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Retrospective Study

Gastric Intestinal Metaplasia Development In African American Predominant United States Population

Ahmad A *et al.* Gastric Intestinal Metaplasia In the US

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Abstract

BACKGROUND

Gastric cancer significantly contributes to cancer mortality globally. Gastric intestinal metaplasia (GIM) is a stage in the Correa cascade and a premalignant lesion of gastric cancer. The natural history of GIM formation and progression over time is not fully understood. Currently, no clear guidelines on GIM surveillance or management in the United States.

AIM

We designed this study to investigate factors associated with GIM development over time in African American-predominant study population.

METHODS

This is a retrospective longitudinal study in a single tertiary hospital in Washington DC. We retrieved upper esophagogastroduodenoscopies (EGDs) with gastric biopsies from the pathology department database from January 2015 to December 2020. Patients included in the study had undergone two or more EGDs with gastric biopsy. Patients with no GIM at baseline were followed up until they developed GIM or until the last available EGD. Exclusion criteria consisted of patients age <18, pregnancy, previous diagnosis of gastric cancer, and missing data including pathology results or endoscopy reports. The study population was divided into two groups based on GIM status. Univariate and multivariate Cox regression was used to estimate the hazard induced by patient demographics, EGD findings, and *Helicobacter pylori* (*H. pylori*) status on the GIM status.

RESULTS

Of 2375 patients who had at least 1 EGD with gastric biopsy, 579 patients were included in the study. 138 patients developed GIM during the study follow-up period of 1087 days on average, compared to 857 days in patients without GIM($P = 0.247$). The

average age of GIM group was 64 years compared to 56 years in the non-GIM group ($P < 0.001$). In the GIM group, adding one year to the age increases the risk for GIM formation by 4% ($P < 0.001$). Over time, African Americans, Hispanic, and other ethnicities/races had an increased risk of GIM compared to Caucasians with an HR of 2.12 (1.16, 3.87), 2.79 (1.09, 7.13), and 3.19 (1.5, 6.76) respectively. No gender difference was observed between the study populations. Gastritis was associated with an increased risk for GIM development with an HR of 1.62 (1.07, 2.44). On the other hand, *H. pylori* infection did not increase the risk for GIM.

CONCLUSION

An increase in age and non-Caucasian race/ethnicity are associated with an increased risk of GIM formation. The effect of *H. pylori* on GIM is limited in low prevalence areas.

Key Words: Gastric intestinal metaplasia; Gastric cancer; *Helicobacter pylori*; Retrospective longitudinal study; Esophagogastroduodenoscopy; African American population

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Core Tip: Gastric intestinal metaplasia is a precancerous lesion, and previous literature showed a higher rate in the United States minorities. Our study highlighted the natural history of gastric intestinal metaplasia over time. It was observed in the study that irrespective of being minorities, Non-Caucasian races/ethnicities have a higher risk for gastric intestinal metaplasia. Gastritis and older age contribute to Gastric intestinal

metaplasia formation. The effect of *H. pylori* infection was not significant in our population.

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INTRODUCTION

Gastric cancer is the fifth most common cancer and the third leading cause of cancer mortality worldwide^[1,2]. Non-cardiac intestinal-type gastric adenocarcinoma represents the majority of cases in the United States (US)^[2]. In 2018, over 26,000 new cases of gastric cancer were reported with 10,600 deaths in the US^[3]; in 2020, more than 700,000 deaths were reported globally^[4]. The high mortality rate of gastric cancer is mostly attributed to the late presentation of the disease. In areas with a high incidence of gastric cancer, the mortality-incidence ratio is decreased by screening programs^[1], while in areas with low incidence, surveillance programs for gastric premalignant lesions in high-risk individuals are likely an optimal screening strategy based on risk stratification.

