Original research

Novel insights into autoimmune gastritis: clinical profile and gastric neoplastic risk from an international multicentre study

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ABSTRACT

Background International comparative data on autoimmune gastritis (AIG) remain limited.

Objective We aimed to describe AIG features and quantify the risk of gastric adenocarcinoma and type 1 gastric neuroendocrine tumours (NETs).

Design Retrospective study across eight tertiary centres in Europe, Türkiye, Latin America, the USA and Japan. Adults with histologically confirmed AIG were included. Clinical and follow-up data were collected to estimate adenocarcinoma and NET incidence and associated factors.

Results 1240 patients were included (female:male 2:1; median age 59, IQR 48–67; median follow-up 68 months, IQR 36–108). Macrocytic anaemia predominated in Europe (45.6%), microcytic anaemia in Türkiye (56.1%) and Latin America (64.7%). Autoimmune comorbidities were most frequent in Latin America (67.7%). 36 (2.9%) gastric adenocarcinomas and 132 (10.6%) NETs occurred. No incident adenocarcinomas were reported in Latin America or Japan cohorts. Crude incidence rates ranged from 1.15 to 1.47 for adenocarcinoma and 0.70 to 1.62/100 person-years for NETs. Factors associated with adenocarcinoma included age >65 years (OR 4.50, 95% CI 2.18 to 9.27), intestinal metaplasia (OR 1.51, 95% CI 1.16 to 1.97), gastrin-17 >1316 pg/mL (OR 15.52, 95% CI 3.61 to 66.71) and prior proton pump inhibitor (PPI) (OR 5.74, 95% CI 2.13 to 15.47). For NETs, prior PPI (OR 2.69, 95% CI 1.12 to 6.46), smoking (OR 2.45, 95% CI 1.75 to 3.42), intestinal metaplasia (OR 2.88, 95% CI 1.38 to 6.01) and gastrin-17 >1316 pg/mL (OR 3.25, 95% CI 1.42 to 7.45), were associated with higher odds, while *Helicobacter pylori* eradication was associated with lower odds of NETs (OR 0.25, 95% CI 0.07 to 0.88).

Conclusion AIG presentation and neoplastic risks differ by region, warranting further research and potentially region-specific follow-up strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a lack of international, comparative studies assessing the clinical features and risk of developing gastric neoplasia in patients with autoimmune gastritis (AIG). This has contributed to variability in clinical practice for managing these patients.

⇒ Whether AIG carries a risk of developing gastric adenocarcinoma is still debated.

WHAT THIS STUDY ADDS

⇒ This international study found regional differences in AIG, with macrocytic anaemia predominating in Europe, microcytic anaemia in Türkiye/Latin America and previous *Helicobacter pylori* infection in Latin America.

⇒ Elevated serum gastrin-17, intestinal metaplasia and use of proton pump inhibitors were associated with both gastric adenocarcinoma and type 1 gastric neuroendocrine tumour risk.

INTRODUCTION

Autoimmune gastritis (AIG) is an organ-specific disorder leading to progressive atrophy and malabsorption of iron, vitamin B_{12} and other micronutrients.[1–5] AIG is estimated to affect approximately

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HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest regional differences in AIG presentation, comorbidities and cancer risk, underscoring the need for further research and possibly region-specific diagnostic strategies and follow-up protocols.

⇒ Identifying associated factors such as age, elevated serum gastrin-17, smoking and use of proton pump inhibitors may refine surveillance guidelines, address international discrepancies and ultimately improve early detection and patient outcomes.

3% of the global population,[6] with an increasing prevalence worldwide, possibly linked to a decrease in *Helicobacter pylori* infections, increased diagnostic endoscopy and growing awareness of the condition.

Initially recognised predominantly in Western geographical regions,[7–11] AIG has more recently been reported across all continents, involving a broad range of ethnic groups, including populations from Türkiye,[12] Asia,[13–15] Africa[16] and South America.[17] Nevertheless, there is a lack of international comparative studies assessing sociodemographic factors, clinical presentations and the risk of gastric neoplastic complications, namely type 1 gastric neuroendocrine tumours (NETs) and gastric adenocarcinoma. To illustrate the persisting uncertainty in this field, it is worth noting that the terms pernicious anaemia and AIG have frequently been used interchangeably,[18] despite pernicious anaemia representing only a small part of the clinical spectrum of AIG.[1] Additionally, while some studies have reported a certain prevalence of *H. pylori* infection in patients with AIG,[19 20] other evidence suggests that AIG may be more common in *H. pylori*-negative individuals.[21–24] Finally, two recent guidelines on the surveillance of gastric premalignant conditions, one from the USA[25] and one from the European Union (EU),[26] arrived at different recommendations, reflecting differences in methodological approaches and weighting of the low certainty of evidence. Indeed, the risk of developing gastric adenocarcinoma in AIG still remains a matter of debate.[27 28]

Building on these premises, we established a multinational collaboration to collect data from patients with AIG, with the aim of characterising their clinical features, assessing the risk of gastric neoplastic complications and identifying potential correlates.

METHODS

Inception of the study group

In 2023, we established an international panel of experts in the field of AIG. Eight enrolling centres located in Pavia (Italy), Ankara (Türkiye), Santiago (Chile), San Juan (Puerto Rico), Okayama (Japan), Magdeburg (Germany), New York (USA) and Nantes (France) were eventually included. For descriptive purposes, we grouped the centres from Italy, Germany and France together as the 'European Union' (EU) group, and the centres from Chile and Puerto Rico as the 'Latin America' group. Though settings may differ, all centres are tertiary referral academic institutions with specialised knowledge in the diagnosis and management of AIG. Of note, the centre from the USA is also a cancer referral centre. Additional experts from the USA, Latvia and Italy also participated in the study and contributed to its development, data gathering and data interpretation.

