surveillance strategies for patients with GIM, while routine surveillance of antrum-limited GIM may provide minimal benefit but increase healthcare burden.

Keywords: gastric intestinal metaplasia (GIM); Gastric cancer (GC); *helicobacter pylori*; Premalignant gastric lesions; Correa cascade; surveillance; risk stratification

1. Introduction

Gastric cancer (GC) remains a major global health challenge, ranking as the fourth leading cause of cancer-related mortality worldwide [1]. Its incidence exhibits pronounced geographic variability, with the highest burdens observed in East Asia, Eastern Europe, and parts of Latin America [2]. This

heterogeneity reflects complex interactions between genetic susceptibility, environmental exposures, and infectious agents [3].

Most gastric adenocarcinomas evolve through a multistep histopathological sequence that is often clinically silent in its early stages, offering a critical window for surveillance. This process, classically described as the *Correa cascade*, involves the transition from normal gastric mucosa to chronic gastritis, atrophic gastritis (AG), multifocal AG (MAG), gastric intestinal metaplasia (GIM), low-grade or high-grade dysplasia (LGD/HGD), and ultimately invasive adenocarcinoma [3]. Among known risk factors, *Helicobacter pylori* infection is predominant, accounting for approximately 75–89% of non-cardia gastric adenocarcinomas [4].

AG, GIM, and dysplasia are recognized as gastric premalignant conditions (GPMCs). GIM is histologically defined as the replacement of oxyntic or antral gastric mucosa by an intestinal-type epithelium containing goblet cells, absorptive cells, and Paneth cells [5]. The likelihood of GIM development and its progression to GC is influenced by multiple determinants, including *H. pylori* exposure history, ethnicity, migration status, age, family history, and environmental cofactors [6]. Reported annual progression rates to GC vary considerably: approximately 0.25% in Western European cohorts compared with up to 10% in certain East Asian populations [7,8].

In high-incidence countries, particularly across Asia, secondary prevention strategies combining endoscopic screening and targeted surveillance of premalignant lesions have been implemented to enable earlier detection and improve prognosis [3]. Nevertheless, the absence of harmonized international guidelines, coupled with the scarcity of large-scale longitudinal studies, limits the global generalizability of these approaches. Existing research on surveillance intervals for GIM has often involved small patient cohorts, and the optimal duration and intensity of follow-up remain a matter of debate.

The present study aims to evaluate the long-term outcomes of GIM and to identify factors that may facilitate its progression to gastric cancer. By considering variables such as GIM extent, presence of additional risk factors, age, and sex, we sought to provide a comprehensive risk assessment for malignant transformation. To our knowledge, this is the largest single-center cohort from Türkiye evaluating GIM progression, thereby offering novel insights from a region with an intermediate incidence of gastric cancer.

2. Materials and Methods

2.1. Study Design and Setting

This single-center, multidisciplinary, retrospective archival study was conducted at the Division of Gastroenterology, Department of Internal Medicine, and the Department of Pathology, Gazi University Faculty of Medicine, Ankara, Türkiye. The primary objective was to assess the risk of gastric cancer progression among patients with GIM based on lesion distribution, presence of additional risk factors, age, and sex. A secondary objective was to determine the prevalence of *Helicobacter pylori*, GIM, gastric adenocarcinoma, gastrointestinal stromal tumors (GIST), and neuroendocrine tumors (NET) among patients undergoing esophagogastroduodenoscopy (EGD) with biopsy.

2.2. Study Population and Data Sources

All patients aged ≥ 18 years who underwent EGD for any indication at Gazi University Hospital between January 2013 and December 2021 were screened. Endoscopic and histopathological records were retrieved from the institutional electronic medical record system and pathology archives.

A total of 25,130 patients underwent EGD during the study period. Of these, 3,368 patients were histologically diagnosed with GIM based on gastric biopsy specimens. The diagnosis of GIM was confirmed by experienced gastrointestinal pathologists using hematoxylin-eosin staining, with ancillary stains (e.g., Alcian blue, PAS) applied when necessary.

2.3. Inclusion and Exclusion Criteria

For the longitudinal risk assessment, only patients with histologically confirmed GIM who had at least one follow-up EGD with biopsy performed ≥ 12 months after the index procedure were included. Patients with incomplete records, prior gastric cancer diagnosis, or follow-up shorter than one year were excluded.