The Correa cascade proposed that intestinal-type gastric adenocarcinoma is formed from normal gastric mucosa that progresses through a series of transition stages: chronic gastritis, atrophic gastritis, gastric intestinal metaplasia (GIM), and dysplasia, which can progress to gastric adenocarcinoma^[5,6]. The latter three histopathological findings are considered as gastric premalignant lesions. GIM is defined as the replacement of normal gastric epithelium with intestinal epithelium consisting of Paneth, goblet, and absorptive cells^[7]. The replacement happens under chronic stressors like inflammation. The prevalence of GIM in the general US population is estimated to be 5-8%^[7] with an 0.13%–0.25%^[6,7] estimated annual risk of progression into gastric cancer and a median time to progression of around 6 years^[6].

Currently, GIM is more recognized as a best pre-malignant stage for surveillance because identifying and treating these lesions can potentially prevent further progression to gastric cancer^[2,5]. Multiple international guidelines recommend surveillance for gastric pre-malignant lesions including GIM^[8,9]; on the contrary, the American Gastroenterology Association recommends against such screening guidelines

for GIM with some exceptions^[2]. Multiple risk factors have been identified to help guide surveillance including smoking, alcohol use, ethnicity, family history of gastric cancer, and genetic factors^[10]. However, long-term effect of surveillance is not well understood in countries with a low incidence of gastric cancer due to the limitation of the available studies. Furthermore, the lack of clear guidelines for GIM medical management after diagnosis has added to the challenge^[2]. Thus, we designed this retrospective longitudinal study to investigate potential risk factors involved in GIM formation from normal mucosa in an African American predominant US population.

MATERIALS AND METHODS

Study design: This is a retrospective longitudinal study conducted at Medstar Washington Hospital Center. The study was reviewed and approved by the Medstar Health Research Institute and Georgetown University Hospital Institutional Review Board.

Study population: Patients with GIM were identified from the Pathology Department's database at Medstar Washington Hospital Center. Patients included in the study had undergone two or more esophagogastroduodenoscopy (EGD)s with gastric biopsy, with at least one EGD performed between January 2015 to December 2020. Exclusion criteria consisted of patients age <18, pregnancy, previous diagnosis of gastric cancer, and missing data including pathology results or endoscopy reports. Patients with a baseline of no GIM were followed up longitudinally. The follow-up period ended at the event occurrence (GIM formation) or the last follow-up EGD. Based on the GIM status from the gastric biopsy at the end of the follow-up period, the study population was divided into two groups – GIM group and non-GIM group. Patients were excluded from the study if they were younger than 18 years old.

Data Collection: Electronic medical records were reviewed to collect and analyze the following patient information: demographics, medication use, EGDs findings, *Helicobacter pylori* (*H. pylori*) status, gastric biopsy reports, and laboratory findings. Patients' *H. pylori* statuses were exclusively based on biopsy testing.

Data analysis: To present the data, we used frequency with percentage for categorical variables and median with first and third quartile (IQR) for non-normal continuous variables. The D'Agostino-Pearson test was used to test normality. Chi-square test with Yate's correction or Kruskal-Wallis rank-sum test were performed to compare the difference between the groups. Kaplan-Meier estimators were calculated, and the curves were plotted to show the probability of GIM at a respective time interval after the baseline. To detect the differences in survival, we used Peto-Peto's weighted Log-rank test. Univariate and multivariate Cox proportional hazards regression model was performed to investigate how the predictors were associated with the risk of GIM over time. All unadjusted and adjusted hazard ratios with 95 percent confidence intervals were presented, along with the unadjusted *P* values. Statistical significance was set at a *P* value less than 0.05 and all statistical analyses were conducted with R software. The statistical methods of this study were reviewed by Jiling Chou from MedStar Health Research institute.

RESULTS

Overall Data summary

Of 2,375 patients who had at least 1 EGD with gastric biopsy during 2015 to 2020, 579 patients met our inclusion criteria. A total of 138 (23.8%) patients developed GIM during the follow-up period of 1087 days on average, compared to 857 days in patients without GIM (*P* = 0.247). The GIM group was older with an average age of 64 years compared to 56 years in the non-GIM group (*P* <0.001). Female patients represented 60.7% (351 patients) of the total study population and there was not a significant difference between study groups (*P* = 0.208). Ethnicity was significantly different between the study groups (*P* = 0.032): African American, Caucasian, Hispanic and other ethnicities/races represented 72.9% (94 patients), 9.3% (12 patients), 5.4% (7 patients), and 12.4% (16 patients) of the GIM group respectively, compared to 71% (287 patients), 18.1% (73 patients), 2.7% (11 patients), and 8.2% (33 patients) in the non-GIM group respectively (Table 1).

