The role of systemic autoimmune disorders in the symptoms, course and prognosis of chronic gastritis and their incidence in gastric cancer

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1 PUBLICATIONS AND CITATIONS

1.1 Scientific metrics

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1.2 Publications related to the thesis (without abstracts)

1. **Zádori N**, Szakó L, Váncsa S, Vörhendi N, Oštarijaš E, Kiss S, Frim L, Hegyi P, Czimmer J. Six Autoimmune Disorders Are Associated With Increased Incidence of Gastric Cancer: A Systematic Review and Meta-Analysis of Half a Million Patients. Front Immunol. 2021 Nov 23;12:750533. **IF: 8.786; Q1/D1**
2. **Zádori N**, Németh D, Szakó L, Váncsa S, Vörhendi N, Szakács Z, Frim L, Hegyi P, Czimmer J. Prevalence of Autoimmune-phenomena behind Chronic Gastritis of Unknown Origin, and their Role in the Poor Histological Outcome of the Stomach: A Single-centre, Retrospective Cross-sectional Study. J Gastrointestin Liver Dis. 2022 Jun 12;31(2):168-175. **IF: 2.142; Q3**
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1.3.1 First author

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2 ABBREVIATIONS

AI: autoimmune

AIG: autoimmune gastritis

AISN: autoantibody seronegative

AISP: autoantibody seropositive

ANA: anti-nuclear antibody

ANCA: anti-neutrophil cytoplasmic antibody

ASCA: anti-Saccaromyces cerevisiae antibody

BMI: body mass index

CG: chronic gastritis

CI: confidence interval

ds-DNA: double-stranded DNA

EASI. European Autoimmunity Standardisation Initiative

ECL: enterochromaffin-like

ELISA: enzyme-linked immunosorbent assay

FD: functional dyspepsia

GERD: gastroesophageal reflux disease

GI: gastrointestinal

H. pylori: Helicobacter pylori

IBD: inflammatory bowel disease

IF: intrinsic factor

IgG: immunoglobulin G

IM: intestinal metaplasia

NSAID: non-steroidal anti-inflammatory drugs

OLGA: Operative Link on Gastritis Assessment

OLGIM: Operative Link on Gastric Intestinal Metaplasia Assessment

OR: odds ratio

PA: pernicious anaemia

PCR: polymerase chain reaction

PPI: proton pump inhibitor

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: The International Prospective Register of Systematic Reviews

QUIPS: Quality in Prognostic Studies

RA: rheumatoid arthritis

RF: anti-rheumatoid factor

REML: restricted maximum likelihood

RR: risk ratio

SD: standard deviation

SIR: standardised incidence ratio

SLE: systemic lupus erythematosus

SSA: anti-Sjögren's syndrome-related antigen A

SSB: anti-Sjögren's syndrome-related antigen B

Ssc: systemic sclerosis

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

T1DM: diabetes mellitus type I

UBT: urea breath test

3 INTRODUCTION

Chronic gastritis (CG) is a multistep, progressive, life-long inflammatory condition of the gastric mucosa, which is likely to evolve towards a progressive disappearance of the mucosal glands. It is one of the most common findings during upper gastrointestinal (GI) endoscopy in Eastern countries [1]. Literature suggests that more than half of the world population may live with CG to some extent [2].

In the past, gastritis was considered a histological finding, not a disease. It changed in 1982 with the discovery of *Helicobacter pylori (H.pylori),* which led to the identification, description and classification of gastritis by Robin Warren and Barry Marshall [3]. There is no universally accepted classification system available which could provide an entirely satisfactory, comprehensive description of all types of gastritis and gastropathy. CG can be classified based on (1.) the aetiology (autoimmunity or environmental: infectious, e.g., H. pylori vs non-infectious, e.g., bile reflux) and (2.) the histopathologic pattern, which can suggest the underlying cause and the clinical course.

It is essential to differentiate between chemical or reactive gastritis (acute or type C gastritis or reactive gastropathy) and chronic metaplastic gastritis. The former mentioned is caused by an injury (e.g., alcohol, non-steroidal anti-inflammatory agents [NSAIDs], bile acid) to the gastric mucosa, leading to epithelial damage, erosion and ulcers followed by regenerative hyperplasia, capillary damage, with mucosal oedema, haemorrhage, and increased smooth muscle in the lamina propria with minimal or no inflammation [4]. In contrast to CG, which is associated with extensive inflammation, leading to mucosal thinning, cell loss in gastric glands, and changes in epithelial cell types (i.e., metaplasia) [5]. CG has two phenotypes representing different stages of the same disease: non-atrophic and atrophic form [2, 6].

3.1 Aetiology of chronic gastritis

The two most frequently recognised causes of CG are: (1.) *H. pylori* infection, (2.) autoimmune gastritis (AIG).

3.1.1 H. pylori-associated chronic gastritis

H. pylori infection is the primary etiological factor of CG: 50% of the world's population is infected with *H. pylori*, which is behind one-third of the CG cases [7]. However, the prevalence of *H. pylori* has markedly declined over the past few decades, which resulted in the decline of CG prevalence in parallel [2].

The infection is usually acquired in early childhood, causing a harmless and often symptom-free but intense inflammatory response in the superficial layer of the stomach [8]. Histopathologic studies indicate that all *H. pylori-infected* individuals will have chronic gastritis, which develops decades later. The superficial inflammation may progress into gastric atrophy, intestinal metaplasia (IM), dysplasia, and cancer. The degree of mucosal inflammation and the progression into cancer depends on several factors, including bacterial virulence, host susceptibility, and environmental factors [9, 10].

The essential factors in transmitting *H. pylori* infection are socioeconomics and environmental hygiene [2]. The improvement in hygiene in industrialised countries and the widespread use of antibiotics led to a decline in the childhood infection rate [11, 12], which lies below 10% in young individuals in western populations [13, 14]. A decrease in the infection rate resulted in a decline in the prevalence of CG caused by *H. pylori* and its sequelae.

3.1.2 Autoimmune gastritis

The second most common, well-known etiological factor besides *H. pylori* infection behind CG is AIG: it occurs in 7.8–19.5% of the CG cases [15]. It is three times more common in females and patients older than 60 [16]. It may lead to chronic, mononuclear inflammation of the stomach, with severe corpus predominant atrophy, hypo- or achlorhydria, reduced or absent pepsin production, and loss of intrinsic factor (IF), causing B-12 deficiency, which may progress to severe anaemia, named pernicious anaemia (PA) [5].

In AIG, autoantibodies are directed against IF and parietal cells (cytoplasmic and plasma membrane antigens). Two types of IF antibodies can be distinguished: type I and II. Type I antibody inhibits the attachment of B12 to IF, and Type II antibody inhibits the connection between vitamin B12-IF complex and the receptors in the ileum [17]. Cell-mediated immunity also plays a significant role: T-cell lymphocytes infiltrate the gastric mucosa and destroy the epithelial cells, resulting in gastric atrophy.

Patients with AIG have a 3-5 times higher risk of co-existing other autoimmune (AI) disorders than the general population, in particular, AI-thyroid disease and diabetes mellitus type I (T1DM) [16]. AIG may be more rapid and progressive than H. pylori gastritis [18, 19].

3.1.3 Other rare forms of chronic gastritis

3.1.3.1 Celiac disease-related gastritis

Studies suggest that lymphocytic gastritis is a common mucosal finding in patients with celiac disease. Lymphocytic gastritis is defined as ≥25 lymphocytes per 100 epithelial cells; it is also reported in association with *H. pylori* infection [12].

3.1.3.2 Crohn's gastritis

Crohn's disease may affect all parts of the GI tract, including the stomach. According to recent studies, upper GI tract involvement was shown in 13% of the patients with Crohn's disease, the stomach was involved in 73% of the patients with upper GI involvement, and noncaseating granulomas were described in one-third of these patients [20, 21]. Crohn's specific inflammatory changes of gastric mucosa indicate a more extensive disease [12].

3.2 Symptoms

Despite the frequent occurrence during upper GI endoscopy, CG does not cause mostly typical signs and symptoms. Former studies could not prove a significant association between CG and GI symptom complex, even in the case of advanced gastric cancer and/or chronic peptic ulcer [22, 23]. However, in clinical practice, some patients complain of GI discomfort, stomachache, bloating, nausea and vomiting, and loss of appetite.

Studies have shown that acute *H. pylori* gastritis is associated with dyspeptic symptoms (e.g., epigastric burning, distention or bloating, belching, episodic nausea, flatulence, and halitosis). However, this association is not justified in chronic infection [24].

3.2.1 Dyspepsia

Dyspepsia is a complex condition, a constellation of symptoms originating from the upper GI region. Two types can be distinguished: organic and functional. The current standard for diagnosis of functional dyspepsia (FD) is the Rome IV criteria: the presence of one or more of the four following symptoms: bothersome postprandial fullness, early satiety, epigastric pain, and epigastric burning sensation, and no evidence of the existence of any organic disease that may explain the symptoms [25, 26].

The prevalence of dyspeptic symptoms in the general population is 20-40% [27, 28], and it is one of the most common indications for upper GI endoscopy, with a controversial diagnostic value of [29]. Endoscopy can be a practical diagnostic approach to differentiate between organic and functional dyspepsia; nevertheless, the majority of the dyspeptic cases are functional [30, 31]. Therefore, performing endoscopy should be considered due to its invasiveness and low-cost effectiveness.

The exact pathophysiological features behind FD are unknown; however, anxiety, visceral hypersensitivity, such as gastric hypersensitivity to distension and acids, abnormal central pain processing, slow gastric motility, and gastric accommodation failure might play an essential role [32-34]. Although FD is defined by the absence of organic pathology that explains the symptoms, the only exception is *H. pylori* infection. Extensive, population-based studies have shown that *H. pylori* might play a crucial role in the pathogenesis of FD [35, 36], and it also was included in the definition of FD according to the ROME III criteria [37].

A recent study described a high prevalence of CG without *H. pylori* infection and more severe disease course in patients with FD [38]. The aetiology of CG in these patients and its role in developing FD are unknown. Data regarding the connection between *H. pylori-negative* chronic gastritis and dyspeptic symptoms are lacking. Clarifying the aetiology behind *H. pylori-negative* CG and FD and the cause of their possible relationship might be beneficial in establishing the optimal treatment strategy.

Studies suggest that immune activation might play a role in the pathogenesis of FD [39, 40]. It has been shown that there is innate immune activation in the mucosa in the case of FD [41, 42], but the prevalence of AI disorders due to immune activation in FD is uncertain.

3.3 Diagnosis of chronic gastritis

The gold standard diagnostic approach for CG is histologic examinations of gastric biopsies. The endoscopic appearance could be normal in the early stages. As the disease progresses, the mucosa can be pseudopolyopid; polypoid areas serve as islands of preserved oxyntic mucosa bordering areas of atrophy. In histological examination, atrophy of the gastric mucosa with the loss of glandular cells and their replacement by metaplastic epithelium can be seen [5].

To correct evaluation, the Updated Sydney System determines a comprehensive endoscopic and histologic sampling protocol in which the biopsy sites are standardised *(Fig.1.)* [6]. At least two biopsies should be taken from the antrum (along lesser and greater curvatures), two biopsies taken from the stomach body, and one from the incisura angularis, which is mainly affected by metaplasia and atrophy [43]. Additional samples from suspicious lesions should also be taken. Biopsies can help determine the severity of atrophy and the subtype of CG, and it is the most reliable tool for diagnosing *H. pylori* [44].

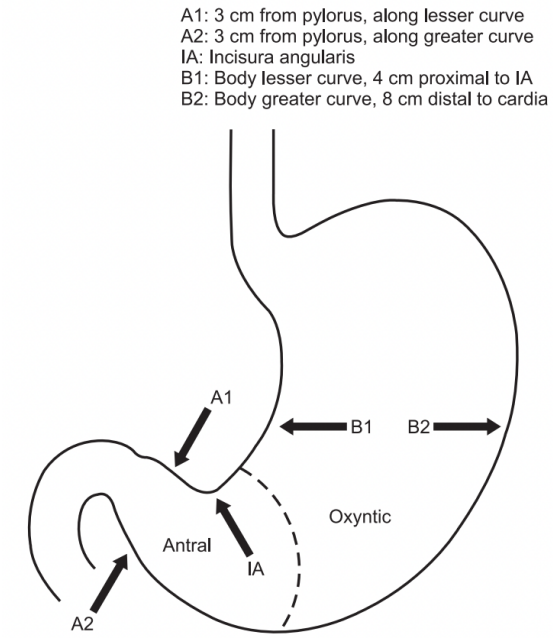


Fig. 1. Standardised biopsy sites according to the Updated Sydney System [45].

3.3.1 Laboratory testing

The measurement of serum pepsinogen level is the most reliable non-invasive marker for screening chronic atrophic gastritis, as the Maastricht V and Kyoto consensus suggested. Low serum pepsinogen levels or/and low pepsinogen I/II ratio can detect advanced gastric atrophy and/or metaplasia stages [46].

3.3.2 Determining the aetiology

It is crucial to clarify the underlying aetiology behind CG, which can be cleared based on histological examinations and clinical history. However, in some cases, additional testing should be performed.

3.3.3 Testing for autoimmune gastritis

Serologic testing for diagnosing AIG includes both anti-intrinsic factors and anti-parietal cell antibodies. These antibodies are particular for AIG but have low sensitivity. Examining fasting gastrin levels is recommended in conjunction with the serological tests [47].

3.3.4 Testing for *H. pylori*

As mentioned above, histology is the gold standard diagnostic method for *H. pylori* gastritis. Maastricht IV Consensus has suggested that to achieve the results' accuracy, proton pump inhibitors (PPI)s should be stopped two weeks before performing histology [44].
However, various other (non-invasive) diagnostic tests are available, and most have high sensitivity and specificity. Despite this, they are mainly recommended for testing whether the eradication therapy was successful.

According to the Maastricht IV/Florence consensus, a urea breath test (UBT) using 13C urea is the best among other diagnostic tests to diagnose *H. pylori* infection, with a diagnostic accuracy of >95% [48]. UBT is widely available and could help assess the efficacy of eradication therapy.

Serum or blood derivates are used for *H. pylori* culture and antibiotic susceptibility testing, which should be performed if the first eradication failed or if primary resistance to clarithromycin exceeds 20% in a given geographical area [44]. Due to the isolation of *H. pylori* being time-consuming and the rising antibiotic resistance, molecular biologic methods could be good alternatives for diagnosing *H. pylori* infection. Polymerase chain reaction (PCR) and real-time PCR are mainly used [49].

The antibody serological test is another possible diagnostic approach with a relatively high negative predictive value [44, 48]. It is the only test not influenced by local changes in the stomach, which could lead to false-negative results. Testing immunoglobulin G (IgG) against *H. pylori* with enzyme-linked immunosorbent assay (ELISA) can be used for validation in case of PPI treatment cannot possibly stop for two weeks before endoscopy [49].

3.4 Clinical significance of chronic gastritis

As mentioned, CG is one of the most common findings during upper GI endoscopy; despite its frequent occurrence, its significance in clinical practice is largely underrated. However, its role in gastric carcinogenesis is well known: gastric cancer is the final result of the progressive changes in the gastric mucosa, starting with CG, followed by atrophy and IM [50]. The estimated annual cancer risk is 0.1% within five years after diagnosis [51]. Correa et al. summarised previous observations and developed a model of gastric carcinogenesis in 1975, updated in 1988 and 1992. This pathway was named Correa's cascade, which is a widely accepted model of the pathogenesis of gastric carcinoma [52] *(Fig.2).*

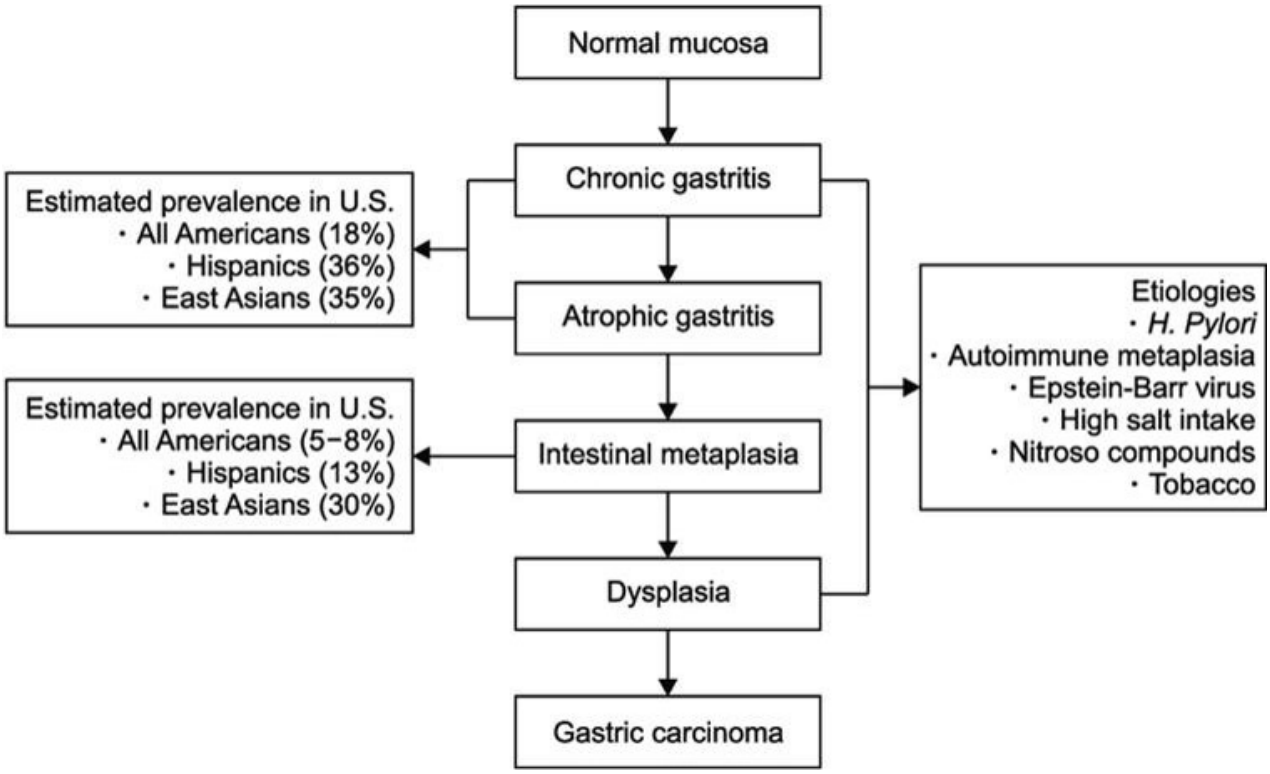


Fig. 2. Correa's cascade of gastric carcinogenesis [45].

The first step in the cascade is forming chronic mucosal inflammation, independent of the underlying cause (H. pylori infection, AIG, environmental factors). Chronic mucosal inflammation will eventually lead to multifocal glandular atrophy with the loss of parietal cells and acid secretion. During further progression, IM will develop by replacing intestinal-type epithelium, characterised by mucin-containing goblet cells, resulting in the decrement of pepsinogen I progression. This promotes dysplasia, characterised by a neoplastic cellular phenotype with large, hyperchromatic cells and disorganised nuclei, respecting cellular boundaries and lack of penetration across the lamina propria. Eventually, invasive carcinoma develops by breaking through cell boundaries and lamina propria *(Fig2.)*.

Identifying high-risk populations would be crucial in implementing an early intervention to improve the prognosis of gastric carcinoma. A histological staging of atrophy may help identify these patients and predict cancer risk. Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) is grading and staging standards developed by the Sydney System [53, 54]. These systems are based on histological findings and provide information on the extent and severity of atrophy and intestinal metaplasia. Even though the OLGA score is more sensitive and applicable than OLGIM, some studies suggest using it together for correct staging [55].

Mucosal atrophy is scored according to the visual analogue scale of the Houston – updated Sydney system. It follows a 4-tiered scale from 0 to 3, depending on the percentage of atrophic glands in each biopsy specimen: no atrophy, 0%, score=0; mild atrophy, 1～ 30%, score=1; moderate atrophy, 31～60%, score=2; severe atrophy, ＞60%, score=3. OLGA score is set by combining the overall score of the topographic locations (oxyntic and angular/ antral) atrophy [56]. Setting OLGIM score is classified similarly. *(Fig.3.)* Patients with OLGA/OLGIM III/IV are considered at high risk for the development of gastric cancer.

A

Atrophy score		Corpus			
		No atroph (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
Antrum (Including incisura angularis)	No atroph (score 0)	Stage 0	Stage I	Stage II	Stage II
	Mild atrophy (score 1)	Stage I	Stage I	Stage II	Stage III
	Moderate atrophy (score 2)	Stage II	Stage II	Stage III	Stage IV
	Severe atrophy (score 3)	Stage III	Stage III	Stage IV	Stage IV

B

IM score		Corpus			
		No IM (score 0)	Mild IM (score 1)	Moderate IM (score 2)	Severe IM (score 3)
Antrum (Including incisura angularis)	No IM (score 0)	Stage 0	Stage I	Stage II	Stage II
	Mild IM (score 1)	Stage I	Stage I	Stage II	Stage III
	Moderate IM (score 2)	Stage II	Stage II	Stage III	Stage IV
	Severe IM (score 3)	Stage III	Stage III	Stage IV	Stage IV

Fig.3. Operative link on gastritis assessment staging system (A) and operative link on gastric intestinal metaplasia assessment (B) staging system [57].

Although there is no specific treatment for chronic gastritis, identifying and treating the underlying cause would be crucial in preventing gastric cancer: it can result in the normalisation of the gastric mucosa in cases where the gastritis is not developed to the atrophic end stages. Therefore, a specific follow-up strategy should be set up; endoscopic surveillance has not been fully established in terms of follow-up intervals and duration.

3.5 Gastric cancer

Patients with CG are at increased risk for developing both gastric neuroendocrine tumours and adenocarcinomas. Neuroendocrine tumours are characteristic of AIG, and in patients with *H. pylori* infection is believed to be rare but has been described [5, 58].

3.5.1 Gastric neuroendocrine (carcinoid) tumours

There are limited data available about carcinoid tumours in patients with CG, but literature data suggest an annual incidence of 0.68 per cent per person-years [59].

These tumours have been associated with elevated serum gastrin levels: they arise from the transformation of enterochromaffin-like (ECL) cells within the oxyntic mucosa. ECL are responsible for histamine secretion and is stimulated by gastrin. Hypochlorhydria/achlorhydria associated with AIG causes hyperplasia in the gastrin-producing G-cells and, consequently, hypergastrinemia [5]. Infection with H. pylori may cause elevated gastrin levels as well.

Carcinoid tumours are usually multiple, small (<1 cm) nodules or polyps, which can be confused with pseudopolyps in the case of AIG [5]. Antrectomy may normalise the plasma gastrin concentration and lead to reverse ECL hyperplasia and reduced tumour size [60, 61].

3.5.2 Gastric adenocarcinomas

Gastric adenocarcinoma is the most common histological type among gastric cancers (about 90 to 95%) [62]. It arises from the gland cells of the mucosa and develops in the milieu of mucosal atrophy and IM.

It is one of the most common cancers worldwide, affecting over 20,000 patients yearly in the USA. At the time of presentations, 50% of the patients already have advanced staged cancer,

which extends beyond locoregional confines, and only half of those can undergo curative resection. Tumours with early stages are usually asymptomatic and can be detected by screening programs. The average 5-year survival rate is less than 20% [63, 64].

The prognosis can be improved by early diagnosis and therapy: detecting the tumour before reaching the muscular layer of the stomach is important. In that case, the 5-year survival rate can be up to 90% [65].

A significant decrease in gastric cancer incidence and mortality has been observed recently [66]. It is possible due to the identification and elimination of the underlying causes, globally decreased incidence of *H. pylori* infection and reduced use of tobacco and dietary salt [63, 67]. Despite this reduction and the effective *H. pylori* eradication strategy, gastric cancer is still the fifth most common cancer worldwide [68], which raises the possibility of further causative factors. Besides AIG and *H. pylori* infection, several studies suggest a potential association between systemic AI disorders and gastric cancer; however, the relevant data have been controversial [69, 70].

4 AIMS, OBJECTIVES AND HYPOTHESES

A) Autoimmune disorders and gastric cancer

Given the controversial data regarding the connection between systemic AI disorders and gastric cancer,

1) we aimed to provide a comprehensive summary of the potential association and the incidence of gastric cancer in AI disorders in a meta-analysis and systematic review.

Based on the literature, we hypothesised that the incidence of gastric cancer is higher in systemic AI disorders.

B) Chronic gastritis and autoimmunity

Although chronic gastritis is one of the most common GI disorders, the aetiology often remains unknown. If the diagnostic tests for *H. pylori* infection and AIG are negative, exploring other possible causative factors, e.g., autoinflammatory diseases, are not carried out routinely. However, clarifying the underlying aetiology might be beneficial for preventing the development of gastric neoplasms**.** In a retrospective study, we aimed to

2) discover the possible etiologic factors of CG;
3) to investigate the possible relationship between these factors and IM and atrophy;
4) to determine the prevalence of systemic AI disorder-related autoantibody positivity in CG in southwestern Hungary;
5) to investigate the role of autoantibody positivity in the course and progression of CG;
6) to revise the current clinical practice in diagnosing and managing CG.

Based on previous studies, we expected a high rate of AI positivity behind CG of unknown origin, causing a worse histological outcome (atrophia, IM).

C. Dyspepsia and autoimmunity in *H. pylori*-negative chronic gastritis

It has been postulated in previous studies that immune activation might play a role in the pathogenesis of FD, but the correlation between systemic AI disorders and FD is uncertain. Regarding the uncertainty in this topic, in a retrospective study, we aimed

7) to determine the prevalence and investigate the possible role of dyspeptic symptoms in patients with *H. pylori*-negative CG;
8) to assess the occurrence and pattern of other GI symptoms in CG.

Based on the literature, we hypothesised that AI positivity predisposes dyspeptic symptoms in patients with CG.

5 METHODS

5.1 Methods of the meta-analysis

To answer our 1st question, our work was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [71]. The study protocol was registered on PROSPERO International Prospective Register of Systematic Reviews under registration number CRD42021262875 (see https://www.crd.york.ac.uk/prospero). We did not deviate from the protocol defined in advance.

5.1.1 Search strategy

The systematic search was performed in four scientific databases—MEDLINE via PubMed; Cochrane Central Register of Controlled Trials (CENTRAL); Embase; and Web of Science, Latin American and Caribbean Health Sciences Literature (LILACS)—up to May 17, 2021. The following search terms were used without any restriction to language or other filters: (stomach OR gastric) AND (neoplas* OR malign* OR cancer OR carcinoma OR lymphoma OR tumor OR tumour) AND ("autoimmun*" OR autoaggressive OR autoantibody OR lupus OR rheuma* OR Addison* OR celiac OR "gluten sensitive" OR dermatomyositis OR Hashimoto OR graves OR sclerosis OR scleroderma OR myasthenia OR arthritis OR Sjögren*). The reference lists of the citing and cited articles were also screened, and all eligible records were included in the analysis.