Study design, inclusion and exclusion criteria

This was a retrospective, observational study in which all participating centres retrieved data from patients with AIG who had been assessed from 2010 to January 2024 (last updated data collection in December 2025). All centres adhered to endoscopic surveillance guidelines as they became available over time, with gastroscopy performed at intervals of approximately 3–5 years,[25 26 29–31] except in Japan, where population-based screening with upper gastrointestinal endoscopy is offered to individuals aged 50 years and older.[32]

No specific protocols were applied for clinical follow-up, as this was a real-world retrospective study, and no dedicated guidelines for this exist. Inclusion criteria adhered to internationally accepted histopathological definitions of AIG.[1 2] We included only adult patients (≥18 years old) with an established histopathological diagnosis of AIG, defined by the presence of typical gastric lesions characterised by any degree of atrophy of the oxyntic mucosa with sparing of the antrum, and no concurrent *H. pylori* infection.[33] In cases of active *H. pylori* infection at diagnosis, patients were classified as having AIG only if histological lesions were confirmed at a subsequent endoscopy after *H. pylori* eradication, and there was no antral involvement of atrophy. A history of *H. pylori* infection was not considered an exclusion criterion. The presence of either anti-parietal cell antibodies (PCAs) or anti-intrinsic factor antibodies was not mandatory, since a subset of patients may be seronegative.[34] We excluded individuals where the diagnosis of AIG was uncertain or those who had atrophic pangastritis.

Variables collected

All variables were obtained from patients' electronic medical records. At each centre, a designated individual was responsible for data collection and for ensuring data quality and consistency. Before data collection began, the study coordinators (MVL and ADS) provided a brief synopsis outlining the main inclusion and exclusion criteria, along with a rubric explaining how to interpret the required variables.

We collected sociodemographic data including sex, age at AIG diagnosis, race, ethnicity, smoking, alcohol use disorder, years of education, marital status and socioeconomic status (categorised as below poverty threshold or wealthy based on the local geographical area). Participants self-identified their race and ethnicity using categories including white, black or African American, Hispanic or Latino, Asian, multiethnic or other. We recorded all potential clinical AIG manifestations at onset, such as haematological alterations, gastrointestinal symptoms, neuropsychiatric symptoms, associated autoimmune disorders and first-degree family history of AIG or gastric adenocarcinoma. Additional information included prior use of proton pump inhibitors (PPIs) for at least 3 months, diagnostic delay of AIG (in months) and any previous misdiagnoses.

Essential laboratory variables included PCA and anti-intrinsic factor antibody status, fasting serum levels of gastrin-17 (normal reference value ranging from <125 to <100 pg/mL, depending on the local kit used) and chromogranin A (normal reference value ranging from <100 to <94 ng/mL, depending on the local kit used) at onset, and history of *H. pylori* infection, as evidenced by histology, a previous positive stool antigen test, or a positive urea breath test. All gastrin-17 and chromogranin A measurements were performed after at least 1 month of PPI withdrawal, when PPIs were used. Histological findings at diagnosis were recorded, including the presence and severity of atrophy and intestinal metaplasia (irrespective of subtype, including complete, incomplete, mixed).

Finally, the occurrence of type 1 gastric NETs or gastric adenocarcinoma was recorded, distinguishing whether these events were present at the time of AIG diagnosis (ie, 'prevalent', a concurrent diagnosis of AIG and neoplastic complication) or developed during follow-up (ie, 'incident', at least 12 months later than the index gastroscopy). Therefore, type 1 gastric NETs or gastric adenocarcinomas occurring within 12 months after AIG diagnosis were considered as 'prevalent' cases in the descriptive analysis and in the Kaplan-Meier curves. Data regarding the site, size, staging, histopathology and treatment of both gastric adenocarcinoma and type 1 gastric NETs were retrieved. The total duration of follow-up (from diagnosis to last assessment) and the time to NET or adenocarcinoma were also documented.

Study endpoints

The primary endpoint was to describe the sociodemographic, clinical and laboratory characteristics of patients with AIG and compare these features across different countries or geographical areas. The secondary endpoints were the incidence and prevalence of gastric adenocarcinoma and NETs, and to identify factors associated with risk of these neoplastic lesions.

Statistical analysis

All data were pseudo-anonymised and stored in a certified electronic database (REDCap (Research Electronic Data Capture)). The sample size was established according to both feasibility and the anticipated precision of the estimated 5-year incidence of oncological complications. For instance, with 600 patients and an expected cumulative neoplastic incidence of 5%, the precision, defined as half the 95% CI, would be ±1.8%. Continuous variables were summarised using the median and IQR, while categorical variables were reported as counts and percentages. In all tables, percentages were calculated by excluding cases with missing data to accurately represent the available dataset, resulting in totals of 100% for each variable. Centre characteristics were compared with the Kruskal-Wallis and the likelihood ratio χ^2 test, when continuous and categorical, respectively. A post hoc Bonferroni correction was applied for pairwise comparisons.

The incidence rates of gastric adenocarcinoma and NETs from the time of AIG diagnosis were reported per 100 person-years, together with their 95% Poisson CI. They were compared using Poisson regression; incidence relative risks and 95% CI were computed. Additionally, Kaplan-Meier event-free survival curves were generated for both gastric adenocarcinoma and NETs.

The prevalence of gastric adenocarcinoma and NETs at diagnosis of AIG was reported together with its exact binomial 95% CI. Due to the relatively low number of prevalent neoplastic outcomes, factors associated with gastric adenocarcinoma and NET were evaluated using univariable and bivariable logistic models. Variables included in all univariable and bivariable models were selected a priori based on their clinical relevance. The serum gastrin-17 cut-off was determined based on the 75th percentile of its distribution. ORs and 95% CI were calculated.

All statistical analyses were conducted using Stata V.19.5 (StataCorp, College Station, Texas, USA). A two-sided p value <0.05 was considered statistically significant; for post hoc Bonferroni corrections, the adjusted p value threshold is specified in the Table footnotes.

The study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure reporting quality. All relevant data are included in this publication; additional raw data are available from the participating centres on reasonable request. Patients and members of the public were not involved in the design, conduct, reporting or dissemination of this research.

RESULTS

Sociodemographic and clinical characteristics

Overall, we collected data from 1240 patients with AIG (female:male ratio 2:1; median age 59 years, IQR 48–67), followed for a median of 68 months (IQR 36–108). Table 1 shows baseline sociodemographic characteristics by geographical region. Median age was lowest in the Turkish group (53 years) and highest in the Japanese group (66 years), with significant differences between groups. Japan also had the highest proportion of patients with AIG over 65 years. The female:male ratio was roughly 2:1 in all regions except Türkiye, where it was 1:1.