Regarding medication use, higher percentage of the GIM group (44 patients (31.9%)) was using 81 mg of aspirin on follow up, compared to 82 patients (18.6%) in the non-GIM group ($P = 0.001$). Lower percentage of the GIM group (31 patients (22.5 %)) was using proton pump inhibitors (PPI) at baseline compared to 156 patients (35.4%) in the non-GIM group ($P = 0.006$). However, aspirin use at baseline, and PPI use on follow up was not significantly different between study groups.

On follow-up EGDs, gastritis was observed more in the GIM group (109 patients (79.0 %)) compared to 261 patients (59.2%) with gastritis in the non-GIM group ($P < 0.001$) (Table 1).

H. pylori was positive in the baseline biopsies of 80 patients (13.2%), compared to those of 43 patients (7.4 %) on follow up. Of this *H. pylori* positive group, 15 patients had positive *H. pylori* at both the baseline and follow up, but this persistent *H. pylori* infection was not different between the two study groups. A detailed summary of the data is presented in Table 1.

Risk of GIM over time

In a group of patients with no GIM at baseline, adding one year in age increases the risk of GIM by 4% over time with P value < 0.001 . In comparison to the age group of 45 years or younger, patients have a hazard ratio (HR) of 2.13 ($P = 0.028$), 2.09 ($P = 0.029$), and 4.03 ($p < 0.001$) for age groups 46-55, 56-64, and ≥ 65 years respectively. Over time, African American, Hispanic, and other ethnicities/races had an increased risk of GIM compared to Caucasians with an HR of 2.12 (1.16, 3.87), 2.79 (1.09, 7.13), and 3.19 (1.5, 6.76) respectively. Gastritis on follow up biopsy was associated with a higher risk of GIM with an HR of 1.62 (1.07, 2.44) ($P = 0.022$), while 81 mg aspirin use increased the risk of GIM by 49% ($P = 0.031$). Obesity at baseline had a 42% less risk of GIM ($p = 0.010$). Using the *H. pylori*-negative group at baseline and follow up as a reference group, *H. pylori* infection at baseline or follow up, as well as the persistence of *H. pylori* infection did not have significant effects on GIM risk over time. Subgroup analysis of patients with *H. pylori* present at baseline shows no major difference from the main study analysis (Table 2).

On multivariate Cox regression analysis, the age ≥ 65 group were continuously associated with a higher risk of GIM with an HR of 3.01 ($P = 0.014$). African Americans and other ethnicities have a higher risk of GIM with an HR of 3.4 ($P = 0.026$) and 7.46 ($P = 0.001$) when compared to Caucasians respectively. Hispanic, other age groups, gastritis, *H. pylori* status, and smoking status did not reach the level of statistical significance on multivariate analysis (Table 3).

We calculated the Kaplan-Meier survival estimate for GIM development over 12 years. The population at risk is limited by the available follow-up EGD and censored observations. At the 12 years follow-up, 26 patients were at GIM risk (Figure 1). Close to 50% of the population at risk developed GIM during 12 years of follow-up. A 12 years survival Curve was done to present the survival probability of developing GIM based on ethnicity, age groups, and gastritis status (Figure 2-4). We observed a significant difference in the GIM development over 12 years based on gastritis status ($P = 0.023$), age group ($P < .0001$), and ethnicity ($P = 0.023$).

