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Autoimmune pancreatitis, pancreatic and extrapancreatic cancer (AIPPEAR): a multicentre, retrospective study protocol

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ABSTRACT

Introduction Autoimmune pancreatitis (AIP) mainly manifests in two distinct forms with different clinical, serological and prognostic characteristics. Previous studies indicated a higher risk of malignancy in AIP patients compared with the general population. However, a direct comparison of cancer incidence in AIP patients with controls from the general population has not been conducted yet.

Methods and analysis This is an international, multicentre, retrospective study on patients diagnosed with AIP after 2005. Retrospective data regarding demography, AIP characteristics and cancer incidence will be extracted from the medical files of AIP patients. The primary outcome is the standardised incidence ratio of any first invasive cancer after AIP diagnosis compared with the general population. The expected number of cancers in the general population will be determined using the 'Cancer Incidence in Five Continents Volume XI' registry. Secondary outcomes are the prevalence of all cancer diagnoses within 12 months prior to AIP diagnosis and AIP features associated with a cancer diagnosis.

Ethics and dissemination This study was approved by the ethics committees of the autoimmune pancreatitis, pancreatic and extrapancreatic cancer (AIPPEAR) core group centres (Halle (Saale), Germany; Aalborg, Denmark; Tartu, Estonia; Munich, Germany; Göttingen, Germany; Maribor, Slovenia, with the following reference numbers: 2023–204, 2023–029953, 382/T-3, 24–0768, 9/7/23, UKC-MB-KME 59/23, respectively). Where required, the study protocol will be reviewed and approved by the ethics committees of participating centres in compliance with local regulations. Data will be stored in an electronic case report form within REDCap. In this context, the AIPPEAR core group will share joint responsibility for the data. All results from this study will be submitted to international, peer-reviewed journals and presented at international conferences.

Trial registration number NCT06328101.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The adoption of a worldwide multicentric design ensures a large, robust and diverse study population, offering a representative cross-section of patients with autoimmune pancreatitis (AIP) and enhancing the generalisability of our findings.
⇒ Standardised incidence ratios are adjusted for confounding factors (eg, age, sex, geography), which will strengthen the validity of our results. The predominant recruitment from tertiary centres may introduce referral bias; consequently, data on the follow-up frequency for each patient will be collected to mitigate this.
⇒ Because establishing the diagnosis of AIP is challenging, the re-evaluation of the collected data, with existing diagnostic algorithms, will be performed.
⇒ Patients may be included based on available data, not random assignment, which can affect the validity of findings.
⇒ Retrospective data collection poses the risk of information and selection bias.

INTRODUCTION

Background

Autoimmune pancreatitis (AIP) is a relapsing form of pancreatitis, comprising mainly two histological entities differing in clinical, serological and prognostic characteristics.[1] Type 1 AIP, histologically defined as lymphoplasmacytic sclerosing pancreatitis, is a pancreatic manifestation of immunoglobulin G4 (IgG4)-related disease, often involving multiple organs. In contrast, type 2 AIP, histologically defined as idiopathic duct-centric pancreatitis, is an isolated pancreatic disorder strongly associated with the simultaneous occurrence of inflammatory bowel disease (IBD). A subset of patients cannot be clearly classified into either type, termed not-otherwise-specified (NOS) AIP.[2 3] The clinical presentation differs between AIP subtypes. Type 1 AIP commonly presents with jaundice and less frequently with abdominal pain in contrast to type 2 AIP, which presents often as abdominal pain and acute pancreatitis and less frequently with jaundice.[4] Treatment is indicated in symptomatic patients or asymptomatic individuals with persistent pancreatic mass or laboratory findings suggesting active disease.[5] Glucocorticoids are the first-line therapy to achieve remission effectively. Relapse is common and can be managed by another glucocorticoid course

or immunosuppressive therapy such as azathioprine or B cell depleting agent, rituximab. Pancreatic exocrine and endocrine insufficiency may occur at diagnosis or develop over time despite treatment.[6–8]

While it is widely acknowledged that chronic pancreatitis increases the risk of pancreatic cancer,[9] the association between AIP and pancreatic cancer remains controversial. AIP can mimic pancreatic cancer, and coincidence has been reported. Retrospective data from Japan suggested an increased risk of pancreatic and bile duct cancer in patients with AIP.[10] Another Japanese study suggested a higher incidence of extrapancreatic cancer in AIP patients compared with the general population.[11] German single-centre data support this claim.[12] The most frequently reported cancers include lung, gastric and prostate cancer, constituting approximately 50% of all cancers detected at or after the diagnosis of AIP. Available data need to be interpreted with caution as no studies have yet compared the incidence of the most common cancers in AIP patients directly to age-grouped and gender-matched controls in the general population.[13]

Objectives

The primary objective of this study is to determine the incidence of any first invasive cancer in all patients diagnosed with AIP compared with the general population.