5.1.2 Selection and eligibility criteria

Duplicates were removed by EndNote X9 software (Clarivate Analytics, Philadelphia, PA, USA) and manually, and then the title-, abstract- and full-text screening was performed by two investigators to accelerate the selection process. Disagreements were resolved by a third investigator.

The inclusion criteria specified any peer-reviewed studies reporting the standardised incidence ratio (SIR) of gastric cancer in an AI disorder in the general population. There were no restrictions on the type of gastric cancer, language, or study design eligible for inclusion. We included only full texts and excluded studies with no event rate of SIR.

5.1.3 Data extraction

At the end of the screening process, relevant data were independently extracted from studies into a standardised data collection form by two independent reviewers. These included: title, first author, year of publication, country, study design, age of the population (mean, standard deviation [SD], median, interquartile ranges), gender distribution, the total number of patients (with autoimmune disorders), type of autoimmune disorders, follow-up time, and standardised incidence ratios of gastric cancer (observed, expected, SIR, confidence interval [CI]). Disagreements were resolved by a third independent co-author.

5.1.4 Data synthesis

We pooled SIRs of gastric cancer in each autoimmune disorder. After the extraction of SIRs, pooling was carried out by the inverse variance method and random-effects model with the restricted maximum likelihood (REML) estimation. These results were displayed on forest plots. Summary SIR estimation, *p*-value, and 95% CI were also calculated.

Statistical heterogeneity was assessed using χ^2 and the I^2 statistics to acquire probability values, and I^2 represents the percentage of effect size heterogeneity that cannot be explained by random chance. Significant heterogeneity is considered when $p < 0.1$. As suggested by the Cochrane Handbook, I^2 values were interpreted as moderate (30%–60%), substantial (50%–90%), and considerable (75%–100%) heterogeneity [72]. To check for publication bias, the visual

inspection of funnel plots and Eggers' tests were performed (alpha = 0·1) [73]. In the case of more than ten studies included, the Eggers test was carried out for each AI disorder.

Subgroup analyses were performed for gender and high-and low-incidence countries in gastric cancer [74]. Quantitative synthesis was performed when more than three articles reported eligible data for analysis. Otherwise, the findings were summarised in the qualitative synthesis. All analyses were performed using R statistical software (R Foundation, Vienna, Austria) with the meta package (Guido Schwarzer, v4.18-2).

5.1.5 Risk of Bias Assessment in Individual Studies

The quality of the included studies was analysed with the Quality in Prognostic Studies (QUIPS) tool, focusing on the definition of prognostic factors and outcomes [75]. A third party resolved disagreements.

5.2 Methods of the studies

To answer questions 2-8, our studies were conducted from January 2016 to January 2020 with the enrolment of all patients with histologically proved CG who underwent immune serological testing. The diagnosis of CG was set up based on multiple biopsy samples (minimum of five) from the predefined sites of the stomach and every detected focal lesion, according to the Updated Sydney system [6]. To avoid performance bias, all included the same single-unit medical team managed patients (single examining endoscopic specialist, one pathologist specialised in GI pathology reviewed all the histological findings). Patients were enrolled on the studies from regular patient care.

We excluded all patients from the studies having any of the followings: (1) acute gastritis; (2) reactive gastropathy; (4) subjects without any serology testing results; (5) *H. pylori* positivity; (6) gastro-oesophageal reflux disease (GERD); (7) ulcer; (8) cancer. The diagnosis of acute gastritis, GERD, ulcer or cancer was confirmed by histology. Reactive gastropathy, also called

reflux gastritis, is determined by specified histological criteria [76]. *H. pylori* infection status was diagnosed with endoscopy followed by histology, serological testing, and urea breath test (UBT). Given the well-known association between *H. pylori* infection and both dyspepsia and chronic atrophic gastritis, *H. pylori* can be considered a confounding factor. Therefore, *H. pylori*-positive CG patients were ruled out from the final analysis to minimise biases.

Eligible patients were identified from an electronic database. The data collection included: baseline characteristics of the analysed population (age, gender and their correlation to the outcome measures); histological findings (localisation of the inflammation; OLGA score; and the presence of atrophy, IM, GERD, ulcer or cancer); autoantibody positivity (celiac disease-, Sjögren's syndrome-, systemic lupus erythematosus (SLE)-, AI hepatitis-, rheumatoid arthritis (RA)-, SSc (systemic sclerosis)-, polymyositis/dermatomyositis-, AI thyroiditis-, IBD-, vasculitis-, AIG-related antibodies); *H. pylori* infection status (histology, results of the UBT and serology); the presence and type of symptoms (key symptoms and presence of dyspepsia-like symptoms: postprandial fullness, early satiety, epigastric pain, and epigastric burning); and data on other risk factors (body mass index, alcohol consumption and smoking). We categorised patients into two groups according to their AI-serology results: autoantibody seropositive (AISP) and autoantibody seronegative (AISN).

AI positivity was determined using the threshold of the laboratory of our clinical centre in line with the European Autoimmunity Standardisation Initiative (EASI) [77, 78]. Autoantibodies were grouped according to their occurrence in certain AI diseases *(Table 1.)*.

Disease	Attributed antibodies
Celiac disease	Anti-gliadin, anti-endomysium, tissue transglutaminase antibody IgA and/or IgG
Sjögren's syndrome	Anti-Sjögren's syndrome-related antigen A (SSA), anti-Sjögren's syndrome-related antigen B (SSB)
Systemic lupus erythematosus (SLE)	Anti-nuclear antibodies (ANA), anti-nucleosome antibodies, anti-cardiolipin, anti-centromere, anti-C1q, anti-b2 glycoprotein, anti-double-stranded DNA (ds-DNA)
Autoimmune hepatitis	Anti-smooth muscle antibodies (SMA), anti-liver kidney microsomal antibodies (LKM-1, LKM-2, LKM-3), anti-soluble liver antigens (SLA), liver–pancreas antigens (LP), anti-mitochondrial antibodies (AMA), anti-filamentous actin 1 antibodies (F1 actin)
Rheumatoid arthritis (RA)	Anti-cyclic citrullinated peptide antibodies (CCP), anti-rheumatoid factor (RF) antibodies
Systemic sclerosis (Ssc)	Anti-Scl-70 antibodies, anti-centromere antibodies
Polymyositis/dermatomyositis	Anti-Jo-1 antibodies
Inflammatory bowel disease (IBD)	Anti-yeast *Saccharomyces cerevisiae* (ASCA), anti-neutrophil cytoplasmic antibodies (ANCA)
AI thyroiditis	Anti-thyroid peroxidase (TPO), anti-TSH receptor antibodies (TRAb), anti-thyroglobulin antibodies (Tg)
AI gastritis	Anti-parietal cell antibodies, anti-intrinsic factor antibody

Table 1. Grouping autoantibodies according to the specific autoimmune disorders in our studies.

The patient's body weight and height were measured at the gastroenterological examination. Based on their body mass index (BMI), following international standards, patients were grouped into high BMI ≥ 25 kg/m^2 and those below with low BMI [79].

5.2.1 Endpoints

5.2.1.1 Endpoints for AIMs 2-6

We assigned a composite endpoint for the primary endpoint, which included gastric atrophy and IM. In addition, the following secondary endpoints were assessed: the prevalence of each antibody positivity and the stage of the atrophy based on the OLGA score. All parameters were analysed at the level of AI disease-, AISP-, and AISN groups. If the sample size reached at least eight patients, additional analysis was performed at the individual level of each autoantibody. The role of simultaneous AI positivity (2 or more AI diseases are present) in elevated risk of precancerous lesions was also examined.

5.2.1.2 Endpoints for AIMs 7-8

The primary endpoint was the association between AI positivity and dyspepsia-like symptoms (according to the Rome IV criteria [26]). Secondary endpoints were the frequency of symptoms in CG, the association between AISP and the most frequently occurring symptoms, the location of the inflammation in the stomach, and the association between AISP and the affected region of the inflammation. All endpoints were analysed on the level of AI disease, AISP-, and AISN groups.

The data collection and research were approved by the director of the Clinical Centre and the director of the First Department of Medicine of the University of Pécs (Institutional Review Board; case number: KK/999-1/2020). The data collection and analysis were carried out following current laws and regulations and ethical guidelines of the Declaration of Helsinki updated in 2013 as reflected in a priori approval by the Institutional Review Board [80]. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [81] was also followed during the study process. To ensure personal data protection and privacy, all included patients received a numeric code. Informed consent was not required due to the retrospective nature of the studies, and the University of Pécs automatically obtains a general allowance for scientific purpose data usage from all patients. However, if patients refused scientific data handling at the time of admission, they were not included in the analyses.

5.2.2 Statistical analysis

SPSS 25.0 software was used for analyses. Descriptive statistics (mean, SD and minimum and maximum values) and univariate analyses were performed for both studies. 2-sided Pearson Chi-square was carried out to compare dichotomous variables for patient frequencies. In the case of significant differences, standardised residuals were also observed to arrive at the exact results. Regarding continuous variables, an independent sample t-test was used. We followed the distribution on Q-Q-plot. A P-value of less than 0.05 was considered statistically significant.

Furthermore, to answer questions 2-6, multivariate analyses (adjusted for gender and age) were performed, and odds ratios (OR)s with a 95% CI were calculated. Multinominal logistic regression was performed when co-factors were also considered.

6 RESULTS

6.1 Results of the meta-analysis

6.1.1 Search and selection

Our systematic search identified 8,206 records, of which 12,420 remained after duplicate removal, of which 43 studies were included in the final analysis. Forty studies were included in the meta-analysis, and nine additional studies were in the systematic review *(Fig.4.)*.

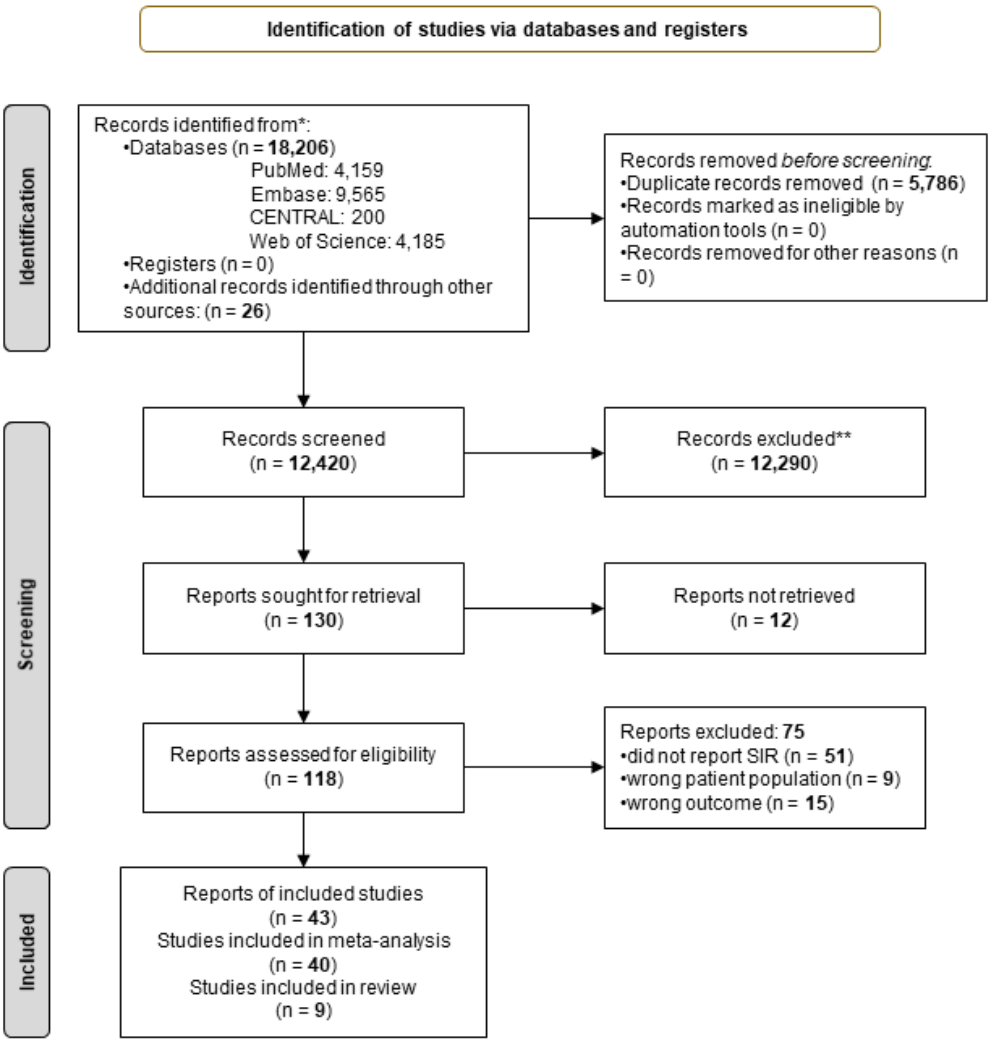


Fig. 4. Preferred Reporting in Systematic Reviews and Meta-analyses 2020 (PRISMA) flowchart showing the selection process [71].

6.1.2 Basic characteristics of the included studies

The included 43 studies describe 36 AI diseases, with 499,427 patients from four continents (America, Europe, Asia, and Australia) and 15 countries. Of the included articles, four studies were retrospective, and 39 were prospective *(Table 2.)*.

Author (year)	Year	Country	Disease(s) studied	Study population (% of females)	SIR of gastric cancer (95% CI)
Asano et al.	2015	Japan	AIP	109 (23)	1.35 (0.03-2.66)
			IgG4-RD	158 (25)	1.43 (0.03-2.83)
Askling et al.	2002	Japan	Celiac disease	11019 (59)	0.90 (0.3-2.0)
			Dermatitis herpetiformis	1354 (43)	1.4 (0.6-2.8)
Bernatsky et al.	2013	Multinational	SLE	16409 (90)	1.19 (0.65-2.00)
Bjørneklett et al.	2007	Norway	Membranous nephropathy	161 (36)	2.74 (0.07-15.3)
Brinton et al.	1989	USA	Perniciosus anaemia	5161 (0)	**3.21 (2.2-4.6)**
Brito-Zerón et al.	2017	Spain	Sjögren's syndrome	1239 (92)	2.23 (0.93-5.36)
Chang et al.	2014	South Korea	RA	2104 (82)	0.663 (0.327-0.998)
Chang et al.	2015	South Korea	SLE	1052 (89)	0.597 (0.123-1.744)
Chang et al.	2016	South Korea	SSc	274 (88)	0.898 (0.109-3.245)
Chang et al.	2017	South Korea	Dermatomyositis	107 (81)	1.629 (0.041-9.076)
Chang et al.	2018	South Korea	Polymyositis	49 (40)	2.113 (0.054-11.774)
Chen et al.	2010	Taiwan	SLE	11763 (88)	**2.08 (1.97-2.19)**
Collin et al.	1996	Finland	Celiac disease	383 (73)	0 (0-6.18)
			Dermatitis herpetiformis	305 (47)	2.86 (0.35-10.3)
Dreyer et al.	2011	Denmark	SLE	576 (88)	N/A
Goldrace et al.	2007	UK	Celiac disease	1997 (NA)	1.83 (0.79-3.62)
			Crohn's disease	5127 (NA)	0.96 (0.44-1.83)
			Ulcerative colitis	6990 (NA)	0.78 (0.39-1.41)
Gridley et al.	1993	Sweden	RA	11683 (68)	0.63 (0.5-0.9)
Harding et al.	2015	Australia	T1DM	80676 (48)	**1.37 (1.01-1.87)**
Hashimoto et al.	2012	Japan	SSc	405 (93)	0.84 (-0.11-1.79)
Hashimoto et al.	2015	Japan	RA	NA (82)	0.83 (0.65-1.02)
Hemminki et al.	2011	Sweden	Addison's disease	1594 (NA)	**2.74 (1.24-5.23)**
			ALS	4262 (NA)	0.96 (0.25-2.49)
			Ankylosing spondylitis	5173 (NA)	0.92 (0.49-1.57)
			Behcet disease	2860 (NA)	1.66 (0.83-2.99)
			Celiac disease	4124 (NA)	N/A
			Chronic rheumatic heart disease	16770 (NA)	**1.4 (1.07-1.81)**
			Crohn's disease	28349 (NA)	0.87 (0.63-1.17)
			Graves'/hyperthyroidism	36240 (NA)	**1.31 (1.07-1.59)**
			Hashimoto/hypothroidism	10682 (NA)	1.34 (0.87-1.96)
			ITP	1709 (NA)	**3.04 (1.09-6.66)**
			Localized scleroderma	3128 (NA)	1.56 (0.7-2.55)
			Multiple sclerosis	12553 (NA)	0.55 (0.28-0.97)
			Myasthenia gravis	17974 (NA)	**1.38 (1.14-1.65)**
			PBC	835 (NA)	1.29 (0.12-4.75)
			Pernicious anemia	11839 (NA)	**4.09 (3.36-4.94)**
			Polyarteritis nodosa	12046 (NA)	1.02 (0.71-1.42)
			Polymyalgia rheumatica	14745 (NA)	**1.45 (1.11-1.85)**
			Polymyositis/dermatomyositis	1256 (NA)	2.74 (0.99-6.01)
			Psoriasis	15592 (NA)	1.28 (0.94-1.69)
			RA	26937 (NA)	1.07 (0.82-1.38)
			Rheumatic fever	3458 (NA)	1.5 (0.86-2.44)
			Sarcoidosis	9053 (NA)	1.45 (0.98-2.06)

Author (year)	Year	Country	Disease(s) studied	Study population (% of females)	SIR of gastric cancer (95% CI)
			Sjögren's syndrome	3769 (NA)	1.42 (0.73-2.48)
			SLE	5318 (NA)	1.2 (0.57-2.21)
			SSc	1195 (NA)	1.32 (0.12-4.87)
			T1DM	20554 (NA)	2.64 (0.83-6.21)
			Ulcerative colitis	16363 (NA)	0.88 (0.49-1.45)
			Wegener granulomatosis	945 (NA)	0.45 (0-2.59)
Hill et al.	2001	Sweden, Denmark, Finland	Dermatomyositis	618 (NA)	**3.5 (1.7-7.3)**
			Polymyositis	914 (NA)	0.3 (0.04-1.9)
Hirano et al.	2004	Japan	IgG4-RD, AIP	113 (20)	0.75 (0.086-2.59)
Hsing et al.	1993	Sweden	Pernicious anemia	4517 (55)	**M: 2.8 (2-3.6)** **F: 3.1 (2.3-4.1)**
Hsu et al.	2015	Taiwan	T1DM	14619 (53)	M: 1.08(0.63-1.72) F: 1.33 (0.73-2.24)
Ilus et al.	2014	Finland	Celiac disease	32439 (65)	0.9 (0.63-1.23)
Isomäki et al.	1978	Finland	Ankylosing spondylitis, Rheumatoid arthritis	46101 (75)	N/A
Ji et al.	2010	Sweden	Addison's disease	NA	1.48 (0.47-3.48)
			ALS	NA	1.18 (0.56-2.18)
			Ankylosing spondylitis	NA	1.31 (0.85-1.92)
			Celiac disease	NA	1.2 (0.78-1.75)
			Chronic rheumatic heart disease	NA	0.52 (0.16-1.22)
			Crohn's disease	NA	**1.41 (1.12-1.75)**
			Discoid lupus erythematosus	NA	1.75 (0.83-3.23)
			Graves'/hyperthyroidism	NA	**1.33 (1.09-1.61)**
			Hashimoto/hypothyroidism	NA	0.9 (0.61-1.27)
			Localized scleroderma	NA	1.13 (0.48-2.24)
			Multiple sclerosis	NA	1.23 (0.87-1.7)
			Myasthenia gravis	NA	**1.64 (1.07-2.41)**
			PBC	NA	0.92 (0.29-2.16)
			Pernicious anemia	NA	2.11 (0.84-4.38)
			Polymyalgia rheumatica	NA	1.32 (0.99-1.73)
			Psoriasis	NA	**1.17 (1-1.35)**
			RA	NA	**1.2 (1.02-1.41)**
			Rheumatic fever	NA	1.78 (0.81-3.39)
			Sarcoidosis	NA	**1.53 (1.09-2.07)**
			Sjögren's syndrome	NA	0.75 (0.43-1.2)
			SLE	NA	1.08 (0.59-1.81)
			SSc	NA	1.09 (0.5-2.09)
			T1DM	NA	**1.27 (1.08-1.48)**
			Ulcerative colitis	NA	**1.39 (1.14-1.69)**
Ji et al.	2018	Sweden	Giant cell arteritis, Polymyalgia rheumatica	35918 (NA)	**1.27 (1.07-1.5)**
Kang et al.	2009	South Korea	SSc	112 (74)	**3 (1.9-4.1)**
Kirkegård et al.	2018	Denmark	Hyperthyroidism	92783 (83)	**1.24 (1.08-1.42)**
			Hypothyroidism	71189 (84)	**1.49 (1.26-1.75)**

Author (year)	Year	Country	Disease(s) studied	Study population (% of females)	SIR of gastric cancer (95% CI)
Koskinen et al.	2021	Finland	Celiac disease	1460 (63)	1.91 (0.95-3.41)
Lee H et al.	2019	South Korea	RA	1885 (84)	M: 1.17 (0.22-2.88) F: 2.03 (0.97-3.48)
Lim et al.	2019	Singapore	RA	1117 (84)	1.43 (0.6-3.44)
Lööf et al.	1994	Sweden	PBC	559 (88)	1.3 (0-7.2)
Nam et al.	2019	South Korea	Ankylosing spondylitis	21780 (0)	0.93 (0.65-1.21)
Park et al.	2014	South Korea	Takayasu arteritis	180 (87)	1.4 (0-7.9)
Shiokawa et al.	2013	Japan	AIP	108 (26)	**2.7 (1.4-3.9)**
Shu X et al.	2010	Sweden	T1DM	24052 (47)	**3.,31 (1.41-6.56)**
Silano et al.	2007	Italy	Celiac disease	3463 (43)	**3 (1.3-4.9)**
Stockton et al.	2000	Scotland	Dermatomyositis	286 (66)	**10 (2.1-29.2)**
Swerdlow et al.	2005	UK	T1DM	29701 (44)	1.2 (0.48-2.47)
Swerdlow et al.	2006	UK	T1DM	29701 (44)	0.77 (0.4-1.35)
Tallbacka et al.	2018	Finland	SLE	205 (89)	1.2 (0.03-6.7)
Thomas et al.	2000	Scotland	RA	26623 (73)	M: 1.05 (0.74-1.46) F: 0.7 (0.5-0.95)
Van Daalen et al.	2017	The Netherlands	ANCA vasculitis	203 (35)	2.37 (0.06-13.2)
Viljaama et al.	2005	Finland	Celiac disease	781 (68)	1.2 (0.2-4.5)
			Dermatitis herpetiformis	366 (48)	2.1 (0.4-6.3)
Weng et al.	2015	Taiwan	Sjögren's syndrome	7852 (88)	1.56 (0.75-2.86)
Yamada et al.	2011	Japan	RA	7566 (82)	1.19 (0.8-1.7)
Yoo et al.	2018	South Korea	ANCA vasculitis	150 (69)	0.36 (0.009-2.012)
Yu et al.	2016	Taiwan	Behçet disease	1620 (57)	N/A
			Dermatomyositis	1119 (67)	1.88 (0.47-7.52)
			Inflammatory bowel disease	2853 (37)	0.53 (0.13-2.11)
			Kawasaki disease	3469 (60)	N/A
			Other vasculitis	644 (36)	N/A
			Polymyositis	811 (67)	N/A
			RA	35182 (77)	0.92 (0.72-1.16)
			Sjögren's syndrome	11988 (89)	1 (0.63-1.58)
			SLE	15623 (88)	1.88 (1.21-2.91)
			SSc	1814 (75)	0.7 (0.17-2.79)

Table 2. Basic characteristics of included studies

SIR: standardised incidence rate, AIP: autoimmune pancreatitis, IgG4-RD: immunoglobulin G4-related disease, SLE: systemic lupus erythematosus, NA: not available, RA: rheumatoid arthritis, SSc: systemic sclerosis, T1DM: type 1 diabetes mellitus, ALS: amyotrophic lateral sclerosis, ITP: immune thrombocytopenic purpura, PBC: primary biliary cirrhosis, M: males, F: females, ANCA: anti-neutrophil cytoplasmic antibody.

6.1.3 Analytical results of associations between autoimmune diseases and gastric cancer

The statistical analysis of the included studies found significantly increased incidence of gastric cancer in the cases **dermatomyositis** (SIR= 3.71; 95%CI: 2.04, 6.75; p< 0.0001) based on four studies, **PA** (SIR= 3.28; 95%CI: 2.71, 3.96; p< 0.0001) based on five studies, **inflammatory myopathies** (SIR= 2.68; 95%CI:1.40; 5.12; p=0.0029) based on seven studies, **SLE** (SIR= 1.48; 95%CI: 1.09, 2.01; p=0.0116) based on seven studies, **T1DM** (SIR= 1.29; 95%CI:1.14, 1.47; p< 0.0001) according to eight studies, and **Graves' disease** (SIR= 1.28; 95%CI: 1.16, 1.41; p< 0.0001) based on three studies. The analysis could not prove increased gastric cancer incidence in AI vasculitis, celiac disease, SSc, dermatitis herpetiformis, Hashimoto thyroiditis, Sjogren's syndrome, IBD, Crohn's disease, RA, ulcerative colitis, ankylosing spondylitis, and primary biliary cirrhosis *(Fig.5.)*.

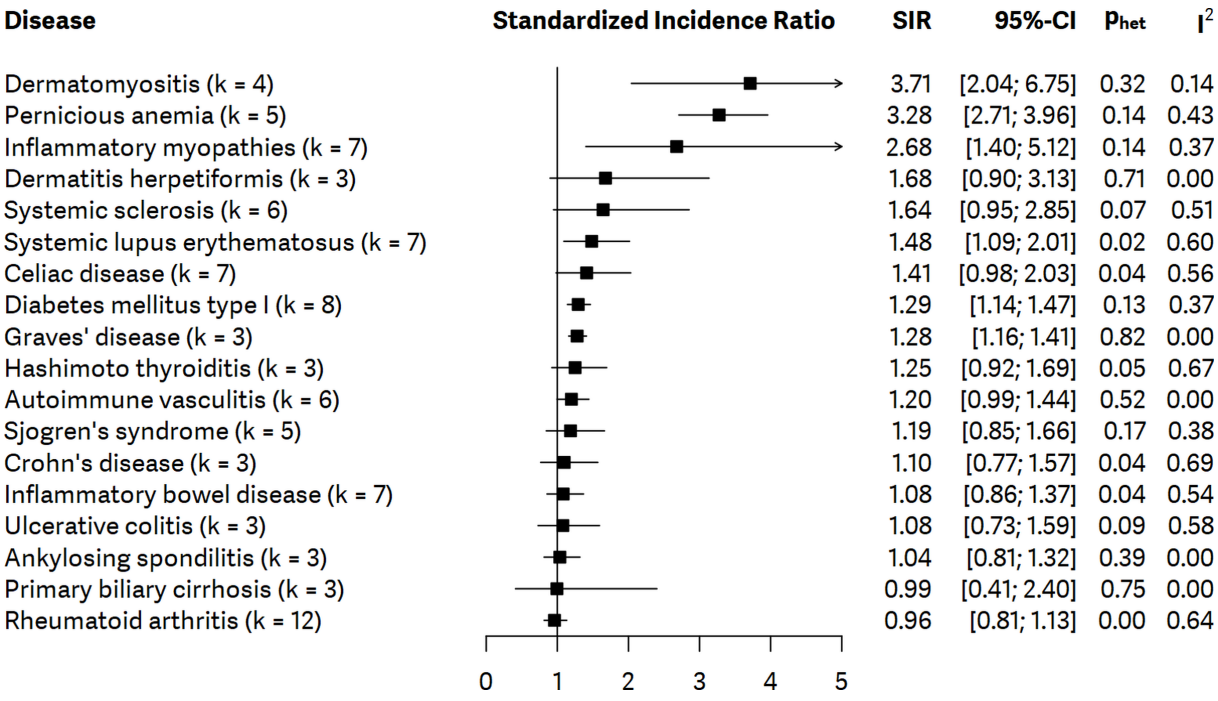


Fig. 5. Summarizing forest plot with pooled standardised incidence ratios (SIRs), representing the incidence of gastric cancer in all patients with autoimmune disorders included in the meta-analysis; the number of studies – k.