Latin American patients had the highest proportion living below the poverty line, while only about one-fourth of Turkish patients reached a high educational level. Turkish patients were also significantly less likely to be single. Regarding race and ethnicity (not shown in table 1), nearly all European and Turkish patients were classified as white (99.5%), all patients from Japan were Asian (100%) and almost all patients from Latin America self-identified as Hispanic or Latino (99.5%).

Table 1 Baseline sociodemographic characteristics of the 1240 included patients with autoimmune gastritis by geographical region

Variable	EU (1)	Türkiye (2)	Latin America (3)	Japan (4)	USA (5)	Post hoc comparisons Significant p value*
N. of patients, n (%)	567 (45.7)	337 (27.2)	155 (12.5)	79 (6.4)	102 (8.2)	/
Follow-up time, months, median (IQR)	96 (60–144)	48 (36–84)	53 (15–72)	60 (34–82)	61 (23–99)	/
Age, years, median (IQR)	59 (48–70)	53 (43–62)	61 (52–67)	66 (57–71)	63 (53–69)	1 vs 2; 1 vs 4; 2 vs 3, 2 vs 4; 2 vs 5
Age >65 years, n (%)	184 (34.5)	42 (12.5)	48 (31.0)	40 (50.6)	42 (41.2)	1 vs 2; 2 vs 3; 2 vs 4; 2 vs 5
Female sex, n (%)	402 (70.9)	187 (55.5)	121 (78.1)	56 (70.9)	76 (74.5)	1 vs 2; 2 vs 3; 2 vs 5
Smoking status (active or former), n (%)	67 (20.5)	24 (7.1)	31 (20.8)	4 (6.3)	10 (10.0)	1 vs 2; 2 vs 3; 3 vs 5
Alcohol use disorder, n (%)	4 (1.3)	0 (0)	1 (0.7)	0 (0)	5 (8.2)	NA
High educational level (≥13 years), n (%)	166 (72.2)	85 (25.2)	98 (100)	79 (100)	Not available	1 vs 2; 1 vs 3; 1 vs 4; 2 vs 3; 2 vs 4
Partnered or married, n (%)	157 (62.5)	255 (75.7)	70 (56.4)	7 (70.0)	66 (66.7)	1 vs 2; 1 vs 3; 1 vs 5; 2 vs 3; 2 vs 5
Below poverty level, n (%)	57 (22.3)	13 (3.9)	71 (64.0)	1 (1.3)	Not available	1 vs 2; 1 vs 3; 1 vs 4; 2 vs 3; 3 vs 4

P value of the model <0.001.
*Post hoc comparison is significant when p value <0.001; global p value <0.001 for all compared variables. NA if too few observations in at least two groups.
EU, European Union; IQR, Interquartile range; NA, not assessed; USA, United States of America.

Table 2 Baseline clinical features of patients with autoimmune gastritis by geographical region

Variable, n (%)	EU (1)	Türkiye (2)	Latin America (3)	Japan (4)	USA (5)	Post hoc comparisons Significant p value*
Microcytic anaemia	54 (29.5)	165 (56.1)	22 (64.7)	1 (1.3)	8 (16.0)	1 vs 2; 1 vs 3; 2 vs 5; 3 vs 5; 1 vs 4; 2 vs 4; 3 vs 4
Normocytic anaemia	30 (16.0)	110 (37.4)	7 (20.6)	0 (0)	25 (50.0)	1 vs 5
Macrocytic anaemia	86 (46.0)	19 (6.5)	4 (11.8)	2 (2.5)	2 (4)	1 vs 2; 1 vs 3; 1 vs 5; 1 vs 4; 3 vs 4
Pancytopenia	17 (9.2)	0 (0)	0 (0)	1 (1.3)	0 (0)	NA
Gastrointestinal symptoms	228 (57.9)	240 (71.4)	83 (69.7)	8 (10.1)	72 (70.6)	1 vs 2; 1 vs 4; 2 vs 4; 3 vs 4; 4 vs 5
Neuropsychiatric symptoms†	73 (18.5)	60 (17.8)	24 (19.8)	0 (0)	12 (11.8)	1 vs 4; 2 vs 4; 3 vs 4; 4 vs 5
Associated autoimmunity	255 (52.2)	76 (22.5)	105 (67.7)	9 (11.5)	44 (43.1)	1 vs 2; 1 vs 4; 2 vs 3; 2 vs 5; 3 vs 4; 3 vs 5; 4 vs 5
First-degree family history of AIG	59 (12.8)	1 (0.3)	4 (3.6)	2 (2.6)	0 (0)	1 vs 2; 1 vs 5
First-degree family history of gastric cancer	33 (8.5)	9 (2.7)	15 (13.5)	4 (5.6)	6 (5.9)	1 vs 2; 2 vs 3
Diagnostic delay >12 months	26 (11.2)	123 (36.6)	6 (5.8)	1 (1.3)	Not available	1 vs 2; 2 vs 3; 2 vs 4
Prior use of PPI for >3 months	129 (32.8)	203 (60.2)	28 (23.9)	2 (2.6)	Not available	1 vs 2; 1 vs 4; 2 vs 3; 2 vs 4; 3 vs 4

P value of the model <0.001.
*Post hoc comparison is significant when p value <0.001; global p value ≤0.001 for all compared variables.
†This includes paraesthesia, psychiatric conditions, memory loss. NA if too few observations in at least two groups.
AIG, autoimmune gastritis; EU, European Union; NA, not assessed; PPI, proton pump inhibitor; USA, United States of America.

The US population was more diverse, with 62.4% white, 12.9% black or African American, 12.9% multiethnic, 10.8% Asian and 1% other.