DISCUSSION

GIM is a recognized gastric pre-malignant lesion with an increased risk for developing gastric cancer. The risk factors for GIM formation and evolution are significant clinical interest thus currently under active investigations, since these factors will likely help design optimal surveillance programs and management of GIM after diagnosis. Our study showed that the GIM group was older compared to the non-GIM group (table 1). In multiple studies including ours, more advanced age was associated with an increased risk of GIM formation, progression, and gastric cancer development, which could be attributable to prolonged exposure of gastric mucosa to the mutagenic factors and inflammation [14,11]. The average age at GIM diagnosis in low gastric cancer incident countries was 60 to 67 years, comparable to the average age of 64 in our GIM group (table 1) [11,12]. A one-year increase in age was associated with a 4% increase in GIM risk in our population. Age groups of 45-54, 55-64, and >65 were associated with an increased risk for GIM development compared to the <45 age group (table 2). The

age group >65 had the highest HR, and it was the only age group associated with increased risk of GIM formation on multivariate analysis (table 3). However, a study in China found that age > 45 is associated with GIM progression^[13]. After five years of follow-up, around 50% of patients in group >65 develop GIM, compared to 10% in <45 age group (figure 3). These results suggest that age close to 65 may be a good threshold for screening for GIM.

Although gastric cancer is known to be more common in males^[14], GIM has equally affected both genders in our study and others^[14]. In contrast, a cohort study in Puerto Rico showed a greater percentage of females affected by GIM compared to males^[12], and in a Thai population, the male sex was a risk factor for GIM development^[11]. The influence of gender on GIM development might be significant, but our study might have failed to detect it due to the small sample size. Alternatively, gender might have an isolated effect on GIM progression to gastric cancer rather than GIM development.

Non-cardia gastric cancer has a higher incident rate in certain US race/ethnicity minorities including, African Americans, Hispanics, and Asians^[15]. Previous studies on the US population have shown that ethnicity is a risk factor for GIM formation, independent of age or *H. pylori* status^[16-18]. Non-Hispanic whites have the lowest risk of GIM in comparison to other races/ethnicities. Hispanics, followed by African Americans, carries the highest risk for GIM compared to non-Hispanic whites, which is consistent with other studies^[16-18]. Our study also showed African American, Hispanic, and other ethnicities/races had an increased risk of GIM compared to Caucasians (table 2). However, the Hispanic population did not reach the statistical significance level on multivariate analysis, likely due to the small size of Hispanic population in our study (table 3). The Asian population is also thought to have a higher risk of GIM, but this population is generally less investigated in US literature due to small number of Asians in US. Asian and different groups of ethnic and racial minorities were combined as the other ethnic/racial group in our study, this group carried the highest HR when compared to Caucasians. After 5 years of follow-up, close to 25% and 50% of the population were at risk to develop GIM in Caucasians and other ethnic/racial groups

(Figure 2). Our study is notable that African Americans represent the majority of our study population and carry a higher risk for GIM.

Currently, the American Gastroenterology Association (AGA) recommends surveillance for ethnic/racial minorities only on a conditional basis^[2]. Place of birth, rather than ethnicity, was shown to be a risk factor for GIM in one study, where only Hispanics born outside the US carry a higher risk for GIM compared to Hispanics born in the US regardless of *H. pylori* status^[19]. The effect of place of birth and race on GIM needs further investigation, as it might be a potential factor that affects surveillance.

The impact of *H. pylori* infection on GIM formation and progression was extensively investigated, but the results in the literature were often conflicting thus suggest complex role of *H. pylori* in GIM and gastric cancer. *H. pylori* infection is thought to affect development and progression of GIM^[20], but few studies have shown either formation or progression but not both^[17]. Ethnicity, genetic makeup, and *H. pylori* virulence factors are additional factors which can further influence the effect of *H. pylori* on GIM^[10,18,21]. However, in the present study, no clear effect of *H. pylori* on GIM development was found as shown in other studies^[4,19,22]. In our study population, only 13.8% patients had *H. pylori* infection, which is lower than the reported average *H. pylori* infection in the US and patients with positive *H. pylori* infection at baseline biopsy, follow up biopsy, or both seem to have the same risk of developing GIM, not different from those who tested negative for *H. pylori*. However, given the known strong association between *H. pylori* and gastric cancer, we agree with the AGA recommendation for testing and treating *H. pylori* and confirming its eradication, especially if positive in GIM, even though our results did not show a direct effect of *H. pylori* on GIM formation.