6.1.4 Subgroup analysis based on gender

Regarding the subgroup analysis based on gender, an increased incidence of gastric cancer was observed in female patients with T1DM (SIR= 1.62; 95% CI: 1.20, 2.18) but not in male patients *(Fig.6.)*. Rheumatoid arthritis did not increase the incidence of gastric cancer, neither in male nor female patients *(Fig.7.)*. Subgroup analysis could not be carried out with other autoimmune diseases due to the lack of data on gender.

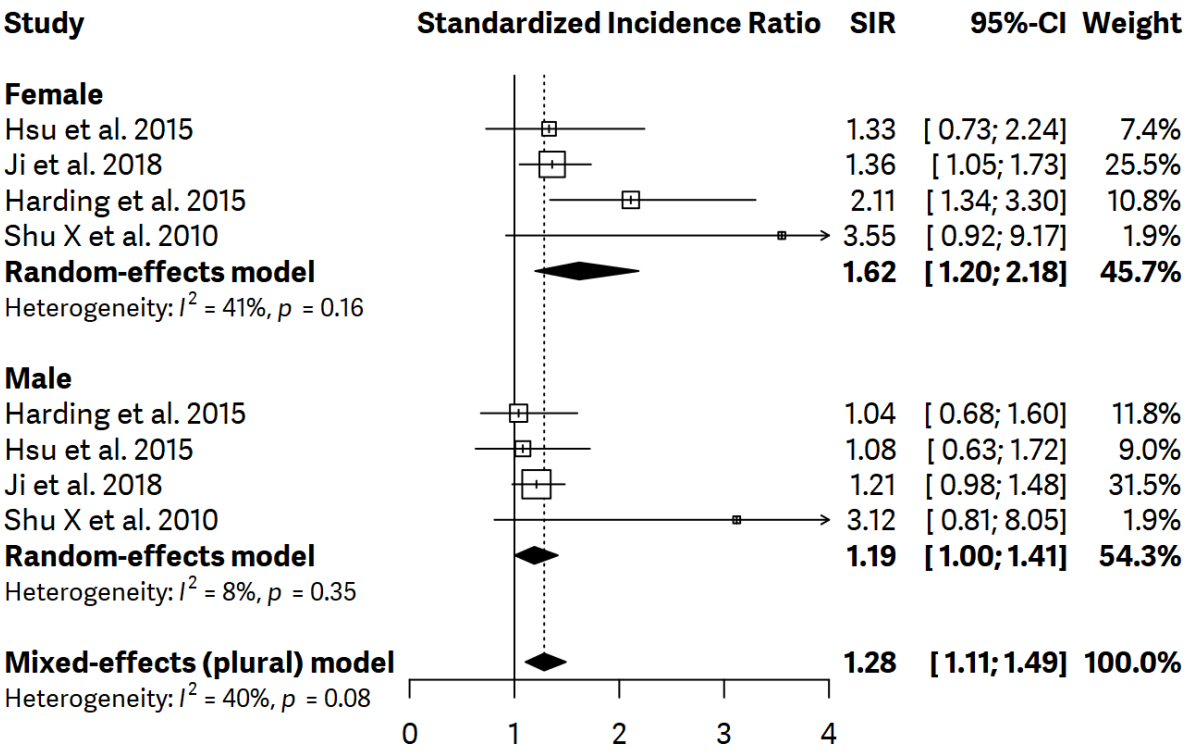


Fig. 6. Forest plot showing subgroup analysis regarding standardized incidence ratios (SIR) of gastric cancer with 95% confidence interval (CI) for diabetes mellitus type 1 based on gender.

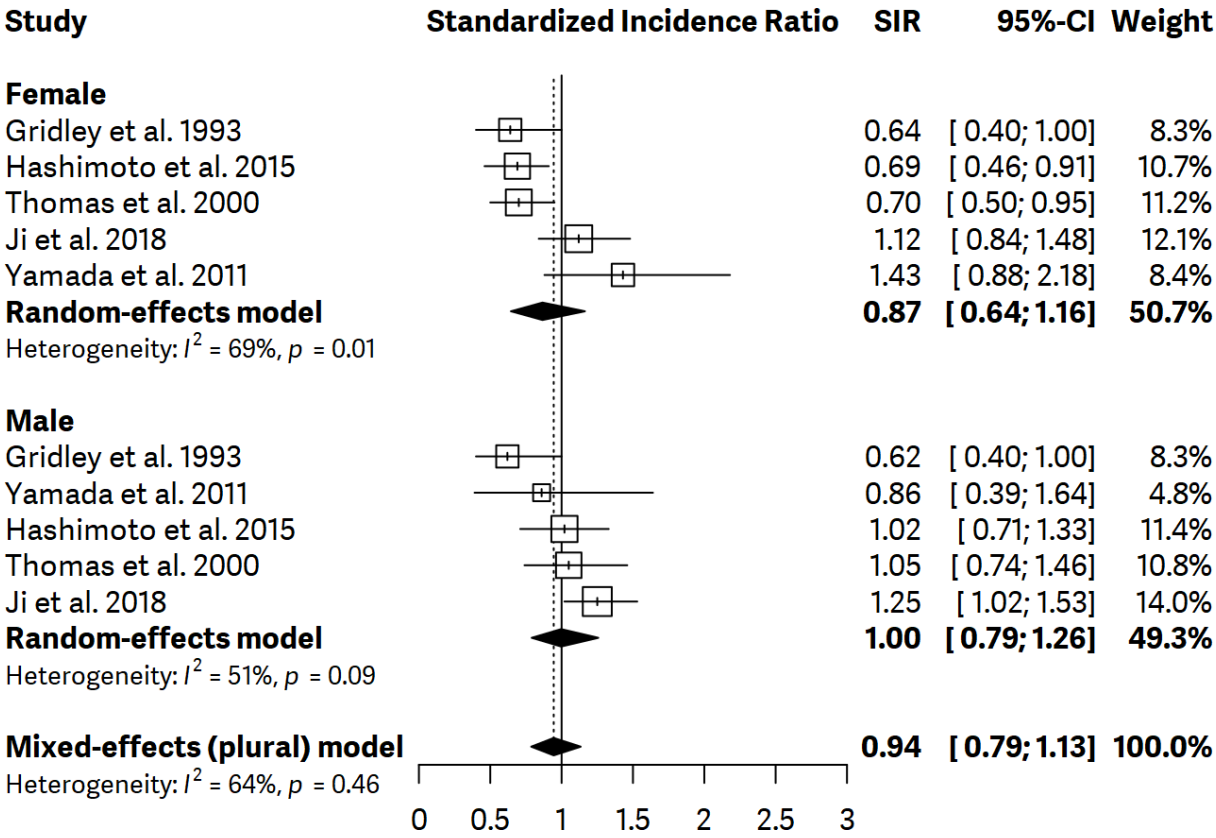


Fig. 7. Forest plot showing subgroup analysis regarding standardised incidence ratios (SIR) of gastric cancer with 95% confidence interval (CI) for rheumatoid arthritis based on gender.

6.1.5 Subgroup analysis based on the incidence of gastric cancer

In low-incidence countries, increased incidence of gastric cancer was observed in case of PA (SIR= 3.28; 95% CI: 2.71, 3.96), T1DM (SIR= 1.41; 95% CI: 1.02, 1.95), Graves' disease (SIR= 1.28; 95% CI: 1.61, 1.41), and autoimmune vasculitis (SIR= 1.21; 95% CI: 1.01, 1.44) *(Fig.8-11.)*. In the case of dermatomyositis (SIR= 5.10; 95% CI: 1.90, 13.67), a higher incidence of gastric cancer was also shown based on two studies; therefore, subgroup analysis could not be carried out *(Fig. 12.)*.

In high-incidence countries, only SLE (SIR= 1.69; 95% CI: 1.21, 2.36) was associated with an increased incidence of gastric cancer (*Fig. 13.).* Regarding other AI disorders, the statistical analysis could not prove any association with gastric cancer.

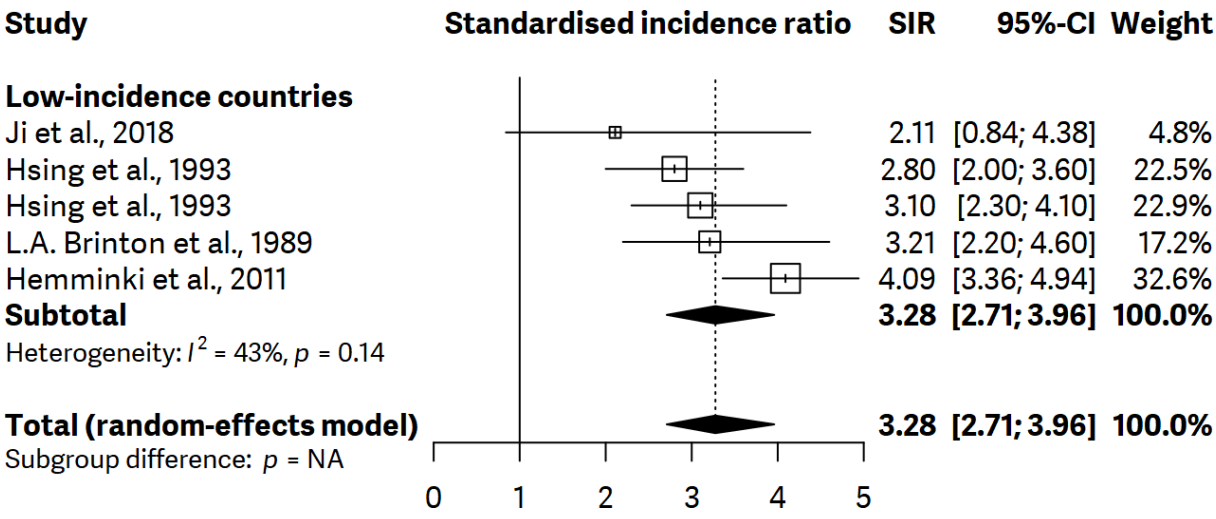


Fig. 8. Forest plot showing subgroup analysis regarding standardized incidence ratios (SIR) of gastric cancer with 95% confidence interval (CI) for pernicious anaemia based on high-, or low-incidence countries of gastric cancer.

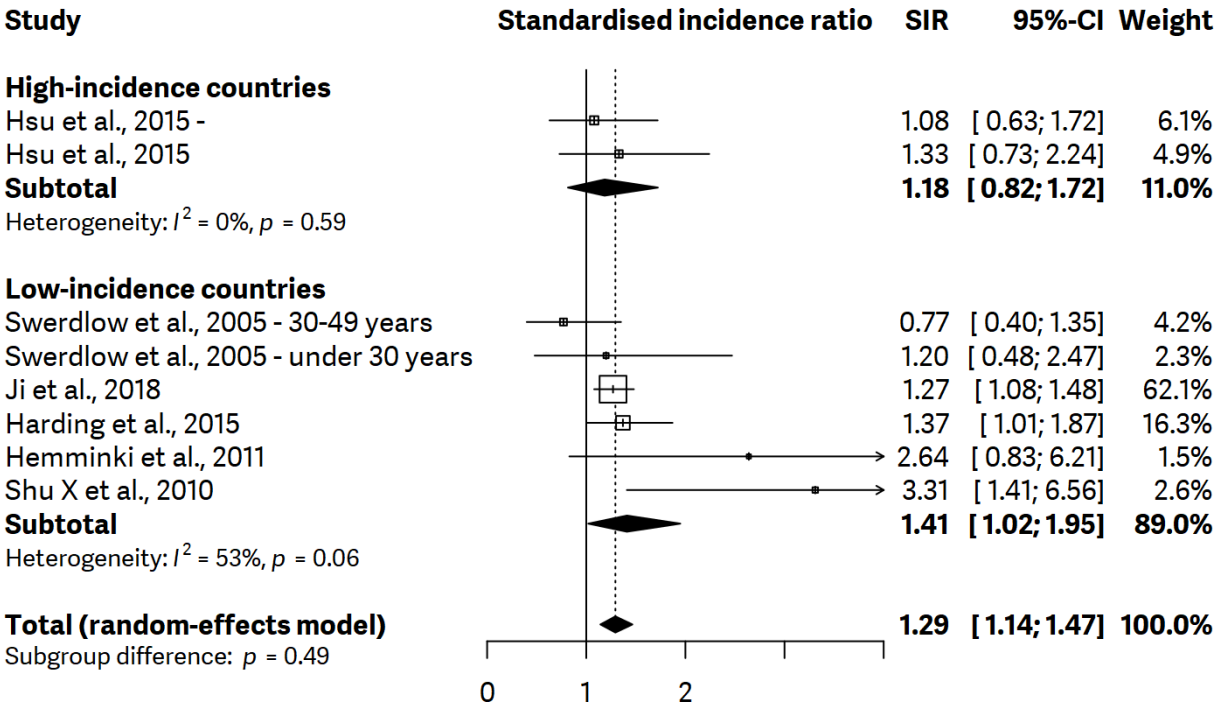


Fig. 9. Forest plot showing subgroup analysis regarding standardized incidence ratios (SIR) of gastric cancer with 95% confidence interval (CI) for diabetes mellitus type I based on high-, or low-incidence countries of gastric cancer.

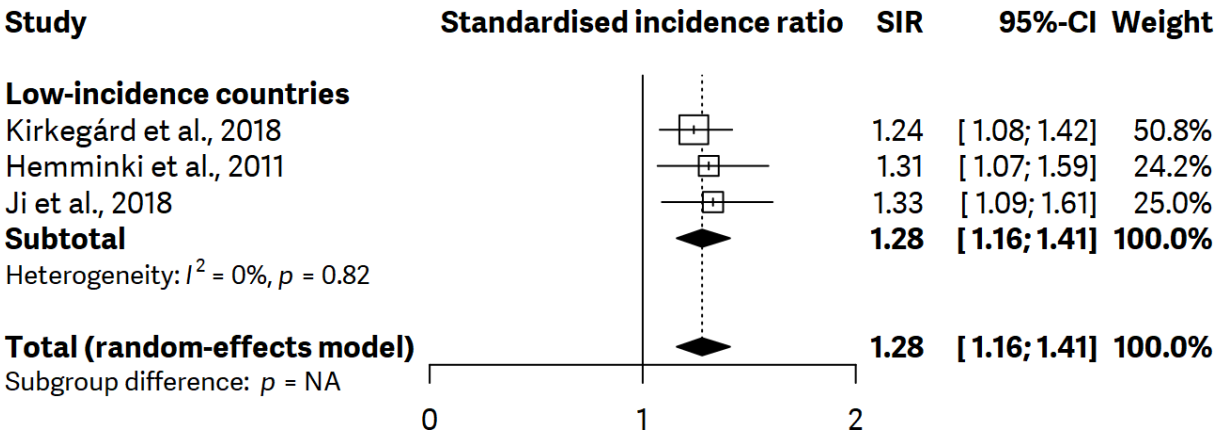


Fig. 10. Forest plot showing subgroup analysis regarding standardized incidence ratios (SIR) of gastric cancer with 95% confidence interval (CI) for Graves' disease based on high-, or low-incidence countries of gastric cancer.

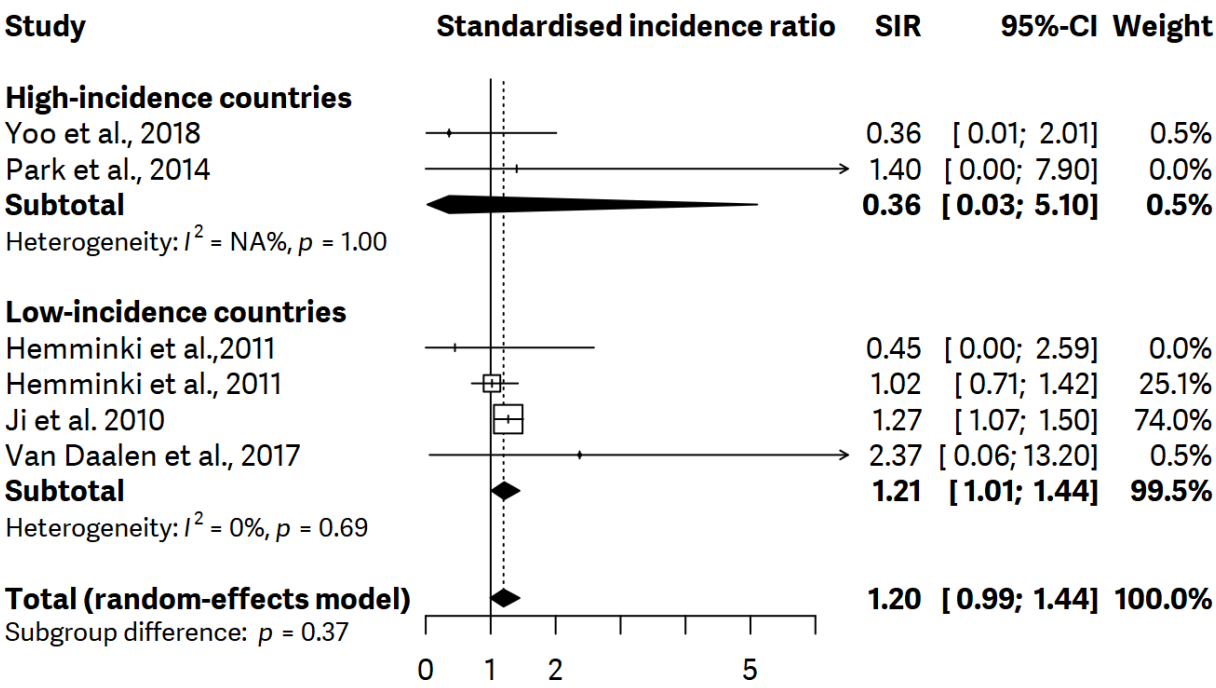


Fig.11. Forest plot showing subgroup analysis regarding standardized incidence ratios (SIR) of gastric cancer with 95% confidence interval (CI) for autoimmune vasculitis based on high-, or low-incidence countries of gastric cancer.

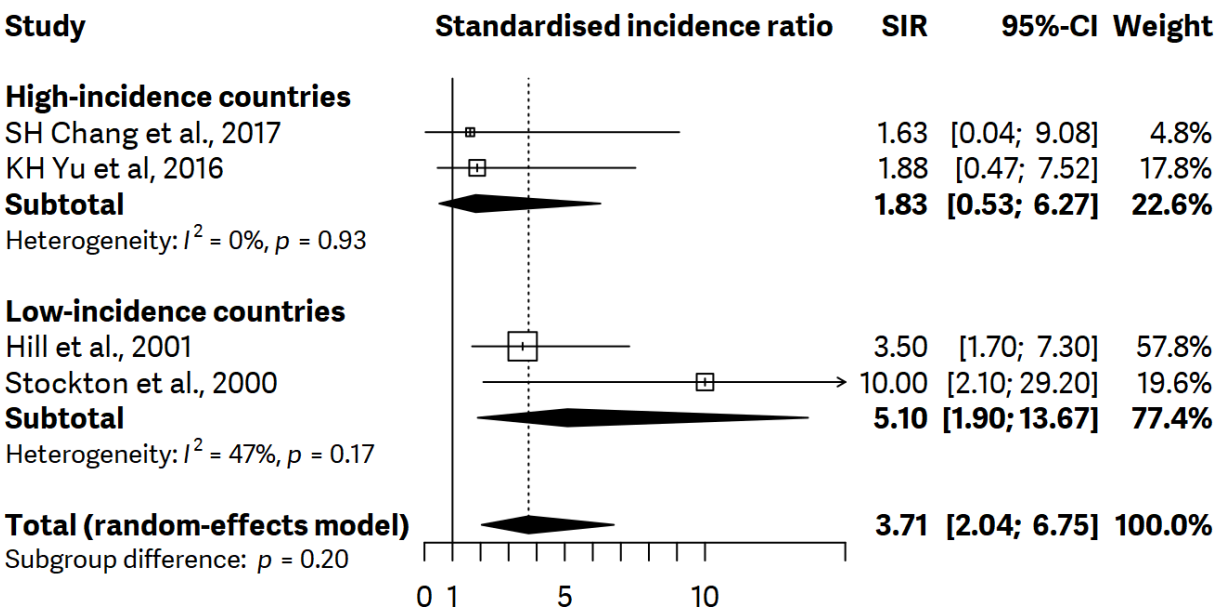


Fig. 12. Forest plot showing subgroup analysis regarding standardized incidence ratios (SIR) of gastric cancer with 95% confidence interval (CI) for dermatomyositis based on high-, or low-incidence countries of gastric cancer.

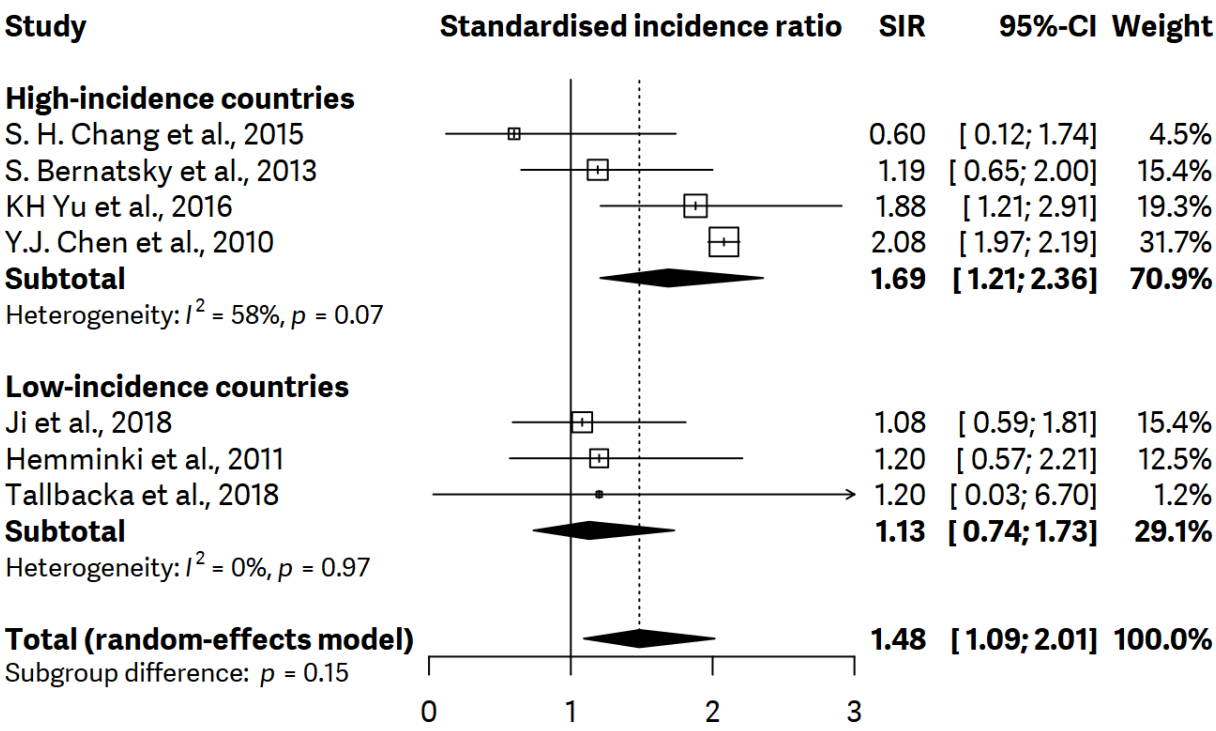


Fig. 13. Forest plot showing subgroup analysis regarding standardized incidence ratios (SIR) of gastric cancer with 95% confidence interval (CI) for systemic lupus erythematosus based on high-, or low-incidence countries of gastric cancer.

6.1.6 Qualitative synthesis

Besides the quantitative synthesis, eighteen other AI disorders were included in the qualitative synthesis. In the individual articles, increased incidence of gastric cancer was described in the cases of immune thrombocytopenic purpura [82], membranous nephropathy [83], Addison's disease [82, 84], discoid lupus [84], Bechet's disease [82, 85], sarcoidosis [82, 84], myasthenia gravis [82, 84], Takayasu arteritis [86], polymyalgia rheumatica [82, 84], localised scleroderma [82, 84], psoriasis [82, 84]. Chronic rheumatic heart disease [82, 84], IgG4-related disease [87, 88], ANCA-vasculitis [89, 90], multiple sclerosis [82, 84], and granulomatosis with polyangiitis[82] seem not to be associated with elevated incidence of gastric cancer according

to the individual studies. The detailed results of the qualitative synthesis are presented in *Fig. 14.*

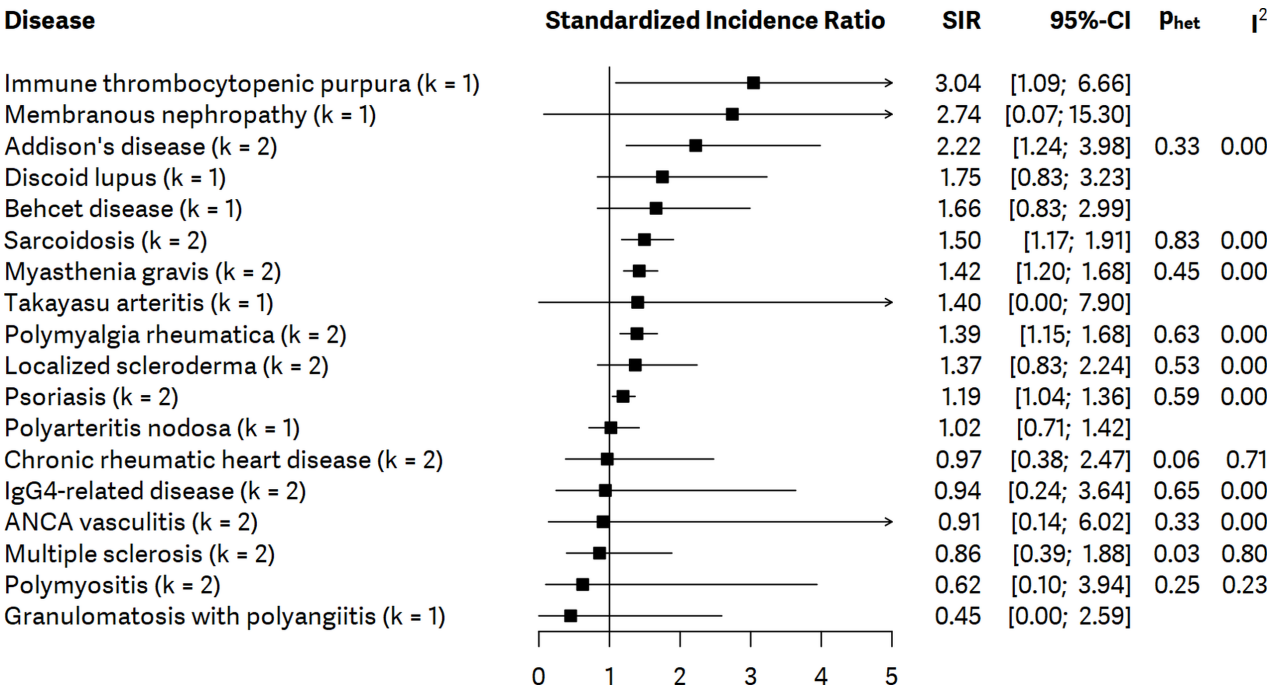


Fig. 14. Summarizing forest plot with pooled standardised incidence ratios (SIRs), representing the incidence of gastric cancer in all patients with autoimmune disorders included in qualitative synthesis; the number of studies – k.