A final cohort of 1,454 patients met the inclusion criteria. These patients were evaluated retrospectively for the development of gastric cancer during follow-up.

2.4. Variables and Definitions

- **GIM extent:** classified as confined to the antrum, confined to the corpus, or involving both antrum and corpus.
- **Additional risk factors:** presence of *H. pylori* infection at baseline (determined histologically), family history of gastric cancer in a first-degree relative, residence in a region of Türkiye endemic for gastric cancer (Eastern Anatolian region) [9], demographic characteristics (age, sex), and other documented risk modifiers.
- **Intestinal metaplasia risk groups:** as outlined in the AJG guidelines, patients with intestinal metaplasia were stratified into two risk groups: the low-risk group, comprising individuals with intestinal metaplasia confined to the antrum; and the high-risk group, which included patients with intestinal metaplasia involving both the antrum and corpus, those with a first-degree relative diagnosed with gastric cancer, and individuals residing in endemic regions [3].
- **Outcome:** development of histologically confirmed gastric adenocarcinoma during follow-up.

2.5. Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Gazi University Faculty of Medicine Medical Ethics Committee (Decision No. 343, dated 24 April 2023).

2.6. Statistical Analysis

All statistical analyses were performed using SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as frequencies and percentages for categorical variables, and as means \pm standard deviation or medians (minimum–maximum) for continuous variables, as appropriate. The normality of variable distributions was assessed both visually (histograms and probability plots) and analytically (Kolmogorov–Smirnov/Shapiro–Wilk tests). Comparisons between independent groups were performed using Pearson’s chi-square test for categorical variables, and one-way ANOVA or Student’s t-test for continuous variables. When significant differences were detected among groups, post-hoc analyses were conducted using the Bonferroni correction. A two-tailed p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient Flow and Baseline Characteristics

A total of 25,130 patients aged ≥ 18 years underwent esophagogastroduodenoscopy (EGD) between January 2013 and December 2021. Gastric intestinal metaplasia (GIM) was histologically diagnosed in 3,368 patients (13.4%). Among these, 1,791 patients met the inclusion criteria for follow-up analysis, defined as having at least 12 months between the index and control EGD with biopsy. Of these, 337 patients were excluded due to a diagnosis of autoimmune gastritis. Consequently, 1,454

patients were included in the study. Among them, 352 patients belonged to the high-risk GIM group, while 1102 were classified as low-risk GIM.

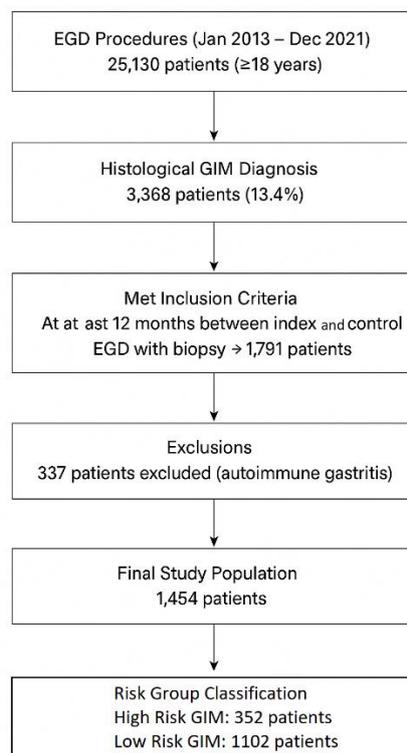


Figure 1. Flowchart of study population.

The median age of the study cohort was 57 years (range: 18–91), and 56.9% were female. Limited GIM, defined as GIM confined to the antrum and incisura, was present in 87.6% of patients, whereas 12.4% had anatomically extensive GIM involving the corpus. *Helicobacter pylori* infection was detected in 23.9% of patients at baseline. Additional risk factors included a family history of gastric cancer in a first-degree relative (22.3%) and residence in a region of Türkiye endemic for gastric cancer (11.6%).

3.2. Follow-up Outcomes of GIM Patients

The mean follow-up period of patients followed with GIM was 38.5 ± 26.5 months. Among 1,454 patients, 47.2% ($n = 687$) had no detectable GIM at the end of follow-up, 49.2% ($n = 716$) showed no change, and 3.5% ($n = 51$) demonstrated disease progression.