Table 2 reports the clinical features at AIG diagnosis by geographical region. Significant differences were noted across regions. Microcytic anaemia was the most common haematological manifestation in Türkiye and Latin America and also common in Europe. Anaemia of any type was rare in Japan and the USA. Macrocytic anaemia was common only in Europe and rare elsewhere. Vitamin B_{12} deficiency at onset was common in Europe (55.6%) and Latin America (44.2%) but was never noticed in Japan (datum not available in the other geographical areas). Apart from Japan, gastrointestinal symptoms were common (>50%), with dyspepsia (50.2%), gastro-oesophageal reflux disease (26.3%) and abdominal pain (22.6%) being most frequent (data not shown). The highest rates of associated autoimmunity were seen in Latin America (67.7%), followed by Europe (52.2%) and the USA (42.1%), while Türkiye (22.5%) and Japan (11.5%) had the lowest rates. The most commonly reported autoimmune disorders were Hashimoto's thyroiditis (62.3%), connective tissue disease (12.8%), Graves' disease (7.4%), vitiligo (6.9%), type I diabetes mellitus (6.3%), coeliac disease (3.7%) and psoriasis (3.0%). Globally, 6% of patients reported a first-degree family history of either AIG or gastric cancer.

Diagnostic delay exceeding 12 months was more common in Europe (11.1%) and Türkiye (36.6%). Prior use of PPIs was more frequent in Europe (32.8%), Türkiye (60.2%) and Latin America (23.9%). Clinical manifestations leading to AIG diagnosis are reported in online supplemental table 1. Notably, nearly 80% of Japanese patients were diagnosed through a national screening programme, not available in other countries. Previous misdiagnosis was more common in Türkiye (online supplemental table 2).

Regarding laboratory findings (online supplemental table 3), seropositive AIG (PCA positivity) was the predominant form (87.8%). Prior *H. pylori* infection was more common in Latin America (19.3%) than in other regions. Corpus atrophy was graded as mild in 243 (21.3%), moderate in 279 (24.5%) and severe in 618 (54.2%; degree of severity not known in 100 patients). Intestinal metaplasia was present in 690 patients (67.3%).

Prevalence and incidence of gastric neoplastic complications

Regarding gastric neoplastic complications, 36 cases of adenocarcinoma (2.9%) and 132 NETs (10.6%) were observed at any time point (figure 1). These were categorised as either concurrent with AIG diagnosis or developing after diagnosis. No cases of gastric adenocarcinoma were reported in Latin America, and a single NET case was observed in Japan. Pathological and endoscopic features, staging, management and outcome of gastric adenocarcinoma and type 1 gastric NETs are reported in online supplemental table 4. Among patients with gastric adenocarcinoma, tumours were most frequently located in the corpus and fundus mucosa; most cancers were diagnosed at an early stage (IA-IB). Treatment was mainly surgical (55.5%), with one-third managed endoscopically, and cancer-related mortality was 13.9%. Similarly, type 1 gastric NETs were predominantly located in the corpus/fundus mucosa. Most NETs were low-grade (G1, 76.5%), and management was largely endoscopic (59.1%), although nearly one-third were managed with surveillance alone. No NET-related deaths were observed.

Prevalence of adenocarcinoma at AIG diagnosis was 0.5% (95% CI 0.5% to 3.0%) in Europe, 0% (95% CI 0% to 1.1%) in Türkiye, 0% (95% CI 0% to 3.4%) in Latin America, 8.2% (95% CI 0.3% to 17.0%) in Japan and 9.0% (95% CI 4.1% to 16.4%) in the USA (notable, a cancer referral centre). Prevalence of NET at AIG diagnosis was 3.7% (95% CI 2.2% to 5.9%) in Europe, 0.3% (95% CI 0.01% to 1.8%) in Türkiye, 4.8% (95% CI 1.5% to 10.9%) in Latin America, 1.4% (95% CI 0% to 7.4%) in Japan and 37.9% (95% CI 28.1% to 48.4%) in the USA.

Crude incidence rates of gastric adenocarcinoma occurring after AIG diagnosis were 1.07 per 100 person-years (95% CI 0.43 to 2.20) in Europe, 1.15 per 100 person-years (95% CI 0.37 to 2.70) in Türkiye and 1.47 per 100 person-years (95% CI 0.17 to 5.3) in the USA, with no significant regional differences (Poisson model p=0.926, online supplemental figure 1). No incident cases of gastric adenocarcinoma were reported in Japan. Type 1 gastric NET crude incidence rates occurring after AIG diagnosis were 0.70 per 100 person-years (95% CI 0.45 to 1.00) in Europe, 1.23 per 100 person-years (95% CI 0.85 to 1.71) in Türkiye, 1.62 per 100 person-years (95% CI 0.44 to 4.16) in Latin America and 1.19 per 100 person-years (95% CI 0.47 to 2.45) in the USA, with no significant regional differences

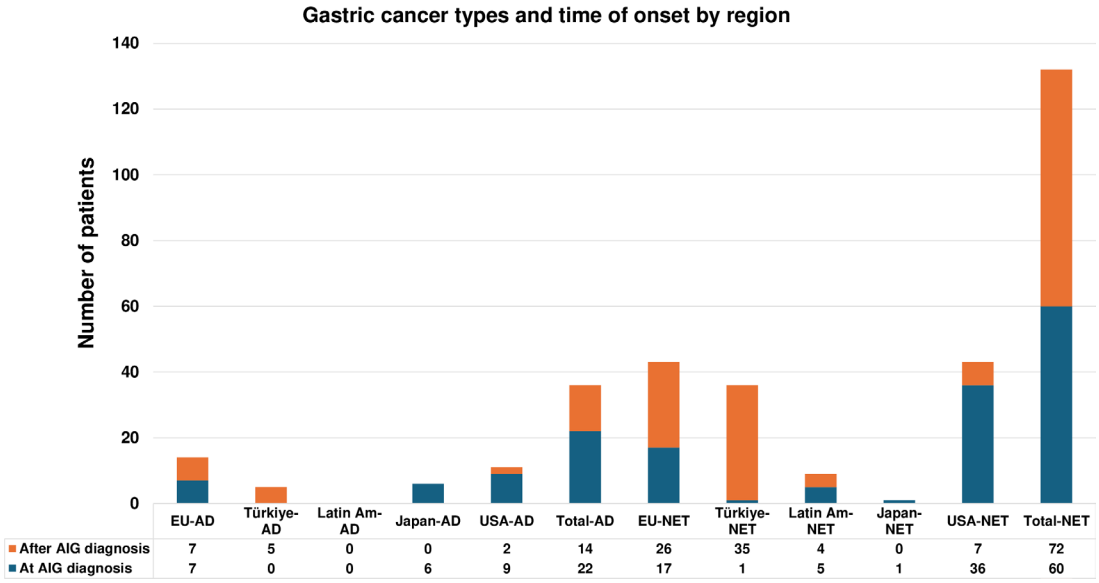

Figure 1 Bar chart showing cancer cases by region, further divided into type of cancer (ie, gastric adenocarcinoma, type 1 gastric NET, other cancers) and time of onset (ie, at the same time of AIG diagnosis, after AIG diagnosis). AD, adenocarcinoma; AIG, autoimmune gastritis; EU, European Union; Latin Am; Latin America; NET, neuroendocrine tumour; USA, United States of America.