6.1.7 Risk of bias assessment

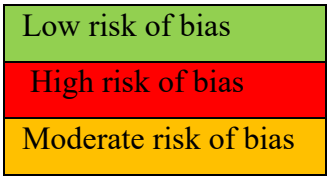
Results and a detailed description of the risk of bias assessment according to the QUIPS tool can be seen in *Table 3*.

Authors	1	2	3	4	5	6	Overall	Included in meta-analysis
Asano et al. [88]								no
Askling et al. [91]								yes
Bernatsky et al. [92]								yes
Bjorneklett et al. [83]								no
Brinton et al. [93]								yes
Briton-Zeron et al. [94]								yes
Chang SH et al. [95]		N/A						yes
Chen JY et al. [96]								yes
Collin et al. [97]								yes
Dreyer et al. [98]								yes
Goldrace et al. [99]								yes
Gridley et al. [100]								yes
Harding et al. [101]								yes
Hashimoto et al.-1 [102]								yes
Hashimoto et al.-2 [103]								yes
Hemminki et al. [82]								yes
Hill et al. [104]								yes
Hirano et al. [87]								no
Hsing et al. [105]								yes
Hsu et al. [106]								yes
Ilus et al. [107]								yes
Ji et al. [84]								yes
KH Yu et al. [85]								yes
Kang et al. [108]								yes
Kirkegaard et al. [109]								yes
Koskinen et al. [110]		N/A						yes
Lee H et al. [111]								yes
Lööf et al. [112]								yes
Nam et al. [113]								yes
Park et al. [86]								yes
Shiokawa et al. [114]		N/A						no
Shu X et al. [115]								yes
Silano et al. [116]								yes
Stockton et al. [117]								yes
Swerdlow et al. [118]								yes
Tallbacka et al. [119]								yes
Thomas et al. [120]								yes
Van Daalen et al. [89]								yes
Viljaama et al. [121]								yes
Weng et al. [122]								yes
Xin Long Lim et al. [123]								yes
Yamada et al. [124]								yes
Yoo et al. [90]		**N/A**						yes

Table 3. Risk of bias assessment using the QUIPS tool [75]

1. Study population, 2. Study attrition, 3. Prognostic factor measurement, 4. Outcome measurement, 5. Study confounding, 6. Statistical analysis and reporting

Results of QUIPS score



Study participation measurement: Low risk of bias was given if a clear description of the basic characteristics of study participants was reported, including inclusion and exclusion criteria. If only a subpopulation were included (e.g., based on sex) high risk of bias was declared. If the work did not provide a description, an unclear risk of bias was attributed.

Prognostic factor measurement: Low risk of bias was given if a clear definition of the autoimmune disorder was provided. In the case of unclear risk of bias, no information about the definition of the autoimmune disorder was available. Studies which described a definition not according to the international definitions of autoimmune diseases were defined as articles of high risk.

Outcome measurement: Low risk of bias was given if a precise definition (histological type of cancer, stage, diagnostic approach), according to the accepted guidelines. In the case of unclear risk of bias, no information about the definition of the outcome was available. Studies which described a definition not according to the accepted definitions of outcomes were defined as high-risk carrying articles.

Study confounding measurement: Low risk of bias was given because the definition of SIR includes age and gender, which are confounders.
The overall risk of bias: Overall, the risk of a study was deemed to be low if every domain was low. In the case of at least one high risk of bias domain, the overall risk was declared high. In every other case, overall unclear risk of bias was given.

Publication bias assessment was performed only in the case of RA. Egger's test did not indicate the presence of Funnel plot asymmetry. Therefore, we concluded that no publication bias was present.

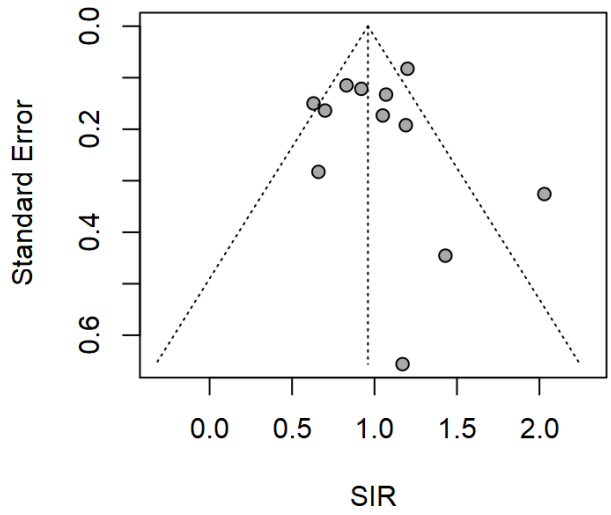


Fig. 15. Funnel plot for rheumatoid arthritis.

6.1.8 Statistical Heterogeneity

Statistical heterogeneity was shown in case of RA ($I^2 = 0.64$; $p = 0.00$), IBD ($I^2 = 0.54$; $p = 0.04$), SLE ($I^2 = 0.60$; $p = 0.02$), coeliac disease ($I^2 = 0.56$; $p = 0.04$), Crohn's disease ($I^2 = 0.69$; $p = 0.04$). Regarding subgroup analyses of gender, in female patients, RA ($I^2 = 0.69$; p=0.01) was proved to be significant. Other comparisons did not prove significant heterogeneity.

6.2 Results of the studies

A total of 285 CG patients were assessed between January 2016 to January 2020, with the final enrolment of 175 patients (52 men and 123 women). Three patients were excluded due to gastric cancer, 56 due to *H. pylori* positivity, 42 due to reactive gastropathy and nine because of a lack of serology testing. The mean age of the population was 61.6 years (±15.13 years), ranging from 21 to 89, and most patients were female (70.29%). The age distribution of the AISP and AISN groups can be seen in *Fig.16*.

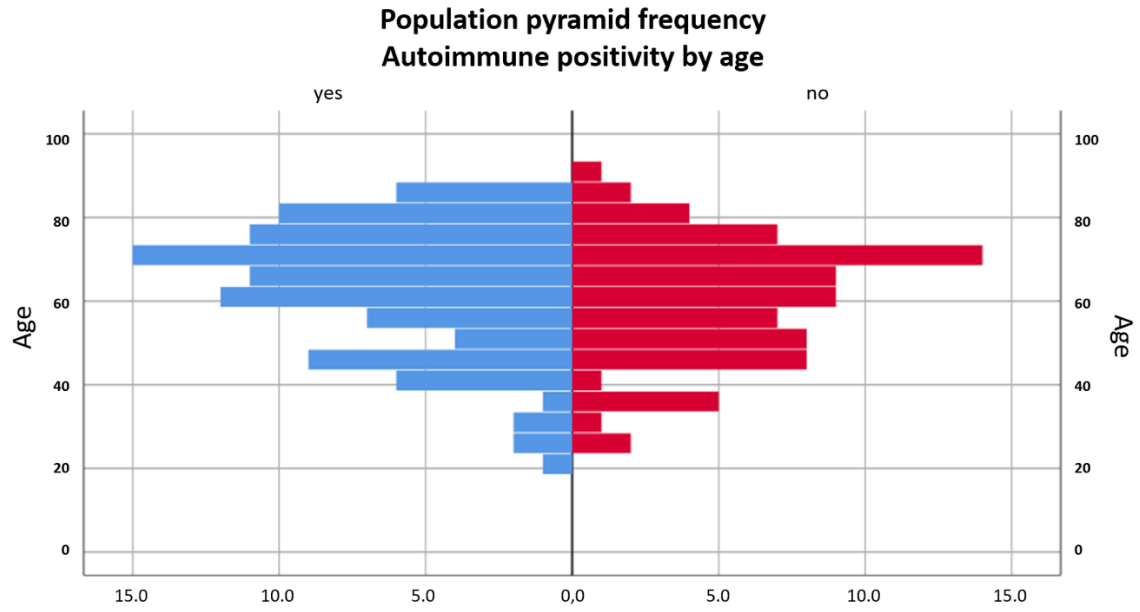


Fig.16. Population distribution by age and autoimmune positivity. Blue columns represent the age distribution of the autoimmune-positive patients, while red columns represent the autoimmune-negative patients.

There were no significant differences regarding baseline characteristics between AISP and AISN groups. The mean BMI of the patients was 25.89 kg/m^2 (±5.42 kg/m^2). Concerning the risk factors, alcohol consumption was present in 39.20% of the patients (29/74), while smoking was in 17.39% of the cases (20/115). Eighty-one patients had GERD, and the *H. pylori* infection was present in 32% of the cases.

Ten patients (out of 167 patients) had anaemia (5.99%), of which eight patients were in the AISP group. In these patients, the antibody positivity was distributed as follows: three patients had AIG-related, one had celiac disease-, one had IBD-, and three had SLE-related antibody positivity. Of 175 included patients with CG, 53 had atrophy with fibrosis (30.29%), and 49 had atrophy with IM (28%). Baseline characteristics of the analysed population can be seen in *Table 4.* in detail.

Parameter	**Overall (n=175)**	**AISP (n=97)**	**AISN (n=78)**	**p-value**
Age (mean, SD)	61.66; 15.13	62.68; 15.03	60.40; 15.13	0.321
Female N^0 (%)	123 (70.29)	64 (65.98)	59 (75.64)	0.641
BMI (mean, SD)	25.89, 5.42	25.81, 5.44	25.81, 5.51	1.000
Alcohol consumption N^0 (%) *	29/74 (39.19)	16/41 (39.02)	13/33 (39.39)	0.946
Smoking N^0 (%) *	20/115 (17.39)	11/58 (18.97)	9/57 (15.79)	0.238
GERD N^0 (%)	81 (46.29)	40 (41.24)	41 (52.56)	0.888
Anaemia N^0 (%) *	10/167 (5.99)	8 (8.25)	2 (2.56)	0.188
Precancerous lesion				
Atrophy with intestinal metaplasia N^0 (%)	49 (28.00)	33 (34.02)	16 (20.51)	<0.001
Atrophy with fibrosis without intestinal metaplasia N^0 (%)	53 (30.29)	37 (38.14)	16 (20.51)	<0.001

Table 4. Baseline characteristics of the population

**Indicates missing data. The total number of patients with information on smoking status is 115, of whom 20 are smokers; in the case of alcohol consumption, the total number is 74, of whom 29 are regular alcohol consumers (daily).*

6.2.1 Prevalence of autoantibody positivity

Out of 175 CG patients, 97 had positive AI serology results (55.43%). The prevalence of AIG was 21.71% (38/175); out of 38 patients with AIG, 35 (20.00%) had anti-parietal cell antibody positivity, and three patients (1.71%) had both anti-parietal cell and anti-intrinsic factor antibody. Celiac disease-related antibody positivity was present in 8% of the patients (14/175), anti-gliadin antibody positivity was found in all 14 patients (100.00%), anti-endomysium antibody positivity in two patients (1.14%), and tissue transglutaminase antibody IgA and/or IgG in six patients (3.43%). AI thyroiditis-related antibody positivity was found in 17.54% (20/114) of the patients, while 11.90% of the subjects (15/126) had ASCA positivity.

The most found antibody was ANA in 19.13% of the patients (22/115). Antibodies against nucleosome (8.70% of CG patients), RF (7.34% of the analysed population) and ds-DNA (6.07% of the patients) were also observed. AI hepatitis-related serology was positive in 9.52% (6/63) of the subjects. In 3.48% of the cases (4/115), anti-b2 glycoprotein positivity was found. Three patients out of 126 (2.38%) had positive serology regarding ANCA), and three out of 111 (2.70%) showed positive SSA. Anti-cardiolipin, anti-centromere, anti-C1q, SSB and myositis-specific antibodies were also found in fewer cases (<1%). Full details of antibody positivity are provided in *Table 5*.

Regarding the prevalence of each antibody positivity, no significant difference was observed between females and males ($p>0.05$). There was no significant relationship between gender and AISP ($p>0.05$).

Autoimmune disease (attributed antibodies)	Positive (n)	Total number of patients tested	%
AI gastritis (AIG)	**38**	175	**21.71**
Anti-parietal cell antibodies	35	175	20.00
Anti-intrinsic factor antibodies	3	175	1.71
Celiac disease	14	175	8.00
Anti-gliadin	14	175	8.00
Anti-endomysium	2	175	1.14
Tissue transglutaminase antibodies IgA	3	175	1.71
Tissue transglutaminase antibodies IgG	3	175	1.71
Sjögren's syndrome	3	111	2.70
Anti-Sjögren's syndrome-related antigen A (SSA)	3	111	2.70
Anti-Sjögren's syndrome-related antigen B (SSB)	0	111	0.00
Systemic lupus erythematosus (SLE)	**31**	**115**	**26.96**
Anti-nuclear antibodies (ANA)	22	115	19.13
Anti-nucleosome antibodies	10	115	8.70
Anti-cardiolipin	2	115	1.74
Anti-centromere	1	115	0.87
Anti-C1q	1	115	0.87
Anti-b2 glycoprotein	4	115	3.48
Anti-double-stranded DNA (ds-DNA)	7	115	6.07
Autoimmune hepatitis	**6**	**63**	**9.52**
Anti-smooth muscle antibodies (SMA)	1	63	1.59
Anti-liver/kidney microsomal antibodies (LKM-1, LKM-2, LKM-3)	0	63	0.00
Anti-soluble liver antigens (SLA)	0	63	0.00
Liver–pancreas antigens (LP)	0	63	0.00
Anti-mitochondrial antibodies (AMA)	3	63	4.76
Anti-filamentous actin 1 antibodies (F1 actin)	2	63	3.17
Rheumatoid arthritis	**8**	**109**	**7.34**
Anti-cyclic citrullinated peptide antibodies (CCP)	0	109	0.00
Anti-rheumatoid factor (RF) antibodies	8	109	7.34
Systemic sclerosis (Ssc)	**1**	**96**	**1.04**
Anti-Scl-70 antibodies	0	96	0.00
Anti-centromere antibodies	1	96	1.04
Polymyositis/dermatomyositis	**0**	**99**	**0.00**
Anti-Jo-1 antibody	0	99	0.00
Inflammatory bowel disease (IBD)	**18**	**126**	**14.29**
Anti-yeast *Saccharomyces cerevisiae* (ASCA)	15	126	11.9
Anti-neutrophil cytoplasmic antibodies (ANCA)	3	126	2.38
AI thyroiditis	**20**	**114**	**17.54**
Anti-thyroid peroxidase (TPO)	13	114	11.40
Anti-TSH receptor antibodies (TRAb)	2	114	1.75
Anti-thyroglobulin antibodies (Tg)	5	114	4.39

Table 5. Prevalence of autoantibody positivity in patients with chronic gastritis. Patients were summarized in each autoimmune disorder group considering multiple autoantibody positivity to avoid duplication.

6.2.2 Poor histological outcomes and autoimmune positivity

Concerning precancerous lesions, the AISP group was associated more with atrophy alone (37 vs 16 patients, p<0.001). Atrophy with IM was observed in 33 (34.02%) and 16 (20.51%) patients in the AISP and AISN groups, respectively (p<0.001) *(Table 4).*

6.2.2.1 Univariate analyses

Based on the results of the univariate analyses, a significant association was observed between AI positivity and precancerous lesions of the stomach. Atrophy was found more frequently in the AISP group (p=0.015). The co-occurrence of atrophy and IM was also correlated with AISP (p=0.039).

AIG-related antibody positivity, especially anti-parietal cell antibody positivity associated with atrophy with IM (p=0.033). No significant correlation was found between any other AI disease-related antibodies and precancerous lesions.
No difference was observed concerning worse OLGA score (OLGA 3–4) and AI positivity. Comparisons on individual AI bodies were not carried out due to the low number of cases.

6.2.2.2 Bivariate analyses

Results of bivariate analyses adjusted for age found significant associations in the following relations: AIG-related antibodies with atrophy (OR 2.250; 95% CI 1.945 to 5.357; p<0.001) and atrophy with IM (OR 2.229; 95% CI 1.019 to 4.877; p<0.001); SLE-related antibodies and atrophy (OR 2.288; 95% CI 1.523 to 3.176; p=0.002) and atrophy with IM (OR 2.340; 95% CI 1.375 to 5.841; p=0.006); IBD-related antibody (ASCA and ANCA) positivity with atrophy with IM (OR 2.760; 95% CI 1.218 to 2.645; p=0.017) and atrophy without IM (OR 5.308; 95% CI 1.480 to 19.036; p=0.001); anti-parietal cell antibody with atrophy with IM (OR 2.229; 95% CI 1.019 to 4.877 p=0.006).

Concerning the results of bivariate analyses adjusted for gender, the following associations was found: AIG-related antibodies with atrophy (OR 2.732; 95% CI 1.350 to 2.349; p<0.001) and atrophy with IM (OR 2.222; 95% CI 1.040 to 4.749; p<0.001); SLE-related antibody positivity with atrophy (OR 2.766; 95% CI 1.755 to 4.132; p<0.001) and atrophy with IM (OR 4.294; 95% CI 1.313 to 14.043; p=0.001); ASCA and ANCA positivity and atrophy without IM (OR 2.352; 95% CI 1.032 to 6.645; p=0.007); ANA positivity (OR 2.044; 95% CI 1.097 to 5.242; p=0.029) and AI thyroiditis-related antibody positivity (OR 2.566; 95% CI 1.574 to 4.274; p=0.048). Anti-parietal cell antibody positivity was also associated with worse histological outcomes (OR 2.222; 95% CI 1.040 to 4.749; p=0.038).

Sjögren's syndrome, AI hepatitis, RA, SSc and polymyositis/dermatomyositis-related antibody positivity did not significantly affect precancerous lesions. Detailed results of univariate and multivariate analyses are presented in *Table 6.*

The analysis regarding simultaneous AI positivity showed a higher risk for precancerous lesions in some cases: SLE-related antibodies (OR 4.778; 95% CI 1.945 to 2.089; p=0.058); AIG-related antibodies (OR 3.182; 95% CI 1.708 to 8.142).

	Univariate analysis (p-value)	**Bivariate analysis – age (p-value)**	**Odds ratio [95% CI]**	**Bivariate analysis – gender (p-value)**	**Odds ratio [95% CI]**
		Atrophy with intestinal metaplasia			
AIG	**0.033**	**<0.001**	**2.229 [1,019;4,877]**	**<0.001**	**2.222 [1.040; 4.749]**
Celiac disease	0.353	0.345	0.469 [0.98;2.240]	0.213	0.374 [0.080; 1.757]
Sjögren's syndrome	1.000	0.358	1.178 [0.101;13.729]	0.969	0.953 [0.083; 10.946]
SLE	0.433	**0.006**	**2.340 [1.375; 5.841]**	**0.001**	**4.294 [1.313; 14.043]**
AI hepatitis	1.000	0.856	0.843 [0.134; 5.316]	0.886	1.143 [0.186; 7.032]
RA	1.000	0.124	1.175 [0.260;5.311]	0.909	1.092 [0.244; 4.889]
Ssc	0.374	0.570	1.039 [1.006; 1.074]	0.241	0.594 [0.248; 1.420]
Polymyositis/dermatomyositis	n/a	n/a	n/a	n/a	n/a
IBD	0.313	**0.017**	**2.760 [1.218; 2.645]**	0.083	1.134 [0.214; 2.324]
AI thyroiditis	0.935	0.814	0.882 [0.308; 2.522]	0.099	1.155 [0.408; 3.268]
Anti-parietal cell antibodies	**0.033**	**0.006**	**2.229 [1.019; 4.877]**	**0.038**	**2.222 [1.040; 4.749]**
Anti-gliadin antibodies	0.111	0.212	0.212 [0.260; 1.700]	0.200	0.185 [0.023; 1.475]
ANA	0.333	0.413	1.221 [0.449; 3.323]	0.155	1.637 [0.626; 4.280]
Anti-dsDNA antibodies	0.683	0.486	1.218 [0.251; 5.914]	0.311	1.857 [0.382; 9.020]
Anti-nucleosome antibodies	0.728	0.484	1.152 [0.292; 4.541]	0.303	1.637 [0.626; 4.280]
Anti-rheumatoid factor	1.000	0.914	1.175 [0.260; 5.311]	0.966	1.092 [0.244; 4.889]
		Atrophy without intestinal metaplasia			

AIG	0.374	**<0.001**	**2.250 [1.945; 5.357]**	**<0.001**	**2.732 [1.350; 2.349]**
Celiac disease	0.228	0.394	0.416 [0.087; 1.991]	0.848	0.343 [0.073; 1.600]
Sjögren's syndrome	0.551	n/a	n/a	n/a	n/a
SLE	0.168	**0.002**	**2.288 [1.523; 3.176]**	**<0.001**	**2.766 [1.755; 4.132]**
AI hepatitis	0.638	0.331	1.354 [0.172; 10.684]	0.160	1.509 [.227; 10.015]
RA	1.000	0.096	1.137 [0.241; 5.638]	0.123	1.040 [0.234; 4.619]
Ssc	0.378	0.559	1.068 [1.020; 1.097]	0.405	1.058 [1.020; 1.97]
Polymyositis/dermatomyositis	n/a	n/a	n/a	n/a	n/a
IBD	0.099	**0.001**	**5.308 [1.480; 19.036]**	**0.007**	**2.352 [1.032; 6.645]**
AI thyroiditis	0.322	0.085	1.359 [0.473;3.909]	**0.048**	**2.566 [1.574; 4.274]**
Anti-parietal cell antibodies	0.374	0.174	1.350 [0.616; 2.958]	0.104	1.446 [0.675; 3.093]
Anti-gliadin antibodies	0.065	0.216	0.186 [0.023; 1.497]	0.182	0.168 [0.021; 1.328]
ANA	0.126	0.110	1.522 [0.561; 4.128]	**0.029**	**2.044 [1.097; 5.242]**
Anti-dsDNA antibodies	1.000	0.924	0.531 [0.094; 2.987]	0.650	0.629 [0.114; 3.465]
Anti-nucleosome antibodies	0.317	0.215	1.646 [0.424; 6.386]	0.079	1.892 [0.510; 7.018]
Anti-rheumatoid factor	1.000	0.353	1.137 [0.241; 5.368]	0.257	1.040 [0.234; 4.619]

Table 6. Detailed results of uni- and bivariate analyses.

6.2.3 Location and extent of the inflammation

In the AISP group, 57 patients out of 97 had pangastritis (58.76%), while 47 out of 78 (60.28%) were in the AISN group. The inflammation affected only the antrum in 33 subjects in the AISP group (34%) and 23 in AISN. Antrum gastritis was associated more with AI positivity (p=0.042). Isolated corpus gastritis was associated with AI positivity also (p=0.023); affection of the corpus was found in 9 (9.28%) AISP and 6 (7.70%) AISN patients, respectively *(Table 7.)*.

6.2.4 Clinical symptoms

The most frequent symptoms in patients with *H. pylori*-negative CG were as follows: retrosternal burning sensation in 17.14% (30/175 patients); bloating and/or diarrhoea in 9.14% (16/175); diffuse abdominal discomfort/pain not relating to meals in 8.57% (15/175); globus sensation in 4% (7/175); nausea in 4.57% (8/175) and vomitus in 2.29% (4/175). Details regarding the symptoms can be seen in *Table 7.*

Diffuse abdominal pain/discomfort was more common in the AISP group than in the AISN (9 vs six patients, respectively, p=0.023). Globus pharyngeus was associated with AISP (p<0.001): 6 patients experienced globus sensation in the AISP group, while one was in the AISN group. Regarding other symptoms, significant differences between AISP and AISN groups could not be observed.

Twelve patients experienced a retrosternal burning sensation in the AISP group and 18 in the AISN group (p=0.0713). Less common symptoms were nausea (4 AISP and 4 AISN patients, p=1.000), vomiting (1 AISP and 3 AISN patients, p=0.325), and bloating and/or diarrhoea (9 AISP and 7 AISN patients, p= 0.152). *(Table 7.)*

	Overall (n=175)	**AISP (n=97)**	**AISN (n=78)**	**p-value**
Key symptom				
Dyspepsia-like symptoms N^0 (%)	95 (54.29)	58 (58.76)	37 (48.72)	**0.012**
Retrosternal burning N^0 (%)	30 (17.14)	12 (12.37)	18 (23.08)	0.0713
Globus pharyngeus N^0 (%)	7 (4.00)	6 (6.19)	1 (1.28)	**<0.001**
Nausea N^0 (%)	8 (4.57)	4 (4.12)	4 (5.13)	1.000
Vomiting N^0 (%)	4 (2.29)	1 (1.03)	3 (3.85)	0.325
Bloating, Diarrhoea N^0 (%)	16 (9.14)	9 (9.28)	7 (8.97)	0.152
Abdominal discomfort/pain N^0 (%)	15 (8.57)	9 (9.28)	6 (7.70)	**0.023**
Location of the gastritis				
Antrum N^0 (%)	56 (32.00)	33 (34.02)	23 (29.49)	**0.042**
Corpus N^0 (%)	15 (8.57)	9 (9.28)	6 (7.70)	**0.023**
Pangastritis N^0 (%)	104 (59.43)	57 (58.76)	47 (60.26)	0.269

Table 7. Distribution of frequently occurring symptoms and location of the inflammation between autoimmune positive and negative groups.

P-values marked with bold indicate statistically significant p-values.