Among the 51 patients with documented progression, the most common pathological outcome was adenocarcinoma (41.3%, $n = 21$), followed by neuroendocrine tumor (NET) (31.4%, $n = 16$), dysplasia (19.6%, $n = 10$), gastrointestinal stromal tumor (GIST) (5.8%, $n = 3$), and lymphoma (1.9%, $n = 1$).

Regarding survival status, 99.0% ($n = 1,440$) of patients were alive at the last follow-up, while 1.0% ($n = 14$) had died.

Table 1. Outcomes and Survival Status of Patients Followed with GIM.

Category	Variable	n	%
Follow-up Outcome (n = 1454)	Not detected	687	47.2
	Unchanged (Intestinal Metaplasia)	716	49.2
	Progressed	51	3.5
Pathology Results in Progressed Cases (n = 51)	Adenocarcinoma	21	41.3
	NET (Neuroendocrine Tumor)	16	31.4
	Dysplasia	10	19.6
	GIST (Gastrointestinal Stromal Tumor)	3	5.8
	Lymphoma	1	1.9
Survival Status (n = 1454)	Alive	1440	99.0
	Deceased	14	1.0

Note: Percentages are reported as column percentages.

Table 2 summarizes the distribution of follow-up outcomes according to clinical and pathological factors in 1,454 patients with GIM. Statistically significant associations were observed between follow-up status and age, sex, presence of enterochromaffin-like cell (ECL) hyperplasia, and *Helicobacter pylori* infection status (all $p < 0.05$). Disease progression was significantly more frequent older age, among males, those with ECL hyperplasia, and those without *H. pylori* infection.

Table 2. Factors Associated with Follow-up Outcomes in Patients with GIM (n = 1454).

Variable	Category	Not Detected n (%) / Mean ± SD	Unchanged n (%) / Mean ± SD	Progressed n (%) / Mean ± SD	p
Gender	Female	427 (51.6)	375 (45.3)	26 (3.1)	0.001
	Male	260 (41.5)	341 (54.5)	25 (4.0)	
Location of Involvement	Antrum	632 (49.6)	600 (47.1)	41 (3.2)	0.023
	Antrum + Corpus	55 (30.4)	116 (64.1)	10 (5.5)	
ECL Hyperplasia	Present	28 (34.1)	49 (59.8)	5 (6.1)	0.034
	Absent	659 (48.0)	667 (48.6)	46 (3.4)	
H. pylori Presence	Present	180 (51.9)	161 (46.4)	6 (1.7)	0.031
	Absent	507 (45.8)	555 (50.1)	45 (4.1)	
Age (years)	—	55.2 ± 12.4	58.1 ± 11.0	57.0 ± 11.8	0.001
Follow-up Duration (months)	—	39.1 ± 26.1	38.2 ± 27.5	32.2 ± 26.6	0.199

A significant association was found between follow-up outcome and survival in patients with IM ($p = 0.001$). Mortality was significantly higher in patients who showed disease progression during follow-up (9.8%) compared to those with unchanged or no detectable IM (0.4% and 0.9%, respectively).

Among 262 patients diagnosed with adenocarcinoma, 83.2% had adenocarcinoma detected at the initial EGD. Prior IM diagnosis was noted in 8.1% of these patients before progression to adenocarcinoma, while 8.7% had no premalignant or malignant lesions identified in previous endoscopies.

The progression rate from IM to adenocarcinoma in this study was calculated as 0.01%.

Table 3. Survival Outcomes by Follow-up Status and Initial EGD Findings in Patients with GIM.

Variable	Category	Alive n (%)	Deceased n (%)	p-value
Survival by Follow-up Status (n=1454)	Not Detected	681 (99.1)	6 (0.9)	0.001
	Unchanged	713 (99.6)	3 (0.4)	
	Progressed	46 (90.2)	5 (9.8)	
Initial EGD Findings in Adenocarcinoma Patients (n=262)	Adenocarcinoma	—	218 (83.2)	—
	Intestinal Metaplasia	—	21 (8.1)	—
	No Premalignant/Malignant Lesion	—	23 (8.7)	—