(Poisson model p=0.091, online supplemental figure 1). Kaplan-Meier estimates for gastric adenocarcinoma-free and type 1 gastric NET-free survival, both overall and by region, are shown in figures 2 and 3.

Overall, 119 (9.6%) patients had at least one non-gastric neoplasia, totalling 209 different cancers; 37 (2.98%) patients had one cancer, 68 (5.48%) patients had two cancers and 12 (0.97%) patients had three cancers. Globally, 78 were gastro-oesophageal junction cancers, followed by breast (31), colorectal (21), urogenital (25), lymphomas (16), thyroid (10), oesophageal (2) and others.

Factors associated with gastric adenocarcinoma and type 1 gastric NET

Univariable and bivariable analyses for prevalent gastric adenocarcinoma and type 1 gastric NET risk are presented in online supplemental tables 5, 6 and tables 3 and 4, respectively.

For gastric adenocarcinoma, univariable analysis demonstrated that age >65 years (OR 4.45, 95% CI 2.14 to 9.23, p<0.001) and gastrin-17 >1316 pg/mL (OR 6.94, 95% CI 2.07 to 23.28, p=0.002) were significantly associated. Other variables were not significantly associated. Bivariable analyses confirmed these findings. Age >65 years remained strongly associated with risk after adjustment for sex (OR 4.50, 95% CI 2.18 to 9.27, p<0.001). Elevated serum gastrin-17 demonstrated the strongest association, both after adjustment for sex (OR 6.89, 95% CI 2.07 to 22.96, p=0.002) and for PPI use (OR 15.52, 95% CI 3.61 to 66.71, p<0.001). After adjusting for intestinal metaplasia, prior PPI use remained strongly associated with cancer (OR 5.74, 95% CI 2.13 to 15.47, p=0.001). Intestinal metaplasia was also independently associated (OR 1.51, 95% CI 1.16 to 1.97, p=0.002). Finally, only after adjusting for prior PPI use, female sex was independently associated with cancer (OR 1.85, 95% CI 1.05 to 3.24, p=0.032).

For NET, univariable analysis demonstrated that prior *H. pylori* eradication was significantly associated with reduced NET likelihood (OR 0.25, 95% CI 0.07 to 0.87, p=0.030). In contrast, prior PPI use >3 months (OR 2.72, 95% CI 1.11 to

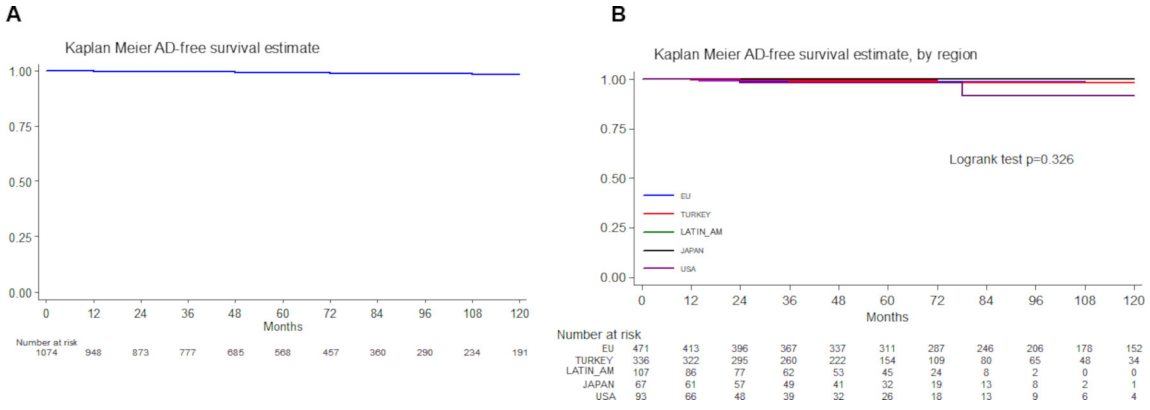

Figure 2 Kaplan-Meier estimates of gastric AD-free survival. (A) Overall AD-free survival estimates in the entire cohort of patients with autoimmune gastritis. (B) AD-free survival stratified by geographical region (EU, Türkiye, Latin America, Japan and USA). No significant differences in event-free survival were observed among the regions (logrank test, p=0.326). The number at risk at each time point is indicated below the plots. AD, adenocarcinoma; EU, European Union; LATIN_AM, Latin America; USA, United States of America.