6.2.5 Dyspepsia-like symptoms in autoimmune seropositivity

The prevalence of dyspepsia-like symptoms was 54.29% and correlated with AISP (p=0.012). Celiac-disease antibody positivity (p=0.045), ANCA and ASCA positivity (p=0.043) were also associated with dyspepsia. However, the analysis could not prove any relation between dyspepsia-like symptoms and other AI-related antibody positivity, like Sjögren's syndrome, SLE, AI hepatitis, RA, SSc, polymyositis/dermatomyositis, AI thyroiditis (p>0,05).

No association was observed between AIG-related antibody positivity and dyspepsia either (p=0.677). Detailed results of the correlation between autoimmunity and dyspepsia-like symptoms can be seen in *Table 8.*

Association with dyspepsia	
AI disease groups / antibodies	**p-value**
AIG	0.677
Celiac disease	**0.045**
Sjögren's syndrome	0.563
SLE	0.585
AI hepatitis	0.617
RA	0.252
Ssc	1.000
Polymyositis/dermatomyositis	n/a
IBD	**0.043**
AI thyeroiditis	0.229
anti-parietal cell antibody	0.677
anti-gliadin antibody	0.065
anti-nuclear antibody	0.230
anti-dsDNA antibody	1.000
anti-nucleosome antibody	1.000
anti-rheumatoid factor	0.252
anti-Saccharomyces cerevisiae antibody	**0.043**
anti-neutrophil cytoplasmic antibody	**0.043**

Table 8. Detailed results regarding the association between autoimmunity and dyspeptic symptoms.

P-values marked with bold indicate statistically significant p-values.

7 DISCUSSION

During upper GI endoscopy, CG is one of the most common findings, but its aetiology often remains unknown. However, chronic inflammation plays a pivotal role in gastric carcinogenesis, leading to atrophy, IM, and gastric cancer. Gastric cancer is still one of the most common types of cancer worldwide, with a high mortality rate, causing a growing clinical and public health problem. Many crucial aspects of the pathophysiology, and aetiology, remain unclear; however, clarification could promote early diagnosis and treatment. AI disorders have been described as a potential etiological factor of gastric cancer; however, the studies are controversial.
These studies were conducted to understand the role of autoimmunity in the symptoms, course and prognosis of CG and its relationship to the pathologies of the stomach. Furthermore, we aimed to revise the current clinical practice in diagnosing and managing chronic gastritis and dyspepsia of unknown origin.

7.1 Autoimmunity and poor histological outcomes in the stomach: from precancerous lesions to gastric cancer

To summarise the results of our study, one of our major findings was that 55% of the patients with CG had positive AI serology. Our results align with previous findings from other countries: the prevalence of AIG was measured at about 20%, and anti-parietal cell antibodies were found to be more common than anti-intrinsic factor antibodies. Regarding AI disorders besides AIG, SLE-related antibodies, AI thyroiditis, IBD-, celiac disease-, and RA- related antibodies were also commonly positive in our patients. Autoimmunity was associated with precancerous lesions in the stomach: atrophy and atrophy combined with IM. AIG-, SLE- and IBD-related (ASCA and ANCA) positivity were also associated with atrophy and atrophy with IM, seeming to be significant risk factors for poor prognosis. AI thyroiditis-related antibodies and ANA positivity by itself correlated with atrophy alone. Our analysis could not prove any role of other examined antibodies in gastric carcinogenesis. Higher OLGA score and AI positivity showed no significant difference.

Concerning the incidence of gastric cancer in AI disorders, our meta-analysis, including data from 499,427 patients collected from 43 studies, showed that PA, Graves' disease, dermatomyositis, T1DM, inflammatory myopathies and SLE were associated with gastric cancer.

Although this kind of correlation between CG and autoimmunity has not been investigated before, it has been shown that AI diseases often have GI manifestations. The literature shows CG is common in patients with IBD and celiac disease [125-127]. SLE can affect the GI tract as well; however, according to previous results, histologically proven gastritis is rare in these patients [128]. Regarding the GI tract involvement of RA, it can affect both the GI tract and the liver [129]. Marcolongo et al. found chronic superficial and chronic atrophic gastritis in 30 and 62.5% of patients with RA [130]. A study by Lecouffe-Desprets et al. described SLE, RA, SSc, inflammatory myopathies, Sjögren's syndrome and scleromyositis or other overlapping connective tissue diseases (5% each) are associated with eosinophilic gastrointestinal disorders [131].

As regards the connection between poor histological prognosis of CG and systemic AI disorders, the context of precancerous lesions was not examined before. However, results of our meta-analysis reassert our study results: AIG, SLE and AI thyroiditis were associated with higher risk for precancerous lesions as well as higher incidence of gastric cancer.

An elevated incidence of various GI tumours has been described in patients with RA, SLE, Sjögren's syndrome, celiac disease, idiopathic inflammatory myositis, and SSc [132-136]. Studies have shown an increased risk of gastric cancer in patients with dermatomyositis, RA, scleroderma, SLE, or T1DM [137-142]. In line with our results, Song et al. concluded that patients with dermatomyositis, PA, Addison's disease, dermatitis herpetiformis, IgG4-related disease, primary biliary cirrhosis, T1DM, SLE, and Graves' disease had increased risk for gastric cancer [143].

The connection between AIG and precancerous lesions of the stomach and/or gastric cancer is well known. A previous prospective cohort study described an annual incidence of 0.25% per person-year for gastric cancer (95% CI 0.07–0.6%), 0.43% per person-year for gastric dysplasia (95% CI 0.2–0.9%) and 0.68% per person-year for type 1 gastric neuroendocrine tumour (95% CI 0.3–1.2%) in patients with AIG [144]. Patients with AIG have 3–7-fold increased risk for gastric adenocarcinoma [145].

Hsing et al. described that PA was associated with gastric cancer since it is in relation to AIG and results from gastric mucosal damage [105]. The mice model of this pathomechanism suggests correlations between carcinogenesis and autoimmunity [70]. The frequent co-occurrence of AI thyroiditis, T1DM, vitiligo, and Addison disease with PA has been shown, which raises the possibility of a direct mechanistic interpretation through its pathological correlate, AIG.

Epidemiologic evidence for an AI contribution to gastric carcinogenesis shows an elevated incidence of AI disorders in patients with neoplasms [146]. Inversely, an increased incidence of tumours has been demonstrated in patients with AI disorders [147]. Recently an increment in the incidence of both AI disorders and parallelly cancers could be observed. The specific AI inflammation is often associated with the tumorous disorder of the affected organ. This phenomenon is most conspicuous in people below 50 years of age, and regarding gastric cancer, it affects females more [148, 149].

Although autoimmunity may significantly affect the development of different neoplasms, the exact pathomechanism remains unclear. Chronic inflammation precedes tumour formation in time. Immune dysregulations, which play a pivotal role in autoimmunity, are also thought to be important in carcinogenesis: AI disorders may lead to antigen specificity-driven tissue damage causing chronic inflammation. Moreover, several other factors can be identified, such as immunosuppression, infections, dietary habits, and environmental factors. These can induce chronic cell damage and trigger AI conditions or cancer.

As mentioned above, it is postulated that chronic stomach inflammation will result in atrophy and IM, the precancerous stomach lesions. Therefore, it can be assumed that if an antibody is more conducive to developing precancerous lesions, it is also more conducive to tumour formation.

7.2 Autoimmunity and dyspepsia-like symptoms

Our dyspepsia and autoimmunity-related study investigated the relationship between autoimmunity and dyspeptic symptoms in patients with *H. pylori-negative* chronic gastritis. To summarise our results, the prevalence of dyspepsia-like symptoms was 54.29%. Regarding the connection with autoimmunity, dyspeptic symptoms, diffuse abdominal pain/discomfort, and globus pharyngeus correlated with presence of autoimmunity. Based on disease specific analysis celiac disease-related antibody positivity, ASCA and ANCA positivity were associated with dyspeptic symptoms. However, the analysis could not prove correlation between any other investigated AI disease-related antibody positivity and dyspepsia of unknown origin in CG patients.

It is well known that *H. pylori* infection might be associated with FD: the prevalence of *H. pylori* infection is more frequent in dyspeptic patients than in healthy controls [150, 151]. A meta-analysis by Zhao B et al. showed that eradication of *H. pylori* resulted in the improvement of dyspeptic symptoms [152]. *H. pylori* infection may alter gastric functions, causing increased gastrin-, pepsinogen-, and acid secretion, which might play an important role in the pathogenesis of FD [153].

However, an increased incidence of dyspepsia-like symptoms was described in *H. pylori*-negative CG as well [38]. As mentioned previously, CG is one of the most common findings during upper GI endoscopy; however, the underlying cause often remains undetectable. In most cases CG is discovered accidentally without causing any symptom. Therefore, we investigated possible etiological factors behind CG that could be associated with dyspepsia-like symptoms.

In our study, 55% of the patients with CG had AI positivity, which was associated with dyspepsia-like symptoms. Several studies suggest a possible connection between AI disorders and dyspepsia in line with our hypothesis and results. These studies described that more than half of the patients with AI disorders have dyspepsia-like symptoms, which may be the

consequence of gastroparesis and antral distension [154, 155]. Since immune dysregulation might play a pivotal role in developing both AI- and functional GI disorders, autoimmunity could be a risk factor for functional diseases such as FD. It is confirmed by Koloski et al., describing that AI diseases are associated with FD and irritable bowel syndrome, independent of psychological distress [156].

In line with our results, Jocelyn A Silvester et al. described that FD occurs in 27% of patients with coeliac disease, which is relieved by a gluten-free diet [157]. A case report by A. Maertens et al. reported how dyspepsia led to a diagnosis of Crohn's disease [158]. Furthermore, our study confirms the work of Lebwohl et al. about the association between *H. pylori*-negative CG with celiac disease [127]. An elevated rate of dyspepsia has also been shown in patients with Sjögren's syndrome, SLE, RA, and AI thyroiditis [154, 155, 159-164]; however, our study could not prove these correlations.

As mentioned previously, AI disorders often have GI manifestations, and the symptoms might be subclinical and non-specific, with considerable overlap among different conditions. Sometimes it can be the only presented sign of an underlying AI disease. Serologic testing for immune-mediated GI disorders (e.g., celiac disease, IBD) allows broader screening, helping differentiate organic disease from functional GI disorders.

7.3 Strengths and limitations of the studies

7.3.1 Meta-analysis

7.3.1.1 Strengths

Regarding the strengths of our meta-analysis, we have included a large number of studies, with a half million participating patients, and a wide coverage of AI disorders from 15 different countries and four continents. This is considerably the largest extent and most

recent analysis so far on this topic. Most of our results were significant; thus, our findings are novel. The study was conducted following a rigorous, pre-defined methodology, thereby increasing the quality of evidence provided by our research. It is highlighted by the considerably large number of screened full-text articles to identify all essential data. We also provided a summary of the incidence of gastric cancer in different AI disorders, on which the threshold of at least three articles could not be reached.

The other meta-analysis on this topic by Song et al. had several limitations [143]. Our search key was more general than that, leading to a higher number of records. We searched four databases compared with two in that work, which helped identify more studies. In this work, relative RR with 95% CI are calculated; hazard ratios, SIRs, RRs, and standardised mortality rates were pooled into RR. Our statistical analysis is more coherent as only SIR-s were calculated consistently.

7.3.1.2 Limitations

Our research had several limitations. First, our results are from a sparse number of retrospective studies. The basis of the diagnosis of AI disorders could be different in countries, which could be the main reason for heterogeneity in some analyses. Ascertainment bias could be present since people with an AI disease visit medical facilities more frequently than the general population, and there can be significant cancer-holding populations with undiagnosed AI diseases, which could change the ratio of cancer diagnoses among AI population. The risk of bias assessment seems in the case of multiple domains as the not low overall risk of bias.

Other confounding factors, which could be risk factors for gastric cancer (e.g., *H. pylori* infection status, smoking, dietary habits, obesity, occupational exposure to dust, high-temperature particulates, and metals such as chromium VI, gastric by-pass surgery, and Epstein-Barr infection) could be present that were not measured or reported. There is

no information about drugs taken for AI disorders, so how it may affect the outcome is unknown.

Most of the included articles are from either North Europe (where the incidence of autoimmunity is higher than in other populations) or Asia (where H. pylori infection and/or gastric cancer is more frequent). We sought to correct this in our analysis; therefore, subgroup analyses were performed based on low- or high-incidence countries of gastric cancer. These results reassert our main results that PA, T1DM, Graves' disease, and AI vasculitis were correlated with gastric cancer in low-incidence countries.

7.3.2 Autoimmunity and chronic gastritis-related study

7.3.2.1 Strengths

Our study followed a rigorous, pre-defined methodology, and our findings are novel. It is the first study which presents epidemiological data on the prevalence of different autoantibody positivity in patients with CG in the world (including in Hungary) and raises the possibility that it could be the aetiology of CG, as well as showing a correlation with poor histological prognosis of the stomach.

7.3.2.2 Limitations

An important limitation of our study is its retrospective nature; therefore, causality cannot be determined (we could report only associations), and the role of the confounder factors cannot be excluded (e.g., smoking, dietary habits, immunosuppressant/modulatory treatment). We excluded patients with H. pylori positivity from the analysis to reduce this bias.

Chronic atrophic gastritis is a common age-related finding, and the female gender is more often prone to autoimmunity. We performed multivariate analyses adjusted for age and gender to address this problem. A low number of event rates in the case of some autoantibodies could be the reason for insignificance. Incidental positivity of AI markers may also occur. Therefore, to confirm our results, we also evaluated the simultaneous effects of 2 or more AI positivity on the outcome.

7.3.3 Autoimmunity and dyspepsia-related study

7.3.3.1 Strengths

Our study is the first in this topic which investigated the possible organic etiological factors behind chronic H. pylori-negative gastritis in association with FD; therefore, all of our findings are novel. As mentioned above, there were previous studies on the possible association between AI diseases and FD; however, a comprehensive study to answer this question in a targeted manner to identify etiological factors behind H. pylori-negative CG has not been conducted until this. Our study contains the broadest coverage of systemic AI disorders, which relation to dyspepsia was investigated. The methodology was rigorous and pre-defined.

7.3.3.2 Limitations

As in our study, the main limitation is the nature of the study, with a relatively low event rate in each antibody positivity. Confounders are not known in all cases; therefore, they cannot be ruled out, such as women's gender, smokers, NSAID users [151], and in the ageing stomach [165]. Chronic atrophic gastritis is an age-related finding, and it may cause dyspeptic symptoms by influencing the level of gastric acid, pepsin, and ghrelin secretion [32, 166].

8 CONCLUSIONS

8.1 Summary of novel findings

1. Our meta-analysis confirmed the relationship between AI disorders and gastric cancer. It concludes that PA, Graves' disease, dermatomyositis, T1DM, inflammatory myopathies, and SLE are associated with higher incidence rates of gastric cancer.
2. Our meta-analysis did not confirm any association between gastric cancer and AI vasculitis, celiac disease, SSC, dermatitis herpetiformis, Hashimoto thyroiditis, Sjogren's syndrome, IBD, Crohn's disease, RA, ulcerative colitis, ankylosing spondylitis or primary biliary cirrhosis.
3. Our study confirmed that AI positivity often underlies gastritis of unknown aetiology and predisposes to precancerous lesions in the stomach. It concludes that in the southwestern Hungarian population, anti-parietal cell antibody, ANA, ANCA and ASCA positivity correlated with a worse histological outcome, such as atrophy with or without IM.
4. Our study did not confirm any association between Sjögren's syndrome, AI hepatitis, RA, SSc and polymyositis/dermatomyositis-related antibody positivity and precancerous lesions of the stomach.
5. Our study confirmed that AI positivity in histologically established *H. pylori*-negative CG may predispose to dyspeptic symptoms and may be the causative factor behind uninvestigated FD. It concludes that celiac disease-related antibody positivity, ASCA and ANCA positivity were associated with dyspeptic symptoms.
6. Our study did not confirm any association between dyspepsia-like symptoms and Sjögren's syndrome, SLE, AI hepatitis, RA, SSc, polymyositis/dermatomyositis, AI thyroiditis, or even AIG.

8.2 Clinical practice and future perspectives

Based on the results of our meta-analysis, close gastroenterological follow-up or routinely performed upper GI endoscopy may be cost-effective and clinically helpful for patients diagnosed with the above-mentioned six AI disorders.

Based on the data of our studies, it is suggested to look for autoimmunity in patients with CG when a clear etiological factor cannot be identified. Antibodies can serve as non-invasive markers to aid in the identification of the optimal timing of an endoscopic follow-up strategy based on the risk of atrophy/IM development. Given that our study population did not suffer from diagnosed manifest AI disorder, it also raises the possibility that gastritis may predict the development of a later AI disease. Thus, if there is no clear explanation for the aetiology of CG or if the symptoms persist after eradication of *H. pylori*, it is advisable to assess these patients for systemic AI-related antibodies and, if positive, to involve an immunologist for a close follow-up; therefore, AI disorders can be recognisable in the early stages of the disease.

Screening for celiac disease or ASCA and ANCA-related AI disorders (IBD, vasculitis) in case of dyspeptic symptoms might be worthwhile as well. Furthermore, it can be helpful in the earlier diagnosis of these AI disorders.

To establish a higher quality of evidence, further prospective studies are required to prove these associations.

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SYSTEMATIC REVIEW
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Six Autoimmune Disorders Are Associated With Increased Incidence of Gastric Cancer: A Systematic Review and Meta-Analysis of Half a Million Patients

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Background: Gastric cancer is one of the most common cancers worldwide, with a high mortality rate. The potential etiological role of autoimmune (AI) disorders has been described in gastric cancer; however, the literature is controversial. This study aims to provide a comprehensive summary of the association between autoimmune disorders and the incidence of gastric cancer.

Methods: This study was registered on PROSPERO under registration number CRD42021262875. The systematic literature search was conducted in four scientific databases up to May 17, 2021. Studies that reported standardized incidence rate (SIR) of gastric cancer in autoimmune disorders were eligible. We calculated pooled SIRs with 95% confidence intervals (CIs) in this meta-analysis.

Results: We included 43 articles describing 36 AI disorders with data of 499,427 patients from four continents in our systematic review and meta-analysis. Significantly increased incidence of gastric cancer was observed in dermatomyositis (SIR = 3.71; CI: 2.04, 6.75), pernicious anemia (SIR = 3.28; CI: 2.71, 3.96), inflammatory myopathies (SIR = 2.68; CI:1.40; 5.12), systemic lupus erythematosus (SIR = 1.48; CI: 1.09, 2.01), diabetes mellitus type I (SIR = 1.29; CI:1.14, 1,47), and Graves' disease (SIR = 1.28; CI: 1.16, 1.41). No significant associations could be found regarding other AI disorders.

Conclusions: Pernicious anemia, Graves' disease, dermatomyositis, diabetes mellitus type I, inflammatory myopathies, and systemic lupus erythematosus are associated with

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higher incidence rates of gastric cancer. Therefore, close gastroenterological follow-up or routinely performed gastroscopy and application of other diagnostic measures may be cost-effective and clinically helpful for patients diagnosed with these autoimmune diseases.

Keywords: : autoimmune disease, gastric cancer, autoimmunity, risk, standardized incidence rate

INTRODUCTION

Malignant neoplasm of the stomach is one of the most common cancers worldwide, affecting over 20,000 patients yearly in the USA. The average 5-year survival rate is less than 20%, underlining the importance of the disease (1, 2). This poor prognosis can be improved by early diagnosis. If the tumor is detected and treated before reaching the muscular layer of the stomach (T1), the 5-year survival rate can be up to 90% (3).

A significant decline in incidence and mortality can be observed over the past few decades (4), which can be attributed to the recognition of certain causative factors, decreased incidence of *Helicobacter pylori* infection, and decreased use of tobacco and dietary salt (2, 5). While the overall rate of gastric cancer has been declining, the distribution of its subtype was changing neoplasms of the cardia and gastro-esophagal junction became more frequent, and an unexplained increased incidence among younger than 50 years of age, particularly in females, could be observed (5–8).

Despite the effective *H. pylori* eradication strategies, gastric cancer remains the fifth most common cancer worldwide (9), highlighting the possibility of further etiological factors. Besides *H. pylori*, autoimmune gastritis is another common cause of gastric cancer, reflecting 7.8%–19.5% of the cases, and thought to be another possible cause of the rising incidence of gastric cancer in females younger than 50 years of age (5, 7, 10).

The incidence of autoimmune gastritis and generally autoimmune diseases has increased in the past few decades (11–13). Several previous studies have described the potential association of autoimmunity and gastric cancer (14, 15), but up to date, data have been controversial regarding cause-effect relationships and underlying pathomechanism. Our study aims to provide a comprehensive summary of the potential association between autoimmune disorders and the incidence of gastric cancer in the form of a meta-analysis and systematic review.

METHODS AND MATERIALS

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement (16). The protocol of this analysis was registered on the PROSPERO International Prospective Register of Systematic Reviews in advance (CRD42021262875). We did not deviate from the protocol.

Systematic Search

The systematic literature search was conducted in four scientific databases—MEDLINE *via* PubMed; Cochrane Central Register of Controlled Trials (CENTRAL); Embase; and Web of Science, Latin American and Caribbean Health Sciences Literature (LILACS)—up to May 17, 2021. The following search terms were used without any restriction to language or other filters: (stomach OR gastric) AND (neoplas* OR malign* OR cancer OR carcinoma OR lymphoma OR tumor OR tumour) AND ("autoimmun*" OR autoaggressive OR autoantibody OR lupus OR rheuma* OR Addison* OR celiac OR "gluten sensitive" OR dermatomyositis OR Hashimoto OR graves OR sclerosis OR scleroderma OR myasthenia OR arthritis OR Sjögren*). Additionally, reference lists of the citing and cited articles were screened for eligibility.

Selection and Eligibility of Studies

Duplicates were removed with EndNote X9 software (Clarivate Analytics, Philadelphia, PA, USA) manually. Two investigators (NV, NZ) screened the titles and abstracts and full texts to identify eligible articles. Disagreements were resolved by another investigator (LF, JC).

We included any peer-reviewed studies reporting the standardized incidence ratio (SIR) *(O)* of gastric cancer in an autoimmune disorder *(E)* in the general population (P). There were no restrictions on the type of gastric cancer, language, or study design eligible for inclusion. Only full texts were included. Studies with no event rate of SIR were excluded.

Data Extraction

Two independent researchers (NZ, NV) extracted data from the eligible studies into a standardized data collection form. Extracted data were validated by a third reviewer (LF). All disagreements were resolved by a fourth independent author (SV). The following data were extracted from each included study: title, first author, year of publication, country, study design, age of the population (mean, standard deviation (SD), median, interquartile ranges), gender distribution, the total number of patients (with autoimmune disorders), type of autoimmune disorders, follow-up time, and standardized incidence ratios of gastric cancer (observed, expected, SIR, confidence interval).

Data Synthesis

We provided summaries of the rate of gastric cancer in each autoimmune disorder (frequency of gastric cancer in each autoimmune disease) by pooling standardized incidence ratios (SIRs) as an outcome for selected autoimmune disorders. SIRs were first extracted and then pooled using the inverse variance method and random-effects model with the restricted maximum-likelihood (REML) estimation. Subsequently, the results were displayed on forest plots. Summary SIR estimation, *p*-value, and 95% confidence interval (CI) were calculated.

Statistical heterogeneity was analyzed using the I^2 statistic and the χ^2 test to acquire probability values; $p < 0.1$ is defined to indicate significant heterogeneity. As suggested by the Cochrane Handbook, I^2 values were interpreted as moderate (30%–60%), substantial (50%–90%), and considerable (75%–100%) heterogeneity (17). Publication bias was checked by Funnel plot and Egger's test (alpha = 0·1) (18). The Eggers test was performed for each autoimmune disorder, where there were more than 10 studies included.

Subgroup analyzes were performed considering high-incidence or low-incidence countries for gastric cancer (10) and based on gender. A minimum number of studies were three for performing quantitative synthesis. Otherwise, findings were summarized in the qualitative synthesis.

All analyses were performed using R statistical software (R Foundation, Vienna, Austria) with the meta package (Guido Schwarzer, v4.18-2).

Risk of Bias Assessment in Individual Studies

Based on the recommendations of Cochrane Prognosis Methods Group (PMG), the Quality in Prognostic Studies (QUIPS) tool was used by two independent investigators (NV, LF) to assess the quality of the studies included, focusing on the definition of prognostic factors and outcomes (19). Disagreements were resolved by a third investigator (NZ). Details of the QUIPS are shown in **Supplementary Table S2**.

RESULTS

Search and Selection

The systemic search yielded 18,206 records, of which 12,420 remained after duplicate removal. Following the selection process, 43 articles were included in the systematic review and meta-analysis. Results of the selection are presented in **Figure 1**.

Basic Characteristics of the Included Studies

Four studies were retrospective from the included 43 articles, and 39 were prospective, describing 36 autoimmune disorders altogether. The overall work, including the qualitative and quantitative synthesis, contains 499,427 patients from four continents (America, Europe, Asia, and Australia) and 15 countries. The general characteristics of the included articles are presented in **Table 1**.

Analytical Results of Associations of Autoimmune Diseases and Gastric Cancer

Significantly increased incidence of gastric cancer was observed in the cases dermatomyositis (SIR = 3.71; 95% CI: 2.04, 6.75; $p < 0.0001$) based on four studies, pernicious anemia (SIR = 3.28; 95% CI: 2.71, 3.96; $p < 0.0001$) based on five studies, inflammatory myopathies (SIR = 2.68; 95% CI:1.40; 5.12; $p = 0.0029$) based on seven articles, systemic lupus erythematosus (SIR = 1.48; 95% CI: 1.09, 2.01; $p = 0.0116$) according to the analysis of seven records, diabetes mellitus type I (SIR = 1.29; 95% CI:1.14, 1.47; $p < 0.0001$) according to eight studies, and Graves' disease (SIR = 1.28; 95% CI: 1.16, 1.41; $p < 0.0001$) in the analysis of three studies. No significant differences could be found regarding autoimmune vasculitis, celiac disease, systemic sclerosis, dermatitis herpetiformis, Hashimoto thyroiditis, Sjogren's syndrome, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, and primary biliary cirrhosis. Detailed results are presented in **Figure 2**.

Subgroup Analysis Based on Gender

Diabetes mellitus type I increased the incidence of gastric cancer in female patients (SIR = 1.62; 95% CI: 1.20, 2.18) but not in male patients. Rheumatoid arthritis did not increase the incidence of gastric cancer in male or female patients. Subgroup analysis could not be performed regarding other autoimmune diseases. Results of the subgroup analysis based on gender are presented in **Supplementary Figures S39, S40**.

Subgroup Analysis Based on the Incidence of Gastric Cancer

Pernicious anemia (SIR = 3.28; 95% CI: 2.71, 3.96), diabetes mellitus type I (SIR = 1.41; 95% CI: 1.02, 1.95), Graves' disease (SIR = 1.28; 95% CI: 1.61, 1.41), and autoimmune vasculitis (SIR = 1.21; 95% CI: 1.01, 1.44) were associated with gastric cancer in low-incidence countries.