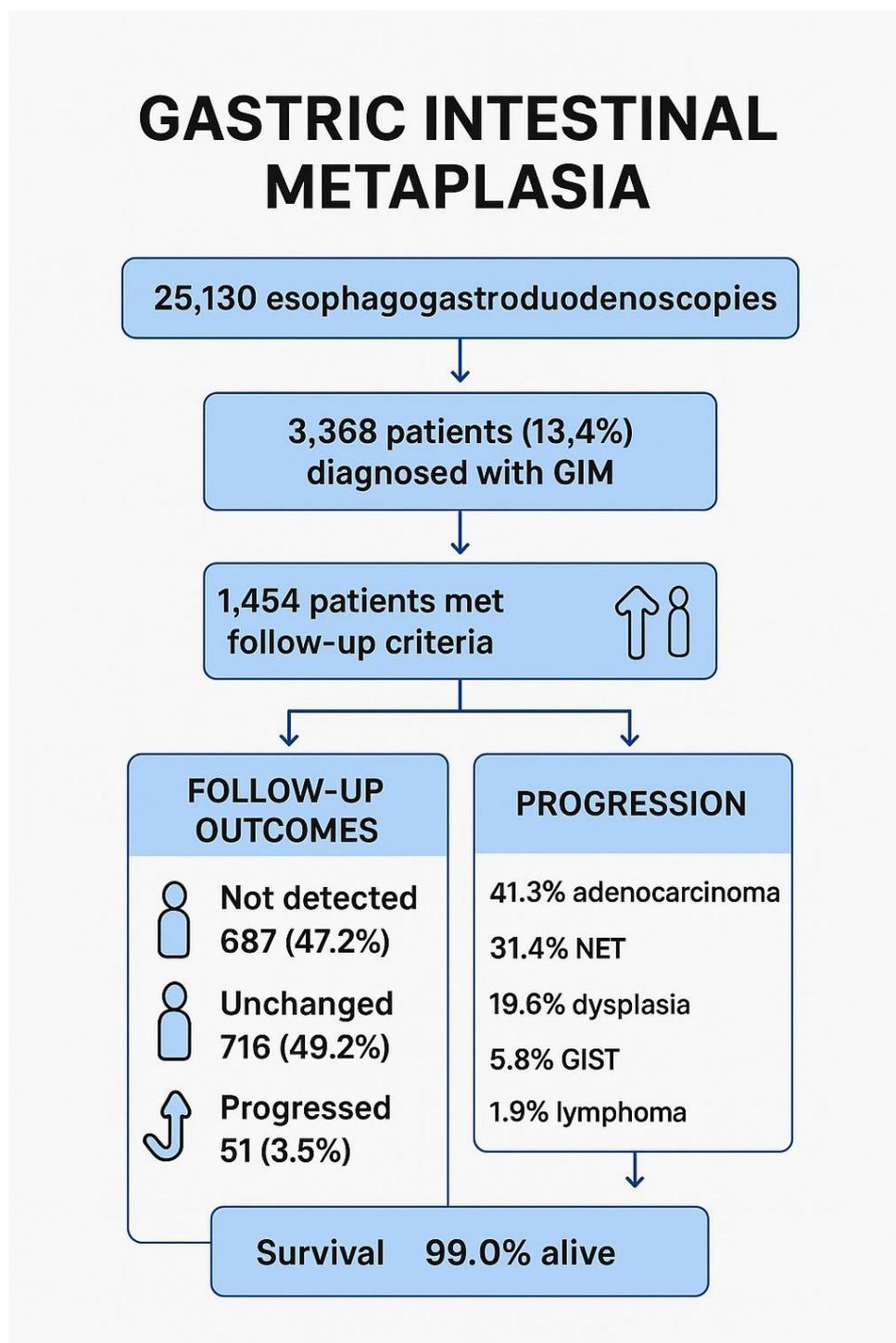


Figure 2. Follow-up outcomes and progression patterns in patients with gastric intestinal metaplasia.

3.3. Disease Progression and Survival Outcomes by Risk Group

Among 1,454 patients categorized into high- and low-risk groups, no significant association was found between risk level and disease progression ($p = 0.160$). Progression rates were 3.6% in the high-risk group and 3.4% in the low-risk group (Table 4).

Table 4. Progression outcomes of GIM risk groups.