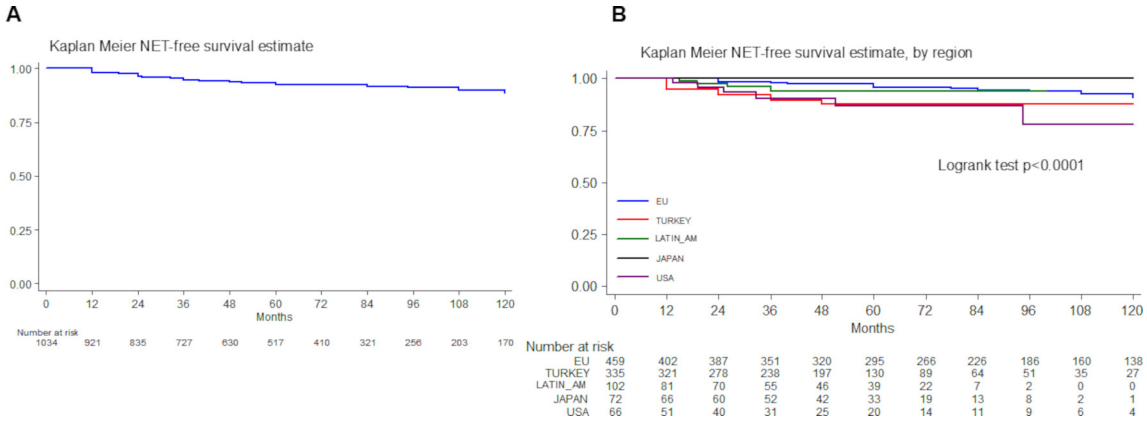

Figure 3 Kaplan-Meier estimates of type 1 gastric NET-free survival. (A) Overall NET-free survival estimates in the entire cohort of patients with autoimmune gastritis. (B) NET-free survival stratified by geographical region (EU, Türkiye, Latin America, Japan and USA). Statistically significant differences in NET-free survival were observed among regions (logrank test, p<0.0001). Numbers at risk at each time point are provided below each plot. EU, European Union; LATIN_AM, Latin America; NET, neuroendocrine tumour; USA, United States of America.

6.69, p=0.029) and active or former smoking (OR 1.86, 95% CI 1.20 to 2.88, p=0.006) were significantly associated with an increased likelihood of NETs. Other variables were not significantly associated. Bivariable analyses confirmed these associations. Age >65 years remained significantly associated with reduced risk after adjustment for PPI use (OR 0.25, 95% CI 0.08 to 0.81, p=0.021). *H. pylori* eradication continued to show an inverse association after adjustment for sex (OR 0.25, 95% CI 0.07 to 0.88, p=0.031). Prior PPI use consistently showed increased likelihood of NET across models, that remained after adjustment for age (OR 2.69, 95% CI 1.12 to 6.46, p=0.027), sex (OR 2.64, 95% CI 1.06 to 6.55, p=0.037), *H. pylori* status (OR 2.68, 95% CI 1.06 to 6.80, p=0.038) and gastrin-17 (OR 3.25, 95% CI 1.42 to 7.45, p=0.005). Smoking was strongly

Table 3 Bivariable analysis for variables correlated with prevalent gastric adenocarcinoma in patients with autoimmune gastritis

Variables adjusted for PPI use	OR	95% CI	P value	Variables adjusted for sex	OR	95% CI	P value
Age			<0.001	Age			0.0002
Prior use of PPI for >3 months	1.80	0.22 to 14.92	0.587	Male sex	0.84	0.38 to 1.83	0.655
Age >65 years	4.63	1.87 to 11.41	0.001	Age >65 years	4.50	2.18 to 9.27	<0.0001
Sex			<0.001	Not applicable			
Prior use of PPI for >3 months	1.90	0.20 to 17.76	0.572				
Female sex	1.85	1.05 to 3.24	0.032				
H. pylori status			0.5218	*H. pylori* status			0.6368
Prior use of PPI for >3 months	1.79	0.16 to 20.32	0.639	Male sex	0.94	0.44 to 2.03	0.880
Eradicated *H. pylori*	0.73	0.05 to 9.77	0.809	Eradicated *H. pylori*	0.46	0.05 to 4.34	0.494
Not applicable				PPI use			<0.001
				Male sex	0.54	0.31 to 0.95	0.032
				Prior use of PPI for >3 months	1.90	0.20 to 17.76	0.572
Smoking status			0.6702	Smoking status			0.1591
Prior use of PPI for >3 months	0.71	0.20 to 2.52	0.592	Male sex	0.76	0.14 to 4.02	0.745
Active or former smoking status	0.32	0.03 to 3.92	0.373	Active or former smoking	0.43	0.18 to 1.02	0.065
Family history			0.3482	Family history			0.4235
Prior use of PPI for >3 months	1.11	0.14 to 9.16	0.920	Male sex	0.77	0.22 to 2.69	0.678
First-degree family history of gastric cancer	3.35	0.34 to 33.04	0.300	First-degree family history of gastric cancer	2.41	0.64 to 9.03	0.191
Metaplasia			<0.001	Metaplasia			0.515
Prior use of PPI for >3 months	5.74	2.13 to 15.47	0.001	Male sex	1.34	0.78 to 2.30	0.292
Intestinal metaplasia (any degree and type)	1.51	1.16 to 1.97	0.002	Intestinal metaplasia (any degree and type)	0.98	0.49 to 1.97	0.963
PCA status			0.2322	PCA status			0.168
Prior use of PPI for >3 months	1.61	0.17 to 15.53	0.682	Male sex	0.79	0.31 to 1.99	0.617
PCA positivity	1.49	0.48 to 4.64	0.495	PCA positivity	0.75	0.30 to 1.87	0.533
Gastrin-17			0.001	Gastrin-17			<0.001
Prior use of PPI for >3 months	0.33	0.07 to 1.64	0.174	Male sex	0.81	0.25 to 2.60	0.718
Gastrin-17 >1316 pg/mL	15.52	3.61 to 66.71	<0.0001	Gastrin-17 >1316 pg/mL	6.89	2.07 to 22.96	0.002

CI, Confidence interval; *H. pylori*, *Helicobacter pylori*; OR, Odds ratio; PCA, parietal cell antibodies; PPI, proton pump inhibitor.

Table 4 Bivariable analysis for variables correlated with prevalent type 1 gastric neuroendocrine tumours in patients with autoimmune gastritis