Systemic lupus erythematosus (SIR = 1.69; 95% CI: 1.21, 2.36) was associated with increased incidence of gastric cancer in high-incidence countries. However, in the case of dermatomyositis, subgroup analysis could not be performed, it was also associated with gastric cancer (SIR = 5.10; 95% CI: 1.90, 13.67) in low-incidence countries, based on two studies. We did not find significant statistical difference concerning the other autoimmune diseases. The detailed results of the subgroup analysis are presented in **Supplementary Figures S41–S56**.

Qualitative Synthesis

Eighteen other autoimmune disorders were included in the qualitative synthesis. The individual articles found an increased incidence of gastric cancer in the cases of immune thrombocytopenic purpura (20), membranous nephropathy (21), Addison's disease (20, 22), discoid lupus (22), Bechet's disease (20, 23), sarcoidosis (20, 22), myasthenia gravis (20, 22), Takayasu arteritis (24), polymyalgia rheumatica (20, 22), localized scleroderma (20, 22), and psoriasis (20, 22). Chronic rheumatic heart disease (20, 22), IgG4-related disease (25, 26), ANCA-vasculitis (27, 28), multiple sclerosis (20, 22), and granulomatosis with polyangiitis (20) seem not to be associated with elevated incidence of gastric cancer. The detailed results of the qualitative synthesis are presented in **Figure 3**.

Risk of Bias Assessment

Results and a detailed description of the risk of bias assessment according to the QUIPS tool are presented in **Supplementary Table S2**.

Publication bias was assessed for rheumatoid arthritis by the Egger's test, which does not indicate the presence of Funnel plot

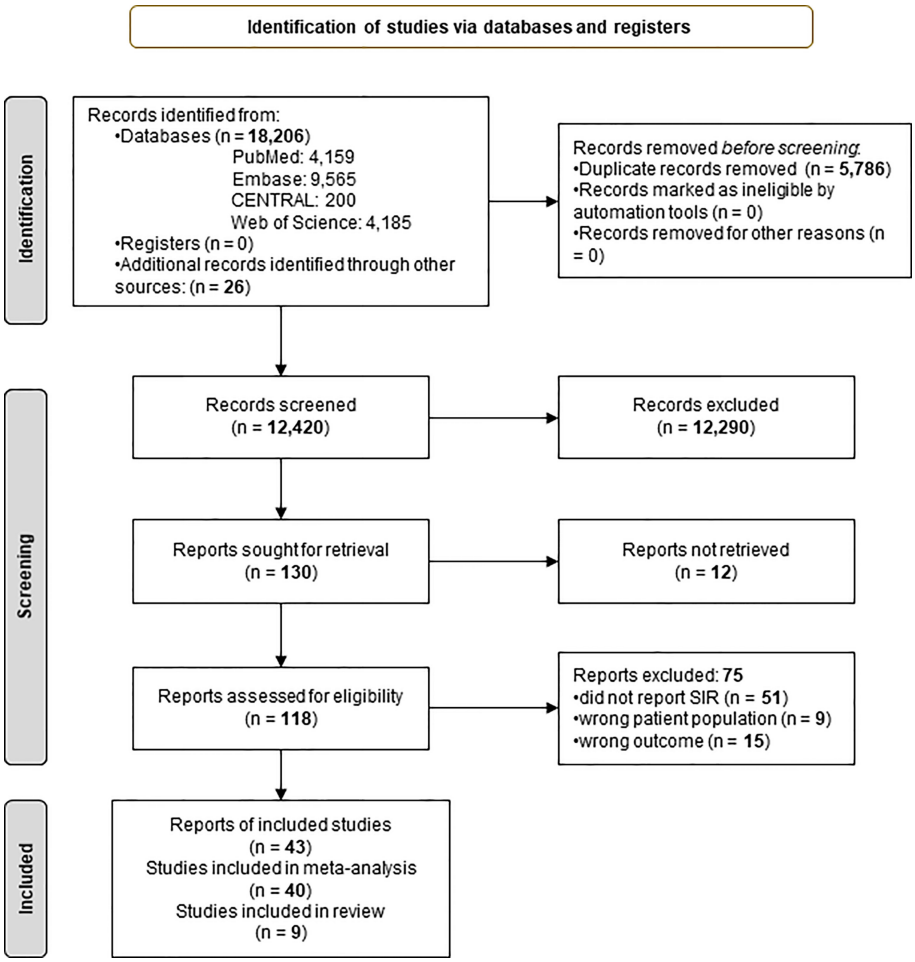

FIGURE 1 | Preferred Reporting in Systematic Reviews and Meta-analyses 2020 (PRISMA) flowchart showing the selection process (16).

asymmetry. Therefore, we concluded that no publication bias was present. Funnel plot is presented in **Supplementary Figure S57**.

Statistical Heterogeneity

The heterogeneity analysis proved to be significant in the analysis of rheumatoid arthritis (I^2 = 0.64; p = 0.00), inflammatory bowel disease (I^2 = 0.54; p = 0.04), systemic lupus erythematosus (I^2 = 0.60; p = 0.02), coeliac disease (I^2 = 0.56; p = 0.04), Crohn's disease (I^2 = 0.69; p = 0.04), and rheumatoid arthritis in the case of subgroup analysis of female patients (I^2 = 0.69; p=0.01). Other comparisons did not prove to be significant regarding heterogeneity. Detailed results of heterogeneity are presented in **Supplementary Figure S1**.

DISCUSSION

This meta-analysis, including data of 499,427 patients collected from 43 studies, was conducted to understand the relationship between autoimmunity and gastric cancer. Based on our results, the incidence of gastric cancer significantly increased in patients with pernicious anemia, Graves' disease, dermatomyositis, diabetes mellitus type I, inflammatory myopathies, and systemic lupus erythematosus.

In line with our results, the literature suggests that patients with dermatomyositis, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, or diabetes mellitus type I may have an increased risk for developing multiple cancers (29–34). Positive associations have been observed between various gastrointestinal tumors and rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, celiac disease, idiopathic inflammatory myositis, and systemic sclerosis (35–39).

A recent meta-analysis described a correlation between autoimmune disorders and increased risk of gastric cancer (40). Song et al. concluded that patients with dermatomyositis, pernicious anemia, Addison's disease, dermatitis herpetiformis, IgG4-related disease, primary biliary cirrhosis, diabetes mellitus type I, systemic lupus erythematosus, and Graves' disease had elevated risk for developing gastric neoplasms.

Pernicious anemia has been demonstrated as a risk factor for gastric cancer (41) since it correlates with autoimmune

TABLE 1 | Basic characteristics of included studies.

Author	Year	Country	Disease(s) Studied	Study Population (% of females)	SIR of Gastric Cancer (95% CI)
Asano et al.	2015	Japan	AIP	109 (23)	1.35 (0.03–2.66)
			IgG4-RD	158 (25)	1.43 (0.03–2.83)
Askling et al.	2002	Japan	Celiac disease	11,019 (59)	0.90 (0.3–2.0)
			Dermatitis herpetiformis	1,354 (43)	1.4 (0.6–2.8)
Bernatsky et al.	2013	Multinational	SLE	16,409 (90)	1.19 (0.65–2.00)
Bjørneklett et al.	2007	Norway	Membranous nephropathy	161 (36)	2.74 (0.07–15.3)
Brinton et al.	1989	USA	Perniciosus anemia	5,161 (0)	**3.21 (2.2–4.6)**
Brito-Zerón et al.	2017	Spain	Sjögren's syndrome	1,239 (92)	2.23 (0.93–5.36)
Chang et al.	2014	South Korea	RA	2,104 (82)	0.663 (0.327–0.998)
Chang et al.	2015	South Korea	SLE	1,052 (89)	0.597 (0.123–1.744)
Chang et al.	2016	South Korea	SSc	274 (88)	0.898 (0.109–3.245)
Chang et al.	2017	South Korea	Dermatomyositis	107 (81)	1.629 (0.041–9.076)
Chang et al.	2018	South Korea	Polymyositis	49 (40)	2.113 (0.054–11.774)
Chen et al.	2010	Taiwan	SLE	11,763 (88)	**2.08 (1.97–2.19)**
Collin et al.	1996	Finland	Celiac disease	383 (73)	0 (0–6.18)
			Dermatitis herpetiformis	305 (47)	2.86 (0.35–10.3)
Dreyer et al.	2011	Denmark	SLE	576 (88)	N/A
Goldrace et al.	2007	UK	Celiac disease	1,997 (NA)	1.83 (0.79–3.62)
			Crohn's disease	5,127 (NA)	0.96 (0.44–1.83)
			Ulcerative colitis	6,990 (NA)	0.78 (0.39–1.41)
Gridley et al.	1993	Sweden	RA	11,683 (68)	0.63 (0.5–0.9)
Harding et al.	2015	Australia	T1DM	80,676 (48)	**1.37 (1.01–1.87)**
Hashimoto et al.	2012	Japan	SSc	405 (93)	0.84 –0.11–1.79)
Hashimoto et al.	2015	Japan	RA	NA (82)	0.83 (0.65–1.02)
Hemminki et al.	2011	Sweden	Addison's disease	1,594 (NA)	**2.74 (1.24–5.23)**
			ALS	4,262 (NA)	0.96 (0.25–2.49)
			Ankylosing spondylitis	5,173 (NA)	0.92 (0.49–1.57)
			Behcet disease	2,860 (NA)	1.66 (0.83–2.99)
			Celiac disease	4,124 (NA)	N/A
			Chronic rheumatic heart disease	16,770 (NA)	**1.4 (1.07–1.81)**
			Crohn's disease	28,349 (NA)	0.87 (0.63–1.17)
			Graves'/hyperthyroidism	36,240 (NA)	**1.31 (1.07–1.59)**
			Hashimoto/hypothroidism	10,682 (NA)	1.34 (0.87–1.96)
			ITP	1,709 (NA)	**3.04 (1.09–6.66)**
			Localized scleroderma	3,128 (NA)	1.56 (0.7–2.55)
			Multiple sclerosis	12,553 (NA)	0.55 (0.28–0.97)
			Myasthenia gravis	17,974 (NA)	**1.38 (1.14–1.65)**
			PBC	835 (NA)	1.29 (0.12–4.75)
			Pernicious anemia	11,839 (NA)	**4.09 (3.36–4.94)**
			Polyarteritis nodosa	12,046 (NA)	1.02 (0.71–1.42)
			Polymyalgia rheumatica	14,745 (NA)	**1.45 (1.11–1.85)**
			Polymyositis/dermatomyositis	1,256 (NA)	2.74 (0.99–6.01)
			Psoriasis	15,592 (NA)	1.28 (0.94–1.69)
			RA	26,937 (NA)	1.07 (0.82–1.38)
			Rheumatic fever	3,458 (NA)	1.5 (0.86–2.44)
			Sarcoidosis	9,053 (NA)	1.45 (0.98–2.06)
			Sjögren's syndrome	3,769 (NA)	1.42 (0.73–2.48)
			SLE	5,318 (NA)	1.2 (0.57–2.21)
			SSc	1,195 (NA)	1.32 (0.12–4.87)
			T1DM	20,554 (NA)	2.64 (0.83–6.21)
			Ulcerative colitis	16,363 (NA)	0.88 (0.49–1.45)
			Wegener granulomatosis	945 (NA)	0.45 (0–2.59)
Hill et al.	2001	Sweden, Denmark, Finland	Dermatomyositis	618 (NA)	**3.5 (1.7–7.3)**
			Polymyositis	914 (NA)	0.3 (0.04–1.9)
Hirano et al.	2004	Japan	IgG4-RD, AIP	113 (20)	0.75 (0.086–2.59)
Hsing et al.	1993	Sweden	Pernicious anemia	4,517 (55)	**M: 2.8 (2–3.6)** **F: 3.1 (2.3–4.1)**
Hsu et al.	2015	Taiwan	T1DM	14,619 (53)	M: 1.08 (0.63–1.72) F: 1.33 (0.73–2.24)
Ilus et al.	2014	Finland	Celiac disease	32,439 (65)	0.9 (0.63–1.23)
Isomäki et al.	1978	Finland	Ankylosing spondylitis, Rheumatoid arthritis	46,101 (75)	N/A

(Continued)

TABLE 1 | Continued

Author	Year	Country	Disease(s) Studied	Study Population (% of females)	SIR of Gastric Cancer (95% CI)
Ji et al.	2010	Sweden	Addison's disease	NA	1.48 (0.47–3.48)
			ALS	NA	1.18 (0.56–2.18)
			Ankylosing spondylitis	NA	1.31 (0.85–1.92)
			Celiac disease	NA	1.2 (0.78–1.75)
			Chronic rheumatic heart disease	NA	0.52 (0.16–1.22)
			Crohn's disease	NA	**1.41 (1.12–1.75)**
			Discoid lupus erythematosus	NA	1.75 (0.83–3.23)
			Graves'/hyperthyroidism	NA	**1.33 (1.09–1.61)**
			Hashimoto/hypothyroidism	NA	0.9 (0.61–1.27)
			Localized scleroderma	NA	1.13 (0.48–2.24)
			Multiple sclerosis	NA	1.23 (0.87–1.7)
			Myasthenia gravis	NA	**1.64 (1.07–2.41)**
			PBC	NA	0.92 (0.29–2.16)
			Pernicious anemia	NA	2.11 (0.84–4.38)
			Polymyalgia rheumatica	NA	1.32 (0.99–1.73)
			Psoriasis	NA	**1.17 (1–1.35)**
			RA	NA	**1.2 (1.02–1.41)**
			Rheumatic fever	NA	1.78 (0.81–3.39)
			Sarcoidosis	NA	**1.53 (1.09–2.07)**
			Sjögren's syndrome	NA	0.75 (0.43–1.2)
			SLE	NA	1.08 (0.59–1.81)
			SSc	NA	1.09 (0.5–2.09)
			T1DM	NA	**1.27 (1.08–1.48)**
			Ulcerative colitis	NA	**1.39 (1.14–1.69)**
Ji et al.	2018	Sweden	Giant cell arteritis, polymyalgia rheumatica	35,918 (NA)	**1.27 (1.07–1.5)**
Kang et al.	2009	South Korea	SSc	112 (74)	**3 (1.9–4.1)**
Kirkegård et al.	2018	Denmark	Hyperthyroidism	92,783 (83)	**1.24 (1.08–1.42)**
			Hypothyroidism	71,189 (84)	**1.49 (1.26–1.75)**
Koskinen et al.	2021	Finland	Celiac disease	1,460 (63)	1.91 (0.95–3.41)
Lee H et al.	2019	South Korea	RA	1,885 (84)	M: 1.17 (0.22–2.88) F: 2.03 (0.97–3.48)
Lim et al.	2019	Singapore	RA	1,117 (84)	1.43 (0.6–3.44)
Lööf et al.	1994	Sweden	PBC	559 (88)	1.3 (0–7.2)
Nam et al.	2019	South Korea	Ankylosing spondylitis	21,780 (0)	0.93 (0.65–1.21)
Park et al.	2014	South Korea	Takayasu arteritis	180 (87)	1.4 (0–7.9)
Shiokawa et al.	2013	Japan	AIP	108 (26)	**2.7 (1.4–3.9)**
Shu et al.	2010	Sweden	T1DM	24,052 (47)	**3.,31 (1.41–6.56)**
Silano et al.	2007	Italy	Celiac disease	3,463 (43)	**3 (1.3–4.9)**
Stockton et al.	2000	Scotland	Dermatomyositis	286 (66)	**10 (2.1–29.2)**
Swerdlow et al.	2005	UK	T1DM	29,701 (44)	1.2 (0.48–2.47)
Swerdlow et al.	2006	UK	T1DM	29,701 (44)	0.77 (0.4–1.35)
Tallbacka et al.	2018	Finland	SLE	205 (89)	1.2 (0.03–6.7)
Thomas et al.	2000	Scotland	RA	26,623 (73)	M: 1.05 (0.74–1.46) F: 0.7 (0.5–0.95)
Van Daalen et al.	2017	The Netherlands	ANCA vasculitis	203 (35)	2.37 (0.06–13.2)
Viljaama et al.	2005	Finland	Celiac disease	781 (68)	1.2 (0.2–4.5)
			Dermatitis herpetiformis	366 (48)	2.1 (0.4–6.3)
Weng et al.	2015	Taiwan	Sjögren's syndrome	7,852 (88)	1.56 (0.75–2.86)
Yamada et al.	2011	Japan	RA	7,566 (82)	1.19 (0.8–1.7)
Yoo et al.	2018	South Korea	ANCA vasculitis	150 (69)	0.36 (0.009–2.012)
Yu et al.	2016	Taiwan	Behçet disease	1,620 (57)	N/A
			Dermatomyositis	1,119 (67)	1.88 (0.47–7.52)
			Inflammatory bowel disease	2,853 (37)	0.53 (0.13–2.11)
			Kawasaki disease	3,469 (60)	N/A
			Other vasculitis	644 (36)	N/A
			Polymyositis	811 (67)	N/A
			RA	35,182 (77)	0.92 (0.72–1.16)
			Sjögren's syndrome	11,988 (89)	1 (0.63–1.58)
			SLE	15,623 (88)	1.88 (1.21–2.91)
			SSc	1,814 (75)	0.7 (0.17–2.79)

SIR, standardized incidence rate; AIP, autoimmune pancreatitis; IgG4-RD, immunglobulin G4-related disease; SLE, systemic lupus erythematosus; NA, not available; RA, rheumatoid arthritis; SSc, systemic sclerosis; T1DM, type 1 diabetes mellitus; ALS, amyotrophic lateral sclerosis; ITP, immune thrombocytopenic purpura; PBC, primary biliary cirrhosis; M, males; F, females; ANCA, antineutrophil cytoplasmic antibody.

Number in bold indicate statistically significant results.

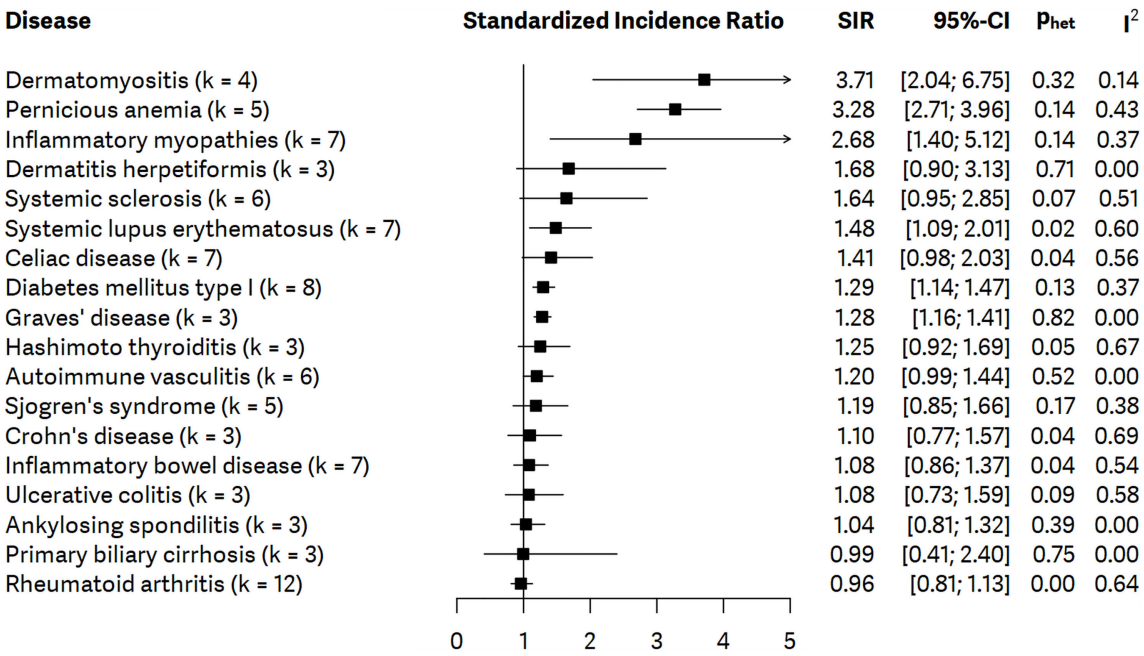

FIGURE 2 | Summarizing forest plot with pooled standardized incidence ratios (SIRs), representing the incidence of gastric cancer in all patients with autoimmune disorders included in meta-analysis; *number of studies – k*.

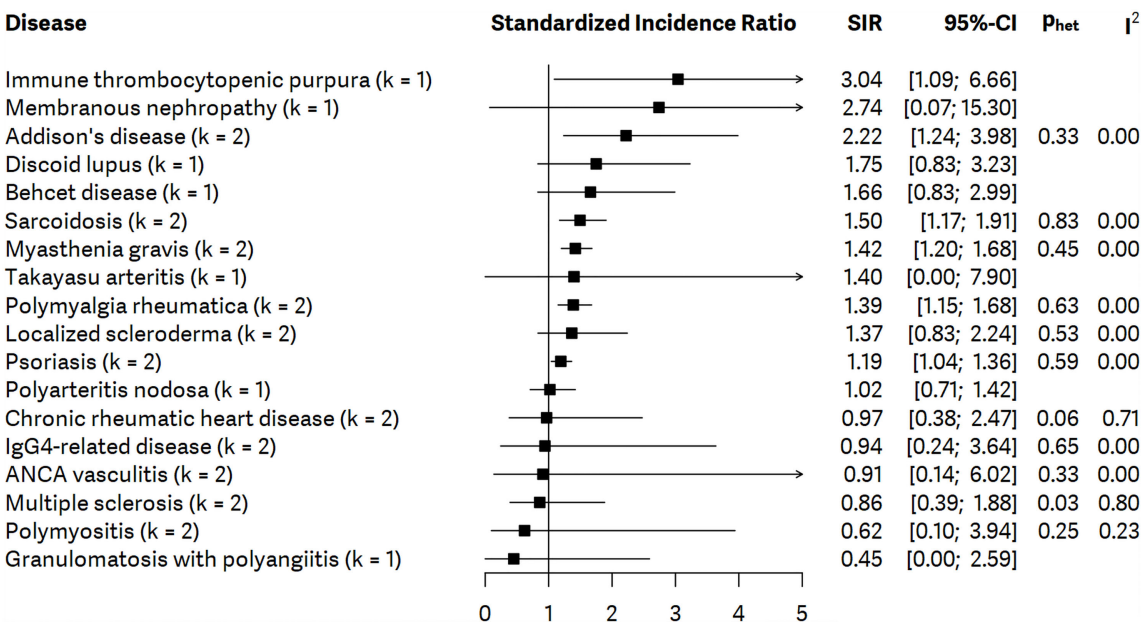

FIGURE 3 | Summarizing forest plot with pooled standardized incidence ratios (SIRs), representing the incidence of gastric cancer in all patients with autoimmune disorders included in qualitative synthesis; *number of studies – k*.

gastritis and results from gastric mucosal damage. This pathomechanism has been modeled in mice and has suggested an association between autoimmunity and carcinogenesis (14). Autoimmune thyroiditis, diabetes mellitus type I, vitiligo, and Addison disease are frequently associated with pernicious anemia.

An increase in the incidence of autoimmune diseases has been observed recently parallelly with the increasing incidence of

cancers. The autoimmune inflammation often correlates with the tumorous disorder of the affected organ. This phenomenon is most conspicuous in people below 50 years of age, and it affects females more considering the development of gastric cancer (7, 8).

Although autoimmune processes can play a significant role in developing different cancers, the exact pathomechanisms remain unclear. Several common factors can be identified, such as immunosuppression/dysregulation, infections, dietary habits, environmental factor, and chronic inflammation. These factors can induce chronic cell damage and can trigger either autoimmune conditions or cancer (12). Autoimmune disorders may lead to antigen specificity-driven tissue damage causing chronic inflammation, whose role in carcinogenesis is well known and precedes the tumor formation in time (42).

Regarding the strengths of our meta-analysis, we included a large number of cohort studies. Many of our analytical results proved to be significant. This comprehensive work contains wide coverage of AI disorders from 15 different countries and four continents of the currently available literature so far. Following the PRISMA Statement and a rigorous methodology, the quality is secured. The key questions of this study were not widely investigated recently; thus, most of our findings are novel.

The formerly mentioned meta-analysis (40) discussing the question of interest had several limitations. Compared with that work, a more general search key was used in our study, which allowed us to find a higher number of relevant records. Our search was conducted in four databases compared with the two in the previous work, which also contributed to the identification of further eligible studies. They calculate pooled relative risk ratios (RR) with 95% CI; however, hazard ratios, SIRs, RRs, and standardized mortality rates were pooled into RR. Statistical analysis of our study is also more coherent as only SIR-s were calculated consistently (43, 44).

However, our analysis has some limitations, which should be considered for a correct interpretation. Firstly, other risk factors for gastric cancer, such as *H. pylori* infection status, smoking, dietary habits, obesity, occupational exposure to dust, high-temperature particulates, and metals such as chromium VI, gastric surgery (by-pass), and Epstein-Barr infection could be present that were not measured or reported. We also did not have information about drugs taken for autoimmune disorders, so how it may affect the outcome is unknown. However, according to 10 included articles, the mean time interval from the diagnosis of AI disorder to the diagnosis of cancer is 2–7.4 years. Although, the mentioned time intervals refer to the development of any type of cancer in general, not only to gastric cancer.

The diagnosis of AI diseases in countries could be different, which could create significant heterogeneity in some of the analyses. The presence of ascertainment cannot be ruled out, since people with an autoimmune disease are subjected to medical examinations more frequently, than the general population, which may lead to a greater number of cancer diagnoses. The low number of enrolled studies regarding certain autoimmune disorders, which could not be meta-analyzed, is also a further limitation. The risk of bias assessment deemed in case of multiple domains as not low overall risk of bias too.

Subgroup analyses regarding the type of gastric cancer could not be performed, because there were no details available on histological type, or location of cancer. However, Ji et al. described that a few autoimmune diseases is an important risk factor for gastric cancer, mainly for corpus cancer (22). Sensitivity analysis was carried out to define the strength of confounding factors, such as *H. pylori* infection, which results suggest the examined association is unlikely to be solely because of confounding.

Most of the included studies originate from either North Europe (where incidence of autoimmunity could be higher compared with other populations) or Asia (where *H. pylori* infection and/or gastric cancer could be more prevalent). To address this problem, we performed subgroup analyses based on low- or high-incidence countries of gastric cancer. The results of the subgroup analysis reassert our main results, namely pernicious anemia, diabetes mellitus type I, Graves' disease, and autoimmune vasculitis were associated with gastric cancer in low-incidence countries.

CONCLUSION

Our meta-analysis of 39 articles concludes that pernicious anemia, Graves' disease, dermatomyositis, diabetes mellitus type I, inflammatory myopathies, and systemic lupus erythematosus are associated with higher incidence rates of gastric cancer. For clinical practice, close gastroenterological follow-up or routinely performed gastroscopy and application of other diagnostic measures may be cost-effective and clinically helpful for patients diagnosed with these six autoimmune diseases. Based on the importance of the problem, conducting further clinical trials on this topic is essential.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

NZ: conceptualization, project administration, formal analysis, and writing—original draft. EO: conceptualization, methodology, and statistical analysis. PH: conceptualization and writing—review and editing. SV: conceptualization, data curation, and writing—review and editing. NV: conceptualization, data curation, and writing—review and editing. SK: conceptualization, methodology, and writing—review and editing. LF: conceptualization, visualization, and writing—review and editing. LS: conceptualization, methodology, visualization, and writing—original draft.