Risk Group	Regressed	Unchanged	Progressed	Total
High	162 (46.1%)	177 (50.3%)	13 (3.6%)	352
Low	525 (47.6%)	539 (48.9%)	38 (3.4%)	1102
Total	687 (47.2%)	716 (49.2%)	51 (3.5%)	1454

Among the 51 patients who exhibited disease progression during follow-up, the distribution of pathological diagnoses was assessed according to risk group. In both the high-risk (n = 13) and low-risk (n = 38) groups, **adenocarcinoma** was the most common diagnosis (38.4% vs. 42.1%), followed by **neuroendocrine tumors (NET)** (30.7% vs. 31.6%) and **dysplasia** (23.1% vs. 18.4%). Less frequent diagnoses included gastrointestinal stromal tumor (GIST) and lymphoma.

Statistical analysis revealed **no significant difference** in the distribution of pathological diagnoses between high- and low-risk groups ($p = 0.901$), indicating that risk classification was not associated with a specific pathological outcome among patients who progressed (Table 5).

Table 5. Pathological outcome outcomes of GIM risk groups.

Pathology Diagnosis	Total n (%)	High Risk n (%)	Low Risk n (%)
Adenocarcinoma	21 (41.3%)	5 (38.4%)	16 (42.1%)
NET (Neuroendocrine Tumor)	16 (31.4%)	4 (30.7%)	12 (31.6%)
Dysplasia	10 (19.6%)	3 (23.1%)	7 (18.4%)
GIST (Gastrointestinal Stromal Tumor)	3 (5.8%)	1 (7.7%)	2 (5.3%)
Lymphoma	1 (1.9%)	0 (0%)	1 (2.6%)
Total	51 (100%)	13 (100%)	38 (100%)

Survival analysis showed no statistically significant difference between high- and low-risk groups ($p = 0.850$). Mortality rates were low in both groups, with 0.8% in the high-risk and 1.0% in the low-risk groups.

Table 6. Survival outcomes of GIM risk groups.

Risk Group	Alive	Deceased	Total
High	349 (99.2%)	3 (0.8%)	352
Low	1091 (99.0%)	11 (1.0%)	1102
Total	1440 (99.1%)	14 (0.9%)	1117

4. Discussion

The prevalence of IM in a given population is largely influenced by the rate of *H. pylori* infection. A Northern European study reported an IM prevalence of 19% [10]. In our cohort of 25,130 individuals undergoing EGD, IM was detected in 13.4%, a figure consistent with a study from Van, Turkey (2010–2014), which reported a prevalence of 13.8% among 4,050 patients. Determining the true prevalence remains challenging due to the asymptomatic nature of IM [11].

In large-scale cohort studies, such as those from the Netherlands (1991–2004), the annual progression rate of IM to adenocarcinoma ranged from 0.1% to 0.9% [12]. Our study demonstrated a markedly lower progression rate of 0.01%.

Gender differences play a role in gastric cancer pathogenesis. Data from the United States indicate that men are more likely to develop proximal gastric cancer [13], and global age-standardized rates are approximately twice as high in men as in women (12.8% vs. 5.7%) [14]. In the

United Kingdom, the male-to-female ratio declines after age 50–55, likely due to reduced protective hormonal effects in postmenopausal women [15]. Long-term estrogen exposure has been associated with a lower gastric cancer risk [16]. In line with previous studies, we observed higher malignant progression rates in men with IM (4%) compared to women (3.1%).

H. pylori infection, a key initiator in the Correa cascade, affects an estimated 4.4 billion people worldwide [17]. In the United Kingdom, 32% of gastric cancers are attributable to *H. pylori* [18]. The World Health Organization (WHO) classifies *H. pylori* as a class I carcinogen [19,20]. However, in advanced gastritis and IM, mucosal changes may render the gastric environment inhospitable to *H. pylori*, leading to spontaneous bacterial clearance [21]. In our study, *H. pylori* was detected in 23.9% of IM patients, and progression was more common in *H. pylori*-negative individuals (4.1%) compared to *H. pylori*-positive individuals (1.7%). Whether this reflects prior eradication therapy could not be determined.

Histologically, IM can be classified into three subtypes (Types 1–3) according to mucin staining [22–24], with incomplete Type 3 IM showing the strongest association with gastric cancer [25,26]. Due to technical challenges and the use of toxic reagents, such staining is now largely restricted to research settings [27], and our study did not perform histologic subtyping.