Chronic gastritis is part of the Correa cascade, and it precedes GIM development. The long-term effect of *H. pylori*-negative chronic gastritis and its role in the development of GIM have been poorly studied. A prospective study in Thailand investigated 400 patients with chronic gastritis and showed that chronic gastritis is associated with an increased risk for progression regardless of *H. pylori* status^[4]. Our study showed that

gastritis is associated with GIM formation over time. The gastric inflammation, rather than the *H. pylori* infection itself, might be driving GIM formation. On the 12 years survival curve, a significant difference in GIM formation is shown between the group with and without gastritis, noticeable as early as 1 year (Figure 4). Thus, an early recognition and treatment of gastritis can impact GIM formation and possibly prevent GIM thus reduce gastric cancer risk.

The study is limited by its retrospective nature. All the patients in the study are from a single tertiary center in Washington, DC. The standard evaluation of GIM in our pathology lab does not involve further grading or classification, which added to the study's limitation. In spite of retrospective nature of the study, the strength of our study is its unique study design and distinct study population to assess the longitudinal data over time between upper endoscopies in a single academic center with predominantly African American population, which has not been adequately investigated in other studies. It is also notable that this study population has a low prevalence of *H. pylori*, thus allowing us to examine other risk factors involved in the development of GIM aside from *H. pylori* infection. Our limitations include the retrospective nature of the study and our population selected from one tertiary center as well as a low number of Asians in our study population who were included as the other ethnic/racial category in our study, thus limiting comparisons with other published studies from Asia.

CONCLUSION

In conclusion, our study demonstrates that race is an important risk factor for GIM and ethnic/racial minorities in the US carry a higher risk of GIM compared to Caucasians. Older age, especially age group >65, was associated with higher GIM risk. Gastritis rather than *H. pylori* infection is also associated with GIM formation in our low *H. pylori* prevalent patient population. These risk factors identified in our study will serve as important components in developing risk stratification models for optimal surveillance programs for GIM and gastric cancer.

ARTICLE HIGHLIGHTS

Research background

Gastric intestinal metaplasia (GIM) is a form of gastric pre-malignant lesions. It falls on the spectrum of Correa cascade. The cascade includes Chronic gastritis, atrophic gastritis, GIM, and dysplasia.

Research motivation

We designed this study to investigate factors leading to GIM formation. There is a lack of literature about this topic in the United States, especially among ethnic minorities, which are considered high-risk populations.

Research objectives

We aimed to identify factors that increase GIM formation in high-risk populations. These factors would help guide the future surveillance of selected patients and possibly suggest treatment modalities.

Research methods

This is a retrospective longitudinal study in a tertiary hospital in Washington, DC. The study includes patients with at least two upper endoscopies with gastric biopsies to assess the evolution of GIM over time. A Cox regression model was built to investigate the significant factors over the study time.

Research results

Our study confirms that Ethnicity-Race minorities have a higher rate of GIM formation. We found that gastritis increases GIM formation over time. H pylori in low-prevalence areas might not be a strong risk factor. Our results emphasize on future surveillance of minorities and management of gastritis as a way to reduce the burden of gastric cancer.

Research conclusions

In conclusion, our study suggests that older age, having gastritis, or being from ethnic-race minorities is associated with an increased risk of GIM.

Research perspectives

Further Studies are needed to clarify factors associated with GIM progression and regression. This would help form a complete picture of the development and progression of gastric pre-malignant lesions.

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PRIMARY SOURCES

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Adnan Malik, Khadija Naseem, Waseem Amjad, Mahum Nadeem, Yousaf Hadi, Sardar M. Shah-Khan, Shyam Thakkar, Shailendra Singh. "Sa1138: STATIN USE AND RISK OF GASTROESOPHAGEAL CANCERS: A SYSTEMATIC REVIEW AND META-ANALYSIS", Gastroenterology, 2022

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