JC: conceptualization, supervision, and writing—original draft. All authors have participated sufficiently to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.750533/full#supplementary-material

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ORIGINAL PAPER

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Prevalence of Autoimmune-phenomena behind Chronic Gastritis of Unknown Origin, and their Role in the Poor Histological Outcome of the Stomach: A Single-centre, Retrospective Cross-sectional Study

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ABSTRACT

Background & Aims: The underlying aetiology of chronic gastritis (CG) often remains unknown due to its underrated significance in clinical practice. However, the role of chronic inflammation of the stomach in the development of atrophy, intestinal metaplasia (IM) and eventually of gastric cancer is well documented. We aimed to explore the possible aetiological factors of CG, determine the prevalence of systemic autoimmune disorders in patients with CG of unknown aetiology, and clarify the role of autoantibodies in the development of precancerous lesions in the stomach.

Methods: This is a retrospective, cross-sectional study, conducted from January 2016 to January 2020, including data from 175 patients with CG. Exclusion criteria were: (1) acute gastritis; (2) reactive gastropathy; (3) gastric cancer; (4) subjects without any serology testing results; and (5) *Helicobacter pylori* positivity. The primary endpoint was a composite endpoint involving gastric atrophy and IM.

Results: Fifty-five per cent of patients with CG had autoantibodies. Systemic lupus erythematosus (SLE)-related antibodies were positive in most of the cases, including antinuclear antibody (ANA) positivity, which was found in 19.13% of the patients. Autoimmune positivity was shown to be associated with precancerous lesions in the stomach ($p<0.001$): IM, atrophy and IM with atrophy. Anti-parietal cell antibody positivity seems to be a significant risk factor for IM and IM with atrophy. Autoimmune thyroiditis-related antibodies and ANA positivity by itself were only associated with atrophy; SLE-related antibodies and inflammatory bowel diseases related antibodies (ASCA and ANCA) correlated either with IM or with atrophy. No significant relationship was found between any other investigated autoimmune disease-related antibodies and precancerous lesions.

Conclusions: Autoimmune positivity often underlies gastritis of unknown aetiology and predisposes to precancerous lesions in the stomach. These antibodies can serve as non-invasive markers for the of optimal timing of an endoscopic follow-up strategy. Furthermore, CG can be an early symptom of a systemic autoimmune disorder.

Key words: chronic gastritis – autoimmunity – autoantibodies – intestinal metaplasia – gastric atrophy – gastric cancer.

Abbreviations: AIG: autoimmune gastritis; AIN: autoantibody negative test; AIP: autoantibody positivity test; ANA: antinuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; ASCA: antibodies against the yeast *Saccharomyces cerevisiae* (ASCA); CI: confidence interval; *H. pylori*: *Helicobacter pylori*; IBD: inflammatory bowel disease; IM: intestinal metaplasia; SLE: systemic lupus erythematosus; SSA: anti-Sjögren's syndrome-related antigen A; SSB: anti-Sjögren's syndrome-related antigen B.

INTRODUCTION

Chronic gastritis is a long-lasting inflammatory condition of the gastric mucosa without specific treatment. Mucosal atrophy with intestinal metaplasia (IM) is the result of a long-lasting inflammation independent of the aetiology [1, 2]. The significance of chronic gastritis is underrated in clinical practice, even though its role in the pathogenesis of gastric cancer is well documented: carcinoma develops in the milieu of mucosal atrophy and IM [3-6], with an estimated annual cancer rate of 0.1% within five years after diagnosis [7].

It is proven by several studies and as suggested by the Maastricht V and Kyoto consensus, the measurement of serum pepsinogen level is the most reliable non-invasive marker

for screening of chronic atrophic gastritis [8]. Screening of serum pepsinogen level in the diagnosis of chronic atrophic gastritis may improve compliance of the population and the cost-effectiveness of screening of gastric tumours, thereby improving mortality [9].

The two most common causes of chronic gastritis are *Helicobacter pylori* (*H. pylori*) infection in one-third of the cases and autoimmune gastritis (AIG) in 7.8–19.5% of the cases [10]. *Helicobacter pylori* was supposed to be the most common cause of chronic atrophic gastritis based on its high prevalence and has been listed as a class I carcinogen in the past three decades [11, 12]. Although the prevalence of *H. pylori* has been declining [13, 14], gastric cancer is still the fifth most common cancer worldwide [15], implying the role of other aetiological factors. Due to the overwhelming attention given to *H. pylori* infection, the relevance of AIG and other possible causative factors has faded.

Although chronic gastritis is one of the most common findings with upper gastrointestinal endoscopy, the underlying aetiology often remains unknown [16]. If the results of *H. pylori* tests and antibodies related to AIG are negative, diagnostic measures for other autoinflammatory diseases are not carried out routinely. However, clarification of the underlying aetiology might be beneficial in the prevention of gastric neoplasm.

In this study, we aimed to explore the possible causes of chronic gastritis in south-western Hungary and to assess the possible relationship between these factors and IM and atrophy. We also aimed to determine the prevalence of systemic autoimmune disorder-related autoantibody positivity in chronic gastritis in our region and to investigate a possible relationship between these conditions in a retrospective study. Furthermore, we aimed to revise the current clinical practice in the diagnosis and management of chronic gastritis.

METHODS

This retrospective study was conducted from January 2016 to January 2020. All patients who were admitted to gastroscopy, and were diagnosed with chronic gastritis, and who underwent any serology testing were included in the analysis consecutively. A diagnosis of gastritis was established based on histologic findings from patients undergoing upper gastrointestinal endoscopy. Multiple biopsy samples (no less than five) were taken from pre-defined sites of the stomach according to the updated Sydney system [2]. Additional biopsy samples were obtained from any detected focal lesion. All included patients were managed by the same medical team (patients, with regular care from one, single examining endoscopic specialist were only considered for enrolment; one pathologist, who specialized in gastrointestinal pathology, reviewed all the histological findings) to avoid performance bias.

The exclusion criteria were: (1) acute gastritis; (2) reactive gastropathy; (3) gastric cancer; and (4) subjects without any serology testing results; (5) *H. pylori* positivity. Reactive gastropathy is also called reflux gastritis or type C gastritis and was identified based on the existence of certain histological criteria [17], determined by the pathologist. *Helicobacter pylori* infection status was assessed by histological assessment, serological tests and urea-breath test as well. Given that the connection between chronic atrophic gastritis and *H. pylori* infection has been shown, it can be considered as a confounding factor. Therefore, to examine the role of autoimmune markers in the development of precancerous lesions of the stomach, *H. pylori* positive patients were excluded from the study in order to minimize bias.

Patients were identified using an electronic database. The following data were collected: baseline characteristics of the analysed population (age, gender and their correlation to the outcome measures), histological findings (localisation of the inflammation; OLGA score; and the presence of atrophy, IM), gastroesophageal reflux disease, ulcer or cancer, autoantibody positivity, *H. pylori* infection status (histology, results of the urea breath test and/or serology), the presence and type of symptoms (key symptoms and presence of dyspepsia-like symptoms) and data regarding other risk factors [body mass index (BMI), alcohol consumption and smoking]. We split the identified patients into those with any autoantibody positivity (AIP) and those with negative autoimmune tests (AIN) for comparison.

Autoantibody positivity was considered using the threshold for the laboratory at our centre in line with the European standard laboratory criteria. Autoantibodies were separated into groups according to the autoimmune diseases of which they are characteristic. These findings are shown in Table I.

Table I. Grouping autoantibodies according to the specific autoimmune disorders in our study

Disease	Attributed antibodies
Celiac disease	Anti-gliadin, anti-endomysium, tissue transglutaminase antibody IgA and/or IgG
Sjögren's syndrome	Anti-Sjögren's syndrome-related antigen A (SSA), anti-Sjögren's syndrome-related antigen B (SSB)
Systemic lupus erythematosus (SLE)	Anti-nuclear antibodies (ANA), anti-nucleosome antibodies, anti-cardiolipin, anti-centromere, anti-C1q, anti-b2 glycoprotein, anti-double-stranded DNA (ds-DNA)
Autoimmune hepatitis	Anti-smooth muscle antibodies (SMA), anti-liver kidney microsomal antibodies (LKM-1, LKM-2, LKM-3), anti-soluble liver antigens (SLA), liver–pancreas antigens (LP), anti-mitochondrial antibodies (AMA), anti-filamentous actin 1 antibodies (F1 actin)
Rheumatoid arthritis (RA)	Anti-cyclic citrullinated peptide antibodies (CCP), anti-rheumatoid factor (RF) antibodies
Systemic sclerosis (Ssc)	Anti-Scl-70 antibodies, anti-centromere antibodies
Polymyositis/ dermatomyositis	Anti-Jo-1 antibodies
Inflammatory bowel disease (IBD)	Anti-yeast *Saccharomyces cerevisiae* (ASCA), anti-neutrophil cytoplasmic antibodies (ANCA)
Autoimmune thyroiditis	Anti-thyroid peroxidase (TPO), anti-TSH receptor antibodies (TRAb), anti-thyroglobulin antibodies (Tg)
Autoimmune gastritis	Anti-parietal cell antibodies, anti-intrinsic factor antibody

Patients' body weight and height were measured during the gastroenterological consultation. Following the international standards, patients were divided into two groups based on BMI: those with high BMI ≥ 25 kg/m^2 and those below [18].

The primary endpoint was a composite endpoint which included gastric atrophy and IM. Secondary endpoints were the prevalence of each antibody positivity and the stage of the atrophy based on the OLGA score. All parameters were assessed at the level of autoimmune disease groups and in autoantibody-positive and negative groups. Assessment of the individual level of each autoantibody was carried out if the sample size reached at least eight patients. Furthermore, we evaluated whether simultaneous positivity to 2 or more autoimmune diseases is related with an even higher risk of precancerous lesions.

The study was approved by the Director of the Clinical Centre and the Director of the First Department of Medicine at the University of Pécs (Institutional Review Board; case number: KK/999-1/2020). The data collection and analysis were carried out in compliance with the current laws and regulations and according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19]. All recruited cases received a numeric code to ensure privacy and personal data protection. No informed consent was required for the study, as the University of Pécs obtains automatically a general allowance for scientific purpose data usage from all patients. Therefore, we have not included data from patients who refused scientific purpose handling of their data at the time of admission.

Statistical Analysis

Data were analysed using SPSS 25.0 software. Mean, standard deviation, and minimum and maximum values were calculated for descriptive statistics. Univariate and multivariate analyses (adjusted for gender and age) were performed. Two-sided Pearson Chi-square was counted to compare dichotomous variables for patient frequencies. Odds ratios (OR) with 95% confidence interval (CI) were used for other analyses. In the case of significant differences, standardized residuals were also observed to arrive at the exact results. Multinominal logistic regression was performed when co-factors were also considered. In the case of continuous variables, an independent sample t-test was used. We observed the distribution on a Q-Q plot. A p-value of less than 0.05 was accepted as statistically significant.

RESULTS

A total of 285 patients with histologically proved chronic gastritis were assessed in the time period noted above. Three patients were excluded due to gastric cancer, 56 due to *H. pylori* positivity, 42 due to reactive gastropathy and 9 because of a lack of serology testing. 175 patients were included in the final analysis (52 men and 123 women). The mean age of the analysed population was 61.6 years (±15.13 years), ranging from 21 to 89, and most patients were female (70.29%). The age distribution as regards AIP and AIN can be seen in Fig. 1.

Significant differences were not seen in the baseline characteristics between the AIP and AIN groups. The mean

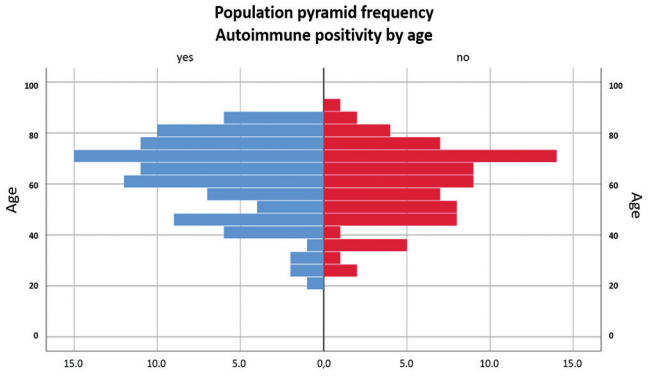

Fig. 1. Population distribution by age and AI positivity. Blue columns represent the age distribution of the autoimmune-positive patients, while red columns represent the autoimmune-negative patients.

BMI of the patients was 25.89 kg/m^2 (±5.42 kg/m^2). There was no significant relation between gender and autoimmune positivity (p=0.641). As regards risk factors, alcohol consumption was present in 39.20% of the cases (29/74), while 17.39% of the patients smoked (20/115). Eighty-one patients suffered from GERD.

In ten cases (out of 167 patients) anaemia was observed (5.99%), from which eight patients had AIP: three patients had AIP for AIG, one for celiac disease, one for inflammatory bowel disease (IBD), and three patients for systemic lupus erythematosus (SLE).

Out of 175 patients with chronic gastritis, 53 (30.29%) had atrophy with fibrosis, and 49 (28%) had atrophy with IM. A detailed description of the baseline characteristics of the patients is presented in Table II.

Prevalence of Autoantibody Positivity

Fifty-five per cent (97/175) of patients with chronic gastritis had AIP. The prevalence of AIG was 21.71% (38/175), of whom 35 (20%) had serum antibodies to parietal cell, and three patients (1.71%) had them to both parietal cell and intrinsic factor. Antibodies related to celiac disease were found in 8% (14/175) of the patients; anti-gliadin was observed in all 14 patients (100%), anti-endomysium in two patients (1.14%), and tissue transglutaminase antibody IgA and/or IgG in six patients (3.43%). Autoimmune thyroiditis was observed in 17.54% (20/114) of the patients examined. 11.90% of the subjects (15/126) had antibodies against the yeast *Saccharomyces cerevisiae* (ASCA).

As regards systemic AI disorder-related serology, the most common antibody was the antinuclear antibody (ANA), found in 19.13% of the patients (22/115). Antibodies were also found against nucleosome (8.7% of chronic gastritis patients), rheumatic factor (7.34% of the analysed population) and double-strand DNA (6.07% of the patients). Autoimmune hepatitis-related serology was positive in 9.52% (6/63) of the examined cases. In 3.48% of the analysed population (4/115), the anti-b2 glycoprotein titre was high. Three individuals out of 126 (2.38%) had elevated titres to antineutrophil cytoplasmic antibodies (ANCA), and three out of 111 (2.70%) showed high titres to anti-Sjögren's syndrome-related antigen A (SSA). Anti-cardiolipin, anti-centromere, anti-C1q and

Table II. Patients' baseline characteristics

Parameter	Overall (n=175)	AIP (n=97)	AIN (n=78)	p
Age (mean, SD)	61.66; 15.13	62.68; 15.03	60.40; 15.13	0.321
Female n, (%)	123 (70.29)	64 (65.98)	59 (75.64)	0.641
BMI (mean, SD)	25.89, 5.42	25.81, 5.44	25.81, 5.51	1.000
Alcohol consumption n, (%)*	29/74 (39.19)	16/41 (39.02)	13/33 (39.39)	0.946
Smoking n, (%)*	20/115 (17.39)	11/58 (18.97)	9/57 (15.79)	0.238
GERD n, (%)	81 (46.29)	40 (41.24)	41 (52.56)	0.888
Anaemia n, (%)*	10/167 (5.99)	8 (8.25)	2 (2.56)	0.188
Precancerous lesion				
Atrophy with intestinal metaplasia n (%)	49 (28.00)	33 (34.02)	16 (20.51)	<0.001
Atrophy with fibrosis without intestinal metaplasia n (%)	53 (30.29)	37 (38.14)	16 (20.51)	<0.001

AIP: autoimmune antibodies positive; AIN: autoimmune negative; BMI: body mass index; SD: standard deviation; GERD: gastroesophageal reflux disease; *indicates missing data. The total number of patients with information on smoking status is 115, of whom 20 are smokers; in the case of alcohol consumption, the total number is 74, of whom 29 are regular alcohol consumers (on a daily basis).

anti-Sjögren's syndrome-related antigen B (SSB) and myositis-specific antibodies were also observed in a low number of cases (<1%) (Table III). There was no significant difference between females and males in the prevalence of each antibody positivity (p>0.05).

Poor Histological Outcomes and Autoimmune Antibodies Positivity

As regards precancerous lesions, the AIP group was associated with a significantly higher rate of atrophy alone (37 vs 16 patients, p<0.001). Atrophy with IM was found in 33 (34.02%) and 16 (20.51%) subjects in the AIP and AIN groups, respectively (p<0.001) (Table II).

Univariate Analyses

With regard to the univariate analyses of the relationship between histological outcomes and autoimmune positivity, it was found that there is a significant correlation between autoimmune positivity and precancerous lesions. Among patients with AIP, atrophy (p=0.015) was presented more frequently. The co-occurrence of atrophy and IM was also associated with AIP (p=0.039).

A link was found between AIG-related antibody positivity, especially anti-parietal cell antibody positivity and atrophy with IM (p=0.033). No significant link was found between any other autoimmune disease-related antibodies and precancerous lesions.

No difference was found regarding the worse OLGA score (OLGA 3–4) and autoimmune positivity. Comparisons on the level of individual autoimmune bodies were not carried out due to the low number of cases.

Bivariate Analyses

Bivariate analyses adjusted for age found significant differences in the following relations: AIG-related antibodies with atrophy (OR=2.250; 95%CI: 1.945-5.357; p<0.001) and atrophy with IM (OR=2.229; 95%CI: 1.019-4.877; p<0.001); SLE-related antibodies and atrophy (OR=2.288; 95%CI: 1.523-3.176; p=0.002) and atrophy with IM (OR=2.340; 95%CI 1.375-5.841; p=0.006); IBD-related antibody (ASCA and ANCA) positivity with atrophy with IM (OR=2.760; 95%CI: 1.218 to 2.645; p=0.017) and atrophy without IM (OR=5.308; 95%CI: 1.480-19.036; p=0.001); anti-parietal cell antibody with atrophy with IM (OR=2.229; 95%CI: 1.019-4.877, p=0.006).

As regards the results of bivariate analyses adjusted for gender, AIG-related antibodies correlated with atrophy (OR=2.732; 95%CI: 1.350-2.349; p<0.001) and atrophy with IM (OR=2.222; 95%CI: 1.040-4.749; p<0.001). SLE-related antibody positivity was associated with atrophy (OR=2.766; 95%CI: 1.755-4.132; p<0.001) and atrophy with IM (OR=4.294; 95%CI: 1.313-14.043; p=0.001). Significant links were found between atrophy without IM and ASCA and ANCA positivity (OR=2.352; 95%CI: 1.032-6.645; p=0.007), ANA positivity (OR=2.044; 95%CI: 1.097-5.242; p=0.029) and autoimmune thyroiditis-related antibody positivity (OR=2.566; 95%CI: 1.574-4.274; p=0.048). Anti-parietal cell antibodies also correlated with worse histological outcome (OR=2.222; 95%CI: 1.040-4.749; p=0.038).

Sjögren's syndrome, autoimmune hepatitis, rheumatoid arthritis, systemic sclerosis and polymyositis/dermatomyositis-related antibody positivity did not show a statistically significant correlation with precancerous lesions. Detailed results of univariate and multivariate analyses are presented in Table IV.

The analysis regarding simultaneous AIP showed a higher risk for precancerous lesions in some cases: SLE related antibodies (OR=4.778; 95%CI: 1.945-2.089; p=0.058); AIG related antibodies (OR=3.182; 95%CI: 1.708-8.142).

DISCUSSION

This retrospective cross-sectional study with data from 175 patients was conducted to explore possible causes behind chronic gastritis of unknown origin and to understand the possible relationship between systemic autoimmune disorders and poor histological outcomes of chronic gastritis. Furthermore, we aimed to revise the current clinical practice in the diagnosis and management of chronic gastritis.

Table III. Prevalence of autoantibody positivity in patients with chronic gastritis

Autoimmune disease (attributed antibodies)	Positive (n)	Total number of patients tested	%
AI gastritis (AIG)	38	175	21.71
Anti-parietal cell antibodies	35	175	20.00
Anti-intrinsic factor antibodies	3	175	1.71
Celiac disease	14	175	8.00
Anti-gliadin	14	175	8.00
Anti-endomysium	2	175	1.14
Tissue transglutaminase antibodies IgA	3	175	1.71
Tissue transglutaminase antibodies IgG	3	175	1.71
Sjögren's syndrome	3	111	2.70
Anti-Sjögren's syndrome-related antigen A (SSA)	3	111	2.70
Anti-Sjögren's syndrome-related antigen B (SSB)	0	111	0.00
Systemic lupus erythematosus (SLE)	31	115	26.96
Anti-nuclear antibodies (ANA)	22	115	19.13
Anti-nucleosome antibodies	10	115	8.70
Anti-cardiolipin	2	115	1.74
Anti-centromere	1	115	0.87
Anti-C1q	1	115	0.87
Anti-b2 glycoprotein	4	115	3.48
Anti-double-stranded DNA (ds-DNA)	7	115	6.07
Autoimmune hepatitis	6	63	9.52
Anti-smooth muscle antibodies (SMA)	1	63	1.59
Anti-liver/kidney microsomal antibodies (LKM-1, LKM-2, LKM-3)	0	63	0.00
Anti-soluble liver antigens (SLA)	0	63	0.00
Liver–pancreas antigens (LP)	0	63	0.00
Anti-mitochondrial antibodies (AMA)	3	63	4.76
Anti-filamentous actin 1 antibodies (F1 actin)	2	63	3.17
Rheumatoid arthritis	8	109	7.34
Anti-cyclic citrullinated peptide antibodies (CCP)	0	109	0.00
Anti-rheumatoid factor (RF) antibodies	8	109	7.34
Systemic sclerosis (Ssc)	1	96	1.04
Anti-Scl-70 antibodies	0	96	0.00
Anti-centromere antibodies	1	96	1.04
Polymyositis/dermatomyositis	0	99	0.00
Anti-Jo-1 antibody	0	99	0.00
Inflammatory bowel disease (IBD)	18	126	14.29
Anti-yeast *Saccharomyces cerevisiae* (ASCA)	15	126	11.9
Anti-neutrophil cytoplasmic antibodies (ANCA)	3	126	2.38
AI thyroiditis	20	114	17.54
Anti-thyroid peroxidase (TPO)	13	114	11.40
Anti-TSH receptor antibodies (TRAb)	2	114	1.75
Anti-thyroglobulin antibodies (Tg)	5	114	4.39

Patients were summarized in each autoimmune disorder group taking multiple autoantibody positivity into consideration to avoid duplication.

One of our major findings was that more than half of the patients with chronic gastritis had positive immunoserology. In line with previous results from other countries, in Hungary, the prevalence of AIG was about 20%, and anti-parietal cell antibodies are more common than anti-intrinsic factor antibodies [10]. The most frequently occurring antibodies in our patients with chronic gastritis besides AIG were SLE-related antibodies in one-quarter of

Table IV. Uni- and bivariate analyses

	Univariate analysis (p)	Bivariate analysis – age (p)	Odds ratio [95% CI]	Bivariate analysis – gender (p-value)	Odds ratio [95% CI]
			Atrophy with intestinal metaplasia		
Autoimmune gastritis	0.033	<0.001	2.229 [1,019-4,877]	<0.001	2.222 [1.040; 4.749]
Celiac disease	0.353	0.345	0.469 [0.98-2.240]	0.213	0.374 [0.080; 1.757]
Sjögren's syndrome	1.000	0.358	1.178 [0.101-13.729]	0.969	0.953 [0.083; 10.946]
Systemic lupus eritematous	0.433	0.006	2.340 [1.375-5.841]	0.001	4.294 [1.313; 14.043]
Autoimmune hepatitis	1.000	0.856	0.843 [0.134-5.316]	0.886	1.143 [0.186; 7.032]
Rheumatoid arthritis	1.000	0.124	1.175 [0.260;5.311]	0.909	1.092 [0.244; 4.889]
Systemic sclerosis	0.374	0.570	1.039 [1.006; 1.074]	0.241	0.594 [0.248; 1.420]
Polymyositis/dermatomyositis	n/a	n/a	n/a	n/a	n/a
Inflammatory bowel diseases	0.313	0.017	2.760 [1.218; 2.645]	0.083	1.134 [0.214; 2.324]
Autoimmune thyroiditis	0.935	0.814	0.882 [0.308; 2.522]	0.099	1.155 [0.408; 3.268]
Anti-parietal cell antibodies	0.033	0.006	2.229 [1.019; 4.877]	0.038	2.222 [1.040; 4.749]
Anti-gliadin antibodies	0.111	0.212	0.212 [0.260; 1.700]	0.200	0.185 [0.023; 1.475]
Antinuclear antibodies	0.333	0.413	1.221 [0.449; 3.323]	0.155	1.637 [0.626; 4.280]
Anti-dsDNA antibodies	0.683	0.486	1.218 [0.251; 5.914]	0.311	1.857 [0.382; 9.020]
Anti-nucleosome antibodies	0.728	0.484	1.152 [0.292; 4.541]	0.303	1.637 [0.626; 4.280]
Anti-rheumatoid factor	1.000	0.914	1.175 [0.260; 5.311]	0.966	1.092 [0.244; 4.889]
			Atrophy without intestinal metaplasia		
Autoimmune gastritis	0.374	<0.001	2.250 [1.945; 5.357]	<0.001	2.732 [1.350; 2.349]
Celiac disease	0.228	0.394	0.416 [0.087; 1.991]	0.848	0.343 [0.073; 1.600]
Sjögren's syndrome	0.551	n/a	n/a	n/a	n/a
Systemic lupus eritematous	0.168	0.002	2.288 [1.523; 3.176]	<0.001	2.766 [1.755; 4.132]
Autoimmune hepatitis	0.638	0.331	1.354 [0.172; 10.684]	0.160	1.509 [.227; 10.015]
Rheumatoid arthritis	1.000	0.096	1.137 [0.241; 5.638]	0.123	1.040 [0.234; 4.619]
Systemic sclerosis	0.378	0.559	1.068 [1.020; 1.097]	0.405	1.058 [1.020; 1.97]
Polymyositis/dermatomyositis	n/a	n/a	n/a	n/a	n/a
Inflammatory bowel diseases	0.099	0.001	5.308 [1.480; 19.036]	0.007	2.352 [1.032; 6.645]
Autoimmune thyroiditis	0.322	0.085	1.359 [0.473;3.909]	0.048	2.566 [1.574; 4.274]
Anti-parietal cell antibodies	0.374	0.174	1.350 [0.616; 2.958]	0.104	1.446 [0.675; 3.093]
Anti-gliadin antibodies	0.065	0.216	0.186 [0.023; 1.497]	0.182	0.168 [0.021; 1.328]
Antinuclear antibodies	0.126	0.110	1.522 [0.561; 4.128]	0.029	2.044 [1.097; 5.242]
Anti-dsDNA antibodies	1.000	0.924	0.531 [0.094; 2.987]	0.650	0.629 [0.114; 3.465]
Anti-nucleosome antibodies	0.317	0.215	1.646 [0.424; 6.386]	0.079	1.892 [0.510; 7.018]
Anti-rheumatoid factor	1.000	0.353	1.137 [0.241; 5.368]	0.257	1.040 [0.234; 4.619]

n/a: not assessed.

the cases, followed by autoimmune thyroiditis, IBD, celiac disease and rheumatoid arthritis-related antibody positivity. Autoimmune positivity was shown to be associated with precancerous lesions in the stomach: atrophy, and atrophy with IM. AIG-related antibodies, especially anti-parietal cell antibody positivity, seem to be a significant risk factor for worse histological outcome. Autoimmune thyroiditis-related antibodies and ANA positivity by itself were associated with atrophy; SLE-related antibodies and IBD-related antibodies (ASCA and ANCA) correlated with atrophy and with atrophy with IM. Any other autoantibodies examined did not show any effect on the histological outcomes of chronic gastritis. No difference was found with regard to a worse OLGA score and autoimmune positivity.