ECL cell hyperplasia, often associated with autoimmune gastritis, was present in 5.6% of our IM patients. Progression occurred in 6.1% of these cases compared to 3.4% without ECL hyperplasia, though no adenocarcinoma developed in the hyperplasia group. The lack of statistical association between ECL hyperplasia and adenocarcinoma aligns with its stronger link to type I neuroendocrine tumors [28–33].

Anatomically, IM is categorized as limited (antrum or incisura only) or extensive (involving corpus and additional sites) [34–37]. Prior studies suggest that extent of involvement may be more prognostically relevant than histological subtype [38]. In our series, progression rates were highest for extensive involvement (5.5%), followed by limited antrum involvement only (3.2%). Adenocarcinoma was significantly more common in cases involving the corpus or both corpus and antrum ($p < 0.05$).

Globally, there is no uniform consensus on IM surveillance. High-incidence countries such as Japan and South Korea recommend population-based endoscopic screening, with national programs in place since the early 2000s [39,40]. In low-incidence European countries, the European Society of Gastrointestinal Endoscopy (ESGE) advises three-year follow-up for patients with IM in both antrum and corpus, but no surveillance for antrum-only disease [41].

According to the latest ACG guidelines, patients with intestinal metaplasia (IM) are categorized into two groups for surveillance: high-risk and low-risk [3]. The high-risk group includes patients with extensive involvement, those with a first-degree relative with gastric cancer, and individuals from regions endemic for gastric cancer. In our study, patients were similarly evaluated in two groups. Patients born in Eastern Anatolia, a gastric cancer endemic region in our country, were included in the high-risk group [9]. However, when comparisons were made, no significant differences were observed between the low- and high-risk groups in terms of progression, malignant transformation, or survival outcomes. The lack of significant differences may be explained by the heterogeneous distribution of risk factors. Individual risk profiles, influenced by factors such as birth in endemic regions, family history of gastric cancer, and extent of intestinal metaplasia, could have masked potential differences between the groups.

Several limitations should be acknowledged. First, this study was retrospective, which may introduce selection and information biases. Second, histological subtyping of IM (Types 1–3) was not performed, limiting the assessment of subtype-specific risk. Third, prior *H. pylori* eradication history was unknown in a subset of patients, which may have influenced the observed association between *H. pylori* status and progression. Fourth, although follow-up data were comprehensive, the relatively low number of progression events limits the statistical power for certain subgroup analyses. Finally, as a single-country study, our findings may not be generalizable to populations with different *H. pylori* prevalence, genetic backgrounds, or gastric cancer incidence.

5. Conclusions

In our large cohort study, intestinal metaplasia was detected in 13.4% of patients undergoing esophagogastroduodenoscopy, with an overall very low progression rate to adenocarcinoma (0.01%). Male sex and extensive gastric involvement were associated with higher progression rates. *H. pylori* infection, while important in the pathogenesis of gastric carcinogenesis, was not predictive of malignant transformation in our cohort, possibly due to prior eradication therapy or spontaneous clearance in advanced lesions. Our findings also suggest that heterogeneous risk profiles, including birth in gastric cancer endemic regions, family history, and extent of IM, may obscure clear stratification between high- and low-risk groups. These results support the need for individualized surveillance strategies based on anatomical extent of IM and patient-specific risk factors rather than *H. pylori* status alone. Routine surveillance of patients with intestinal metaplasia limited to the antrum appears to provide minimal clinical benefit while imposing unnecessary procedural burden and healthcare costs.

Author Contributions: Conceptualization, V.B.T. and A.K.; methodology, V.B.T., A.K., and A.A.; validation, M.C., T.K., and M.K.; formal analysis, V.B.T. and A.K.; investigation, V.B.T., A.K., A.A., H.C.A., and S.D.; resources, M.C., T.K., and M.K.; data curation, V.B.T., A.K., and A.A.; writing—original draft preparation, V.B.T.; writing—review and editing, V.B.T., A.K., A.A., H.C.A., S.D., M.C., T.K., M.K., S.H., E.Ö., and M.A.I.; visualization, V.B.T.; supervision, M.C., T.K., and M.K.; project administration, V.B.T. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Gazi University Faculty of Medicine Medical Ethics Committee (Decision No. 343, dated 24 April 2023).

Informed Consent Statement: Patient consent was waived due to the retrospective design of the study and anonymization of all data.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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