Variables adjusted for PPI use	OR	95% CI	P value	Variables adjusted for sex	OR	95% CI	P value
Age			0.0013	Age			
Prior use of PPI for >3 months	2.69	1.12 to 6.46	0.027	Male sex	1.18	0.94 to 1.49	0.159
Age >65 years	0.25	0.08 to 0.81	0.021	Age >65 years	0.82	0.37 to 1.85	0.640
Sex			0.009	Not applicable			
Prior use of PPI for >3 months	2.64	1.06 to 6.55	0.037				
Female sex	0.78	0.57 to 1.08	0.134				
H. pylori status			<0.001	*H. pylori* status			<0.001
Prior use of PPI for >3 months	2.68	1.06 to 6.80	0.038	Male sex	1.11	0.88 to 1.41	0.373
Eradicated *H. pylori*	0.35	0.13 to 0.92	0.034	Eradicated *H. pylori*	0.25	0.07 to 0.88	0.031
Not applicable				PPI use			0.009
				Male sex	1.28	0.93 to 1.76	0.134
				Prior use of PPI for >3 months	2.64	1.06 to 6.55	0.037
Smoking status			<0.001	Smoking status			0.0194
Prior use of PPI for >3 months	2.40	0.93 to 6.21	0.071	Male sex	1.06	0.71 to 1.58	0.768
Active or former smoking	2.45	1.75 to 3.42	<0.0001	Active or former smoking	1.83	1.19 to 2.80	0.005
Family history			<0.001	Family history			0.3220
Prior use of PPI for >3 months	2.55	0.99 to 6.54	0.052	Male sex	1.24	0.90 to 1.72	0.184
First-degree family history of gastric cancer	0.58	0.12 to 2.95	0.514	First-degree family history of gastric cancer	0.74	0.28 to 1.90	0.526
Metaplasia			<0.001	Metaplasia			0.5502
Prior use of PPI for >3 months	2.57	0.91 to 7.25	0.073	Male sex	1.09	0.80 to 1.48	0.593
Intestinal metaplasia (any degree and type)	2.88	1.38 to 6.01	0.005	Intestinal metaplasia (any degree and type)	1.02	0.44 to 2.46	0.275
PCA status			0.0129	PCA status			0.0365
Prior use of PPI for >3 months	2.59	1.03 to 6.56	0.044	Male sex	1.39	0.96 to 2.02	0.084
PCA positivity	1.71	0.65 to 4.50	0.276	PCA positivity	2.75	0.62 to 12.23	0.184
Gastrin-17			<0.001	Gastrin-17			0.0188
Prior use of PPI for >3 months	3.25	1.42 to 7.45	0.005	Male sex	1.42	0.93 to 2.17	0.105
Gastrin-17 >1316 pg/mL	2.68	1.06 to 6.78	0.037	Gastrin-17 >1316 pg/mL	2.63	1.20 to 5.73	0.015

CI, Confidence interval; *H. pylori*, *Helicobacter pylori*; OR, Odds ratio; PCA, parietal cell antibodies; PPI, proton pump inhibitor.

associated with increased risk after adjustment for PPI use (OR 2.45, 95% CI 1.75 to 3.42, p<0.0001) and for sex (OR 1.83, 95% CI 1.19 to 2.80, p=0.005). Intestinal metaplasia was also significantly associated with increased risk after adjustment for PPI use (OR 2.88, 95% CI 1.38 to 6.01, p=0.005). Elevated gastrin-17 >1316 pg/mL remained associated with increased risk after adjustment for sex (OR 2.63, 95% CI 1.20 to 5.73, p=0.015) and for PPI use (OR 2.68, 95% CI 1.06 to 6.78, p=0.037).

DISCUSSION

Sociodemographic and clinical differences across geographical areas

Our study included 1240 patients with well-characterised AIG, providing the first direct comparison across diverse regions. Approximately half of adenocarcinoma and NET cases were identified coincident with AIG diagnosis, either reflecting long-standing unrecognised AIG or effective endoscopic screening as in the case of Japan. Except in Latin America, *H. pylori* infection rates were generally low. The risk of incident gastric neoplasia was essentially absent in Japan and Latin America and higher elsewhere, with age >65 years, intestinal metaplasia and marked gastrin-17 increase being the main risk factors. These novel findings provide valuable insights and help narrow critical gaps in both clinical and epidemiological knowledge.

Indeed, comparing data across regions allowed for a more nuanced interpretation. Socioeconomic analysis showed that AIG affects all groups regardless of education or income, though regional differences may reflect broader population trends. AIG was mainly diagnosed in middle-aged and elderly individuals, with the median age at onset lowest in Türkiye and highest in Japan. Interestingly, other autoimmune diseases, such as rheumatoid arthritis, have also been reported to affect younger patients in Türkiye compared with another European country.[35] Türkiye also showed a distinct sex distribution, with a female:male ratio close to 1:1, while in a previous Turkish series it was 2:1.[12] This shift may be explained by inequalities in access to care, which appear to affect women more than men in Türkiye.[36]

Several clinical differences also emerged. Macrocytic anaemia, typically developing later in the disease course,[1 37] was predominantly observed in European cohorts, while microcytic anaemia, usually arising earlier, was more common in Turkish and Latin American populations. These findings underscore the need to consider both early and late haematological manifestations. Furthermore, vitamin B_{12} deficiency was generally common, reinforcing its importance as a critical disease marker while highlighting regional variability in its clinical expression.

Gastrointestinal symptoms were very common, as already reported in studies by Miceli *et al* and Carabotti *et al*,[11 38] and were confirmed to also be a source of misdiagnosis and diagnostic delay, as previously noticed in a single-centre study by Lenti *et al*.[39] Of note, in the work-up of dyspepsia, testing for PCA is not recommended,[40] potentially prolonging the diagnostic delay. Gastro-oesophageal reflux disease was also relatively frequent,

and its presence should not be taken as evidence against AIG. Indeed, non-acid reflux is recognised as a contributing factor and may account for part of this association.[41]

Japan exhibited a noticeably low symptom burden, since most patients were diagnosed during routine health checks. Since 2016, Japan has implemented a nationwide programme offering upper gastrointestinal endoscopy every 2 years, which has proven highly effective in reducing both the incidence and mortality of gastric cancer.[42 43] Therefore, Japan offers a unique opportunity to study the natural history of AIG, while simultaneously protecting patients from developing clinical manifestations and AIG-related complications.