Although these relationships were not examined in this context, gastrointestinal manifestations can occur in various autoimmune disorders. Frequent occurrence of gastritis has been described in patients with IBD and celiac disease [20-22]. Rheumatoid arthritis can affect both the gastrointestinal tract and the liver [23]; chronic superficial and chronic atrophic gastritis can be seen in 30 and 62.5% in patients with rheumatoid arthritis, respectively [24]. Systemic lupus erythematous may involve the gastrointestinal tract as well; however, according to the literature, manifest gastritis is rare in patients with SLE [25]. Lecouffe-Desprets et al. [26] reported that SLE, rheumatoid arthritis, systemic sclerosis, inflammatory myopathies, Sjögren's syndrome and scleromyositis or other overlapping connective tissue diseases (5% each) are related to eosinophilic gastrointestinal disorders [26].

Regarding the relationship between histological outcomes and autoimmunity, a recent meta-analysis has shown that a wide range of autoimmune diseases was associated with an increased risk of gastric cancer. It concluded that dermatomyositis, pernicious anaemia, Addison's disease, dermatitis herpetiformis, IgG4-related disease, primary biliary cirrhosis, diabetes mellitus type 1, systemic lupus erythematosus and Graves' disease were associated with a significantly increased gastric cancer risk [27].

Chronic inflammation precedes the development of many types of cancer in time. Immune dysregulations, which play a pivotal role in autoimmunity, are thought to be important in malignancies as well. Moreover, autoimmune disorders have been observed in patients with neoplastic tumors [28]. Inversely, increased incidence of neoplasms has been described among patients with autoimmune diseases [29]. Rheumatoid arthritis, SLE, Sjögren's syndrome, celiac disease, idiopathic inflammatory myositis and systemic sclerosis were associated with various neoplasms, including gastrointestinal tumors [30-34].

Although these studies examined the relationship between autoimmune disorders and gastric cancer, it is well-known that chronic inflammation predisposes to atrophy and IM, which are the precancerous lesions in the stomach. Therefore, it can be assumed that, if an antibody is associated to the development of IM and/or atrophy, it is also indirectly related to gastric cancer. If some autoimmune disorders predispose to the development of gastric cancer, close monitoring may be recommended in those cases. Routine measurement of these immuno-serological markers may be useful in the evaluation of the etiology and follow-up of patients with chronic gastritis.

Given that our study population did not suffer from diagnosed manifest autoimmune disorders, it also raises the possibility that gastritis may predict the development of a later autoimmune disease. Thus, if there is no clear explanation for the etiology of chronic gastritis or if the symptoms persist after eradication of *H. pylori*, it is advisable to assess these patients for systemic autoimmune-related antibodies and, if positive, to involve an immunologist for a close follow-up.

To our knowledge, this is the first study to present epidemiological data on the prevalence of different autoantibody positivity in patients with chronic gastritis in south-western Hungary and to raise the possibility that it may be worthwhile to investigate the etiology of chronic gastritis further when *H. pylori* is negative or after successful *H. pylori* eradication therapy. The study was conducted following a rigorous, pre-defined methodology.

However, our research had several limitations, so our results should be interpreted with caution. First, these results are based on a single-center retrospective medical database analysis; therefore, the role of the confounder factors cannot be excluded (e.g. smoking, dietary habits, immunosuppressant/modulatory treatment). To minimize the role of confounders, we excluded patients with *H. pylori* positivity from the analysis. Moreover, chronic atrophic gastritis is a common age-related finding, and female gender is more often prone to autoimmunity. To address this problem, we performed multivariate analyses adjusted for age and gender. Due to the observational nature of our study, causality cannot be determined; therefore, we report only possible associations. Second, the number of enrolled patients is relatively low (or the event rate was rather low for some antibodies), which could be the reason for the insignificance in some cases. Since we examined the presence of autoimmune markers, the possibility of incidental positivity may also arise. Therefore, to confirm our results, we also evaluated simultaneous effects of two or more AIP for the outcome.

Our results raise interesting questions, and due to the limited information on this topic and the limitations of our research, it could serve as a subject for future studies. Prospective studies with long-term follow up and larger event rate are required for confirmation and could revise the current clinical practice in the diagnosis and management of chronic gastritis and offer a more thorough insight into this topic. Autoimmune antibodies can serve as non-invasive markers for the optimal timing of an endoscopic follow-up strategy. Furthermore, chronic gastritis can be the first sign of an incipient autoimmune disorder, and with proper diagnostic approaches, autoimmunity may be recognisable in the early stages of the disease. Therefore, these patients may also be worth following immunologically for the later development of a manifest autoimmune disorder.

CONCLUSION

Autoimmune positivity often underlies gastritis of unknown etiology and predisposes to precancerous lesions in the stomach. Thus, if a clear etiological factor cannot be identified in the cause of chronic gastritis, it may be worthwhile to look for autoimmunity in these patients. In the south-western Hungarian population, anti-parietal cell antibody, ANA, ANCA and ASCA positivity correlated with a worse histological outcome, such as atrophy with or without IM. Further prospective observational studies on this topic are required to confirm our findings.

Conflicts of intersest: None to declare.

Authors' contribution: N.Z. and J.C. designed the study. N.Z., N.V. and L.F. extracted the data. S.V., S.L. and D. validated the extracted data. D.N. did the statistical analysis. S.V., L.F and N.Z. prepared the tables. N.Z. and L.S. wrote the first draft of the manuscript. P.H., Z.S. and J.C. supervised the manuscript and approved the submitted draft. J.C. is the guarantor of this paper and managed the patients. All the authors critically revised and approved the final version of the manuscript.

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ORIGINAL RESEARCH

Dyspepsia-Like Symptoms in *Helicobacter pylori*-Negative Chronic Gastritis are Associated with ASCA-, ANCA-, and Celiac Seropositivity but Not with Other Autoimmune Parameters: A Single-Centre, Retrospective Cross-Sectional Study

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Introduction: Dyspeptic symptoms are frequent in the general population, with a high socioeconomic burden. *Helicobacter pylori* (*H. pylori*) might be a possible etiological factor; however, it is also common in *H. pylori* negative gastritis. Clarification of the underlying aetiology might be beneficial to set up the optimal treatment strategy for dyspepsia and chronic gastritis (CG) itself. We aimed to assess the prevalence of dyspeptic symptoms in patients with *H. pylori* negative CG and explore autoimmunity's possible role.

Methods: This retrospective study included data from patients with *H. pylori* negative CG. Exclusion criteria were (1) acute gastritis; (2) reactive gastropathy; (3) subjects without any serology testing results; (4) *H. pylori* positivity; (5) presence of atrophy, intestinal metaplasia (IM), gastroesophageal reflux disease (GERD), ulcer, or cancer. The following endpoints were assessed (1) the rate of dyspepsia-like symptoms; (2) association between dyspepsia and autoimmune disease-related seromarker positivity (AISP); (3) frequency of other symptoms in CG and its association with AISP; (4) location of the inflammation and its association with AISP.

Results: From a total of 285 patients, 175 were included in this study. Among these patients, 95 experienced dyspeptic symptoms (54.29%) and were associated more with AISP ($p = 0.012$), especially with celiac seropositivity ($p = 0.045$), anti-neutrophil cytoplasmic antibody (ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) positivity ($p = 0.043$). A significant association was not found with other tested autoimmune (AI)-related antibody positivity.

Conclusion: Positivity of seromarkers of autoimmune diseases in chronic gastritis may predispose to have dyspeptic symptoms and may be the causative factor behind some cases of uninvestigated dyspepsia. These data suggest that further prospective studies are needed to clarify whether screening for autoantibodies in patients with dyspepsia is cost-effective and helps the earlier diagnosis of autoimmune diseases.

Keywords: chronic gastritis, autoimmunity, auto-antibody, dyspepsia

Introduction

Dyspepsia is a complex condition, refers to a group of symptoms, which originate from the upper gastrointestinal region. The Rome IV criteria define dyspepsia as any combination of the four following symptoms: postprandial fullness, early satiety, epigastric pain, and epigastric burning sensation.[1] Regarding the aetiology, organic and functional dyspepsia can

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be distinguished. When dyspeptic symptoms are not manifestations of organic pathologies, such as gastroesophageal reflux disease (GERD), peptic ulcer disease, or gastric tumour, it is classified as functional dyspepsia (FD).

Dyspeptic symptoms are frequent in the general population, with a prevalence of 20–40%,[2–4] and it is the most common indication for upper gastrointestinal (GI) endoscopy.[5] The diagnostic value of gastroscopy in diagnosing dyspepsia is controversial. Although it is a possible method to differentiate patients with organic dyspepsia from those with functional, referring the patients to endoscopy should be considered due to its invasiveness and low cost-effectivity. Furthermore, a large number of uninvestigated dyspepsia cases are functional.[6,7]

The exact pathogenesis of FD is unknown; however, visceral hypersensitivity, such as gastric hypersensitivity to distension and acids and abnormal gastric motility, might play a role in developing dyspeptic symptoms.[8,9] According to the definition, functional disorders are characterised by the absence of any organic pathology explaining the symptoms. A notable exception can be the *Helicobacter pylori* (*H. pylori*) infection, which is included in the definition of FD according to the Rome III criteria.[10] Moreover, extensive population-based studies indicate that *H. pylori* might be a possible etiological factor in the pathogenesis of FD.[11,12]

A recent study has shown that patients with FD had a high prevalence and severity of chronic gastritis (CG) without *H. pylori* infection.[13] Nevertheless, *H. pylori* infection was thought to be the leading cause of chronic gastritis.[14] The aetiology of CG in *H. pylori*-negative patients was unknown and its implications in the pathogenesis in FD. Data regarding the relationship between *H. pylori* negative chronic gastritis and specific dyspeptic symptoms are lacking. Therefore, clarification of the underlying aetiology might be beneficial to set up the optimal treatment strategy for dyspepsia, and the *H. pylori* negative CG itself.

Studies suggest that immune activation might play a role in the pathogenesis of FD.[15,16] Innate immune activation in the mucosa in FD has been described,[17,18] but the prevalence of AI disorders due to immune activation in FD is uncertain.

This study aimed to assess the occurrence and pattern of GI symptoms, the prevalence of dyspeptic symptoms in patients with *H. pylori*-negative CG, and explore the possible role of the established etiological factors behind CG autoimmunity in the expression of dyspeptic symptoms.

Materials and Methods

Patients histologically diagnosed with chronic gastritis who underwent immune-serological testing between January 2016 and January 2020 were enrolled. For diagnosing gastritis, multiple biopsies (minimum of five) were taken from definite sites of the stomach, predefined by the updated Sydney system.[19] Additional biopsies were performed from the areas of every detected focal lesion if any presented. To avoid performance bias, diagnosis and treatment of enrolled patients were carried out by the same single-unit medical team (one pathologist specialised in GI pathology reviewed all the histological findings, and one gastroenterologist performed all the endoscopy). Another, no dyspepsia-related study was previously performed on this population.[20]

All patients having any of the followings: (1) acute gastritis; (2) reactive gastropathy;[21] (3) subjects without any serology testing results; (4) *H. pylori* positivity; (5) GERD, ulcer, or cancer were excluded from this study. Diagnosis of *H. pylori* infection was established by endoscopy, serological testing, followed by a urea breath test. The diagnosis of acute gastritis, reactive gastropathy, GERD, ulcer or cancer was confirmed by histological findings. Regarding the well-known association between dyspepsia and *H. pylori* infection, *H. pylori* can be considered as a confounding factor. Therefore, patients with *H. pylori* infection were excluded from the analysis to reduce bias.

Possible eligible patients from all clinical records of the outpatient unit led by a single specialist investigator were identified from an electronic database. Data collection was performed focusing on baseline characteristics of the population, histological results (location of the inflammation); autoantibody positivity (celiac disease-, Sjögren's syndrome-, systemic lupus erythematosus (SLE)-, AI hepatitis-, rheumatoid arthritis (RA)-, SSc (systemic sclerosis)-, polymyositis/dermatomyositis-, AI thyroiditis-, IBD-, vasculitis-, AIG-related antibodies); *H. pylori* infection status (histology, results of the urea breath test and/or serology), symptoms (key symptoms, presence of dyspepsia-like symptoms: postprandial fullness, early satiety, epigastric pain, and epigastric burning). Patients were also categorised

according to their autoantibody positivity: autoantibody seropositive (AISP) and autoantibody seronegative (AISN) groups. Patients were categorised into AISP group in case of at least one antibody positivity.

Autoantibody positivity was assessed using the threshold of our laboratory in accordance with the European Autoimmunity Standardisation Initiative (EASI).[22,23] According to their occurrence in these conditions, detected autoantibodies were divided into autoimmune disease groups (Supplementary File 1). Grouping of patients was performed as per our previous autoimmune seromarker positivity and CG-related study.[20]

The following primary endpoint was investigated: association between AI positivity and dyspepsia-like symptoms (according to the Rome IV criteria[1]). In the case of the presence of one or more of the following symptoms: postprandial fullness, early satiety, epigastric pain, and epigastric burning, patients were categorized into the dyspepsia group.

The following secondary endpoints were assessed (1) the frequency of symptoms in CG, assessed in each patient by the same gastroenterologist; (2) the association between AISP and the most frequently occurred symptoms; (3) the location of the inflammation in the stomach assessed in each patient during endoscopy by the same gastroenterologist and confirmed by histopathological results; (4) association between AISP and the affected region of the inflammation.

The assessment of all variables was done on the level of AI disease and according to AISP and AISN groups.

Approval for this study was retrieved officially from the president of the Clinical Centre and the director of the First Department of Medicine of the University of Pécs (Institutional Review Board; case number: KK/999-1/2020). This study complies with the ethical guidelines of the Declaration of Helsinki updated in 2013 as reflected in a priori approval by the Institutional Review Board.[24]

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline[25] was followed during the data collection and analysis and the current legal environment (Supplementary File 2). According to the GDPR, all participating patients received a numeric code to protect privacy and personal data. Informed consent was not required in this retrospective set, although the data of those patients who refused data handling for scientific causes were not included.

Statistical Analysis

SPSS 25.0 software was used for the analysis of the data. Descriptive statistics (mean, standard deviation, minimum, maximum), and univariate analyses were performed. A 2-sided Pearson Chi-square test was done to compare dichotomous variables. In case of significant differences, standardised residuals were also observed to reveal the exact results. In the case of continuous variables, an independent sample *t*-test was used. We observed the distribution on Q-Q-plot. A P-value of less than 0.05 was considered statistically significant.

Results

In the final analysis, 175 patients (52 men and 123 women) with *H. pylori*-negative chronic gastritis were included. The mean age of the study population was 61.6 years (±15.13 years), ranging from 21 to 89. As described in our previous study, fifty-five per cent (97/175) of the analyzed patients had positive immunoserology (AISP group).[20]

Clinical Symptoms

Most frequently occurred symptoms were the followings: retrosternal burning sensation in 17.14% (30/175 patients); bloating and/or diarrhoea in 9.14% (16/175); diffuse abdominal discomfort/pain not relating to meals in 8.57% (15/175); globus sensation in 4% (7/175); nausea in 4.57% (8/175) and vomitus in 2.29% (4/175). All details about the symptoms can be seen in Table 1.

Diffuse abdominal pain/discomfort in the AISP group was significantly more common than in the AISN group (9 vs 6 patients, respectively, $p = 0.023$). Globus pharyngeus was more common in group AISP than the AISN group ($p < 0.001$): 6 patients experienced globus sensation in the AISP group, while one patient in the AISN group.

We did not find any significant differences with the other symptoms between AISP and AISN groups in our analysis. Retrosternal burning occurred in 12 patients in the AISP group and 18 patients in the AISN group ($p = 0.0713$). Less common symptoms included nausea (4 AISP and 4 AISN patients, $p = 1.000$), vomiting (1 AISP and 3 AISN patients, $p = 0.325$), and bloating and/or diarrhoea (9 AISP and 7 AISN patients, $p = 0.152$) (Table 1).

Table 1 Distribution of Frequently Occurred Symptoms and Location of the Inflammation Between AI Positive and Negative Groups

	Overall (n=175)	AI+ (n=97)	AI- (n=78)	p-value
Key symptom				
Dyspepsia-like symptoms N^0 (%)	95 (54.29)	58 (58.76)	37 (48.72)	**0.012**
Retrosternal burning N^0 (%)	30 (17.14)	12 (12.37)	18 (23.08)	0.0713
Globus pharyngeus N^0 (%)	7 (4.00)	6 (6.19)	1 (1.28)	**<0.001**
Nausea N^0 (%)	8 (4.57)	4 (4.12)	4 (5.13)	1.000
Vomiting N^0 (%)	4 (2.29)	1 (1.03)	3 (3.85)	0.325
Bloating, diarrhea N^0 (%)	16 (9.14)	9 (9.28)	7 (8.97)	0.152
Abdominal discomfort/pain N^0 (%)	15 (8.57)	9 (9.28)	6 (7.70)	**0.023**
Location of the gastritis				
Antrum N^0 (%)	56 (32.00)	33 (34.02)	23 (29.49)	**0.042**
Corpus N^0 (%)	15 (8.57)	9 (9.28)	6 (7.70)	**0.023**
Pangastritis N^0 (%)	104 (59.43)	57 (58.76)	47 (60.26)	0.269

Note: P-values marked in bold indicate statistically significant p-values.

Dyspepsia-Like Symptoms in Autoimmune Seropositivity

Dyspepsia-like symptoms were present in 54.29% of the patients (95/175) and were associated more with AISP ($p = 0.012$). Association was found regarding celiac disease-related antibody positivity and dyspepsia ($p = 0.045$), while ANCA and ASCA positivity were also associated with dyspepsia-like symptoms ($p = 0.043$). However, the analysis could not find a significant association between dyspepsia-like symptoms and other AI-related antibody positivity, like Sjögren's syndrome, SLE, AI hepatitis, RA, SSc, polymyositis/dermatomyositis, and AI thyroiditis ($p > 0.05$). No significant association was found considering AIG-related antibody positivity and dyspepsia either ($p = 0.677$). Detailed results regarding the association between autoimmunity and dyspeptic symptoms are given in Table 2.

Table 2 Detailed Results Regarding the Association Between Autoimmunity and Dyspeptic Symptoms

Association with Dyspepsia	
AI Disease Groups/Antibodies	**p-value**
AIG	0.677
Celiac disease	**0.045**
Sjögren's syndrome	0.563
SLE	0.585
AI hepatitis	0.617
RA	0.252
Ssc	1.000

(*Continued*)

Table 2 (Continued).

Association with Dyspepsia	
AI Disease Groups/Antibodies	**p-value**
Polymyositis/dermatomyositis	n/a
IBD	**0.043**
AI thyroiditis	0.229
Anti-parietal cell antibody	0.677
Anti-gliadin antibody	0.065
Anti-nuclear antibody	0.230
Anti-dsDNA antibody	1.000
Anti-nucleosome antibody	1.000
Anti-rheumatoid factor	0.252
Anti-Saccharomyces cerevisiae antibody	**0.043**
Anti-neutrophil cytoplasmic antibody	**0.043**

Note: P-values marked with bold indicate statistically significant p-values.

Location and Extent of the Inflammation

Most of the examined patients had pangastritis (59.43%); the inflammation affects the entire stomach in 57 (58.76%) patients of the AISP group and 47 (60.26%) patients of the AISN group. Lesions of gastritis were found in the antrum in 33 (34%) AISP and 23 AISN patients and were associated with autoimmune positivity ($p = 0.042$). Isolated corpus affection was related to autoimmunity as well ($p = 0.023$); inflammation of the corpus was found in 9 (9.28%) AISP and 6 (7.70%) AISN patients, respectively (Table 2.).

Discussion

This retrospective cross-sectional study, including data of 175 patients, aimed to investigate the possible relationship between autoimmunity and dyspeptic symptoms in patients with *H. pylori* negative chronic gastritis. One of our significant findings was that the prevalence of dyspepsia-like symptoms was 54.29%. Regarding the association between the symptoms and autoimmunity, dyspeptic symptoms, diffuse abdominal pain/discomfort, and globus pharyngeus seem to be more common in patients with AISP. A significant association was found between celiac disease-related antibody positivity, ASCA and ANCA positivity and dyspeptic symptoms. However, the analysis could not prove that other AI disease-related antibody positivity was more common in CG patients with FD.

It was previously shown in the literature that *H. pylori* infection might be associated with FD: the prevalence of *H. pylori* infection is more frequent in dyspeptic patients than in healthy controls.[26,27] A meta-analysis of 12 randomized controlled studies concluded that eradication of *H. pylori* is associated with improvement of dyspeptic symptoms in patients with FD.[28] Several studies suggested that *H. pylori* can alter gastric functions: it causes hypergastrinemia, hyperpepsinogenemia, and acid hypersecretion, which might play a role in the pathogenesis of FD.[29]

A high prevalence of dyspeptic symptoms was also reported in patients with *H. pylori*-negative CG.[13] Although CG is a prevalent pathology found in upper GI endoscopy, the underlying aetiology often remains unknown;[30] therefore, we looked for possible causative factors behind CG that may be associated with dyspeptic symptoms.

In our study, more than half of the patients with non-investigated chronic gastritis showed systemic autoantibody positivity, and it was associated with dyspeptic symptoms. Several articles in the literature mention the possible association

between autoimmune diseases and dyspepsia. Dyspeptic symptoms are presented in 50–60% of the patients with AI disorders and may result from gastroparesis and antral distension.[31,32] However, Koloski et al concluded that autoimmune diseases are risk factors for functional gastrointestinal disorders, such as FD, due to immune dysregulation.[33]

In line with our results, Jocelyn A Silvester et al showed that FD occurs in 27% of patients with coeliac disease, which is relieved in most cases following the treatment of a gluten-free diet,[34] and A. Maertens et al reported a case about how dyspepsia led a diagnosis of Morbus Crohn.[35] Furthermore, our study confirms the investigation of Lebwohl et al about the association between *H. pylori*-negative CG with celiac disease.[36] Higher incidence of dyspeptic symptoms has also been observed in patients with Sjögren's syndrome, SLE, RA, and AI thyroiditis;[31,32,37–42] however, our study could not confirm these associations.

Gastrointestinal manifestation occurs in most patients with systemic autoimmune disorders,[43–45] and these symptoms might be subclinical, non-specific, with considerable overlap among different conditions. Sometimes it can be the only presented sign of an underlying AI disease. The advent of serologic testing for immune-mediated GI disorders (eg, celiac disease, IBD) allows broader screening, helping differentiate organic disease from functional GI disorders.

To our knowledge, this is the first study, which investigated the possible organic etiological factors behind chronic *H. pylori-negative* gastritis in association with FD. As mentioned above, there were previous descriptions of the possible connection between certain autoimmune disorders and dyspepsia; however, a comprehensive study, excluding confounding factors to answer this question in a targeted manner, has not been performed previously. This work contains the investigation of the widest coverage of systemic AI disorders related antibody positivity and dyspepsia, and the study was conducted following a rigorous, pre-defined methodology. Furthermore, in the chronic gastritis patient population, where there is no identified etiological factor behind chronic inflammation, the cause of dyspepsia-like symptoms has not been investigated before.

However, our research had several limitations, which should be considered for a correct interpretation. The results are based on a single-centre, retrospective analysis, with a relatively low event rate in each antibody positivity, which might be the reason for insignificance in some cases. It is well known that the prevalence of FD is significantly higher in women, smokers, non-steroidal anti-inflammatory drug (NSAID) users,[27] and in the ageing stomach;[46] they should be considered confounding factors in our study. Moreover, chronic atrophic gastritis itself may contribute to the development of dyspeptic symptoms by influencing the level of gastric acid, pepsin, and ghrelin secretion;[8,47] however, data regarding the relationship between atrophic gastritis and specific dyspeptic symptoms are lacking. The limited information on this topic and our research's limitations could serve as a subject for conducting prospective clinical studies with a larger event rate.

Conclusion

In conclusion, autoimmune positivity in histologically established *H. pylori*-negative CG may predispose to dyspeptic symptoms and may be the causative factor behind uninvestigated FD. In this study, celiac disease-related antibody positivity, ASCA and ANCA positivity were associated with dyspeptic symptoms. However, our analysis could not prove any association between dyspepsia-like symptoms and Sjögren's syndrome, SLE, AI hepatitis, RA, SSc, Polymyositis/dermatomyositis, AI thyroiditis, or even AIG.

Based on our data, screening for celiac disease or ASCA and ANCA-related AI disorders (IBD, vasculitis) in the presence of dyspeptic symptoms might be crucial. Furthermore, screening for these autoantibodies (ANCA-, ASCA-, celiac-disease-related antibodies) in patients with FD can be more cost-effective, considering the earlier diagnosis of these autoimmune diseases. However, our results should be interpreted with caution since the retrospective nature of this study. To establish a higher quality of evidence, further prospective studies are required to prove the association between AI disorders (especially GI-related AI disorders; eg, IBD, celiac disease and vasculitis) and dyspeptic symptoms.

Abbreviations

AI, autoimmune; AISN, autoimmune disease-related seromarker negativity; AISP, autoimmune disease-related seromarker positivity; ANCA, anti-neutrophil cytoplasmic antibody; ASCA, anti-Saccharomyces cerevisiae antibody; CG, chronic gastritis; FD, functional dyspepsia; GERD, gastro-esophageal reflux disease; GI, gastrointestinal; *H. pylori*,

Helicobacter pylori; IBD, inflammatory bowel disorders; IM, intestinal metaplasia; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; Ssc, systemic sclerosis.

Ethics and Dissemination

Ethical approval: University of Pécs, Clinical Centre, Institutional Review Board; case number: KK/999-1/2020.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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