About 6% of patients with AIG, highest in Europe and lowest in the USA, reported a first-degree family history. This highlights the value of targeted screening in high-risk relatives, which may partly compensate for the lack of broader population-based programmes that may detect many asymptomatic cases.[44]

The prevalence of autoimmune comorbidities was confirmed to be high, particularly for autoimmune thyroid disease. Although not a novel finding, our study documents this in an international cohort encompassing multiple ethnicities, strengthening the concept of thyrogastric autoimmunity as part of a unifying theory of shared autoimmune pathways.[45]

Our data also underscored the importance of serological markers. PCA positivity was common, but not universal, confirming the existence of seronegative AIG cases, reinforcing the need for histopathological confirmation. It has been previously reported that older age[46] and concomitant common variable immunodeficiency[47] are the major factors determining seronegativity. Elevated gastrin-17 not only was confirmed to be an indicator of AIG itself,[48] but also had a prognostic relevance as discussed below. Data on *H. pylori* are of particular interest. First, we observed a low overall prevalence of prior *H. pylori* infection, with a global mean of approximately 5%. This finding challenges the theory that *H. pylori* may act as a major potential trigger for AIG.[49] Second, even in Latin America, a region where *H. pylori* is common (52% in Chile[50] and 33% in Puerto Rico),[51] the prevalence of previous infection among patients with AIG was only about 19%, markedly lower than compared with the general population. This again does not support the hypothesis that *H. pylori* plays a major role in AIG pathogenesis. The argument of under-reported *H. pylori* infection is also unlikely to account for such low *H. pylori* prevalence in the AIG population.

Novel comparative data on gastric adenocarcinoma and type 1 gastric NET in AIG

While the risk of developing type 1 gastric NETs in AIG is established,[52] our data on gastric adenocarcinoma provide valuable contributions to a field where this association remains debated. Notably, in a previous series of patients with 'pure' AIG, no cases of gastric adenocarcinoma were reported[28]; the same result was shown in two studies on the natural history of AIG, where the prevalence of previous *H. pylori* was very low.[23 24] However, some series of gastric adenocarcinoma arising in the context of AIG have been reported, regardless of the *H. pylori* status, suggesting that this complication may occur in previously undiagnosed patients or those in whom surveillance was not offered.[53 54] Not only did we observe a mildly increased risk of gastric adenocarcinoma, but we also identified important factors associated with this risk, namely, age >65 years, markedly elevated serum gastrin-17 levels, the presence of intestinal metaplasia, prior use of PPIs and a slight female predominance. The association with intestinal metaplasia aligns with recent findings identifying cancer-related metaplastic cells, which provide a plausible biological basis for the development of this complication.[55] Although previous studies have highlighted a potential relationship between long-term PPI use and gastric cancer, especially in *H. pylori*-eradicated individuals,[56 57] our analysis represents the first multicentre international evidence of this association among patients with AIG. This observation reinforces the need for cautious use of PPIs in this group, in whom acid suppression may confer limited benefit and potential risk.

Data on mortality from gastric adenocarcinoma in AIG are scant. We have found here a cancer-related mortality of 13.9%, and most cases of cancers were diagnosed at an early stage (IA-IB). Although this figure seems to be lower compared with data of gastric cancer mortality in the general population, caution is needed in interpreting these data. Larger comparative studies are needed.[58] Regarding NETs, we identified both smoking and prior use of PPIs as significant predictors. To our knowledge, this is the first report of such a strong association between smoking and NETs in AIG, warranting further investigation. The link with prior PPI use, previously suggested in a study by Dilaghi *et al*,[59] is here confirmed. Notably, we also found that NETs occurred significantly more often in patients younger than 65 years, suggesting that they may represent an early complication of AIG. In addition, the observed inverse correlation with *H. pylori* status may reflect differing pathogenic pathways in gastric NET development and further supports our earlier observation of two distinct forms of AIG, the *H. pylori*-associated variant, which is generally less clinically evident and less severe, and the classical autoimmune form.[20]

Incident cases of gastric neoplasia varied by region, being essentially absent in Latin America and Japan, but comparable across the other regions. This heterogeneity may be partially explained by referral bias, as the US cohort was enrolled at a cancer centre. To mitigate this, we considered only newly incident cancers, excluding those present at the time of AIG diagnosis. Nevertheless, further studies investigating additional risk factors underlying this geographic variability are warranted.

Clinical implications of our findings

Our study has important clinical and research implications. The marked geographical variability observed indicates that surveillance guidelines should reflect local epidemiology and patient profiles. In real-world settings, AIG poses a measurable risk of progression to gastric cancer, and predictors such as gastrin-17 levels may help refine risk stratification and personalise follow-up. However, the link between elevated gastrin-17 and cancer risk should be interpreted cautiously, as gastrin likely reflects advanced oxyntic atrophy rather than a causal factor. Establishing this large multinational cohort provides a foundation for prospective studies on AIG pathophysiology, natural history and preventive strategies. In summary, endoscopic surveillance could be risk-stratified using clinical and biochemical predictors including age, intestinal metaplasia and elevated gastrin-17.

Limitations of the study and generalisability

Several limitations warrant consideration. The retrospective design and variability in data availability may have introduced some biases. Specifically, there may have been variability in the clinical and endoscopic follow-up of patients due to differences in local policies, heterogeneity of national or international guidelines over the enrolment period and

across regions, variation in the settings of enrolment (eg, cancer centres) and a lack of information on interrupted follow-up because of age limits, severe comorbidities or patient choice. The participating centres may also differ in patterns of patient referral that could influence the clinical characteristics observed. A central review of histological specimens was not performed, which may have led to under-reporting of patients with milder atrophy and to potential misclassification with other forms of gastritis. In addition, because we cannot exclude the possibility that some patients had unreported *H. pylori* infection, and because anti-*H. pylori* antibody data were unavailable for most patients, some individuals with prior *H. pylori* infection may have been missed. Finally, the total number of cancers was relatively low, preventing a multivariable analysis; however, we addressed this by controlling for potential confounders using bivariable analyses. Nonetheless, our study also has some strengths, including the involvement of tertiary referral centres with long-standing expertise in the management of AIG, a large and well-characterised sample size and the first international comparison of a disease that had previously been described only in single-centre or national series. The generalisability of our findings is limited to patients managed in tertiary referral centres, and caution is warranted when extrapolating these results to other clinical settings.

CONCLUSIONS

In conclusion, this study highlights the heterogeneity of AIG, identifies clinically relevant correlates of neoplastic risk, underscores the need for tailored diagnostic and surveillance strategies and lays the groundwork for the future development of high-quality international studies. Sustained international collaboration, expanded to additional geographical areas and non-specialised care settings, will be critical to further elucidate the complexity of AIG and improve patient outcomes worldwide.

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