The secondary objectives are to determine the characteristics of AIP patients associated with the incidence of cancer and to assess the overall prevalence of cancer in AIP patients.

Study design

This is a worldwide, multicentre, retrospective cohort study of AIP patients. The study is embedded in the Pancreas2000 framework and will include several international study centres with expertise in the observation and treatment of patients with AIP.

METHODS AND ANALYSIS

Participants and setting

Centres specialising in the treatment of pancreatitis worldwide will be invited to participate in the study. The recruitment of participating centres is scheduled to commence in May 2024, with the anticipated completion of patient enrolment set for September 2025. An extension of the enrolment period may be considered if necessary. Patients with AIP will be identified locally, and information for characterisation of risk factors, AIP and cancer will be retrospectively extracted from the medical files. The core group comprises six centres from Denmark, Germany, Slovenia and Estonia.

Eligibility criteria

Inclusion criteria

- Patients diagnosed with AIP after 2005, including type 1, type 2 and NOS AIP, regardless of the diagnostic criteria used.

Exclusion criteria

- Patients younger than 18 years at last contact.
- Patients with less than 12 months of follow-up after AIP diagnosis.
- Patients with immune checkpoint inhibitor-induced pancreatitis.

Follow-up time

Follow-up time is defined as from the date of diagnosis until the last available contact with the patient.

Outcomes

The primary outcome is the following:

- The standardised incidence ratio (SIR) of the first invasive cancer occurring after the diagnosis of AIP compared with the general population. The SIRs are adjusted for confounding factors (age, sex, geography).

Secondary outcomes are the following:

- The prevalence of all cancer diagnoses within 12 months prior to AIP diagnosis.
- AIP features associated with cancer diagnosis.

Data collection

As part of the electronic case report form, demographic information, AIP diagnosis details, clinical AIP characteristics and AIP treatment characteristics are recorded. Basic patient data, including age, gender, height, weight, ethnicity and survival are supplemented with a cancer-specific risk profile, encompassing factors such as smoking, alcohol consumption, family history of cancer and AIP-related comorbidities like other autoimmune diseases and IBDs. Individual diagnostic criteria of the international consensus diagnostic criteria (ICDC), such as histology, IgG4 levels, imaging findings and steroid sensitivity, are queried separately. The manifestation of AIP (involvement of other organs, symptoms, complications), the course of treatment (medications, interventions, surgeries, relapses) and frequency of follow-up will also be recorded. Cancer is defined in alignment with the definitions given by the WHO[14] and subsequently grouped into pancreatic cancer, other hepatobiliary cancers, other digestive system cancers and all other cancers. Additionally, details about the duration and intensity of follow-up are requested.

The core dataset of the AIPPEAR study is presented in table 1.

Data management

Retrospective data will be transferred to an electronic case report form kept within the electronic and secure REDCap database[15] with all core group sites sharing joint data responsibility. All data will be pseudonymised on entry into the electronic case report form, and the principal investigator will securely keep the codes at each participating site. The principal investigator at each site will also be responsible for the quality of data collection at their site.

Table 1 Core dataset of the AIPPEAR study

Demographic details	AIP characteristics	Cancer diagnosis
Month and year of birth	Month and year of diagnosis AIP	Month and year of diagnosis of cancer
Survival status month and year of death, if applicable	The classification system used for original diagnosis (ICDC, HISORT, Asian, Unify)	Number of cancer diseases (1,2,3,4)
Gender (male, female)	ICDC diagnosis type (type 1, type 2, NOS AIP)	Cancer type (list according to the WHO)
Ethnicity (Caucasian, Hispanic, African, Asian, Arabic, Other, Unknown)	ICDC diagnosis level (definite, probable)	Cancer-related death (yes, no)
Weight and height for the purpose of calculating body mass index	ICDC parameters fulfilled for diagnosis (histology, serum IgG4, imaging, improvement after steroid treatment, other organ involvement)	In case of more than one cancer, specifically which cancer caused death
Tobacco status (current, former, never) including 'smoking pack-years', if applicable	Serum IgG4 (1–2 over upper limit, >2 over the upper limit, >4 over the upper limit)	
Alcohol consumption (current daily, current occasionally, former, never, not available)	Imaging (focal enlargement, whole organ enlargement (sausage-like), other)	
History of other autoimmune diseases (not IgG4-related) (no, Sjögren's' syndrome, rheumatoid arthritis, sarcoidosis, autoimmune thyroiditis (not IgG4 related), other)	Other organ involvement (salivary/lacrymal glands, retroperitoneum/kidneys, bile ducts/liver, musculoskeletal system, gastrointestinal tract: intestines, colon, oesophagus, vasculitis (eg, aortitis), enlarged lymph nodes, IBD)	
History of IBD (yes, no, unknown)	Presenting symptoms of AIP (none, jaundice, acute pancreatitis, weight loss, abdominal pain, new onset of diabetes)	
Family history of cancer (yes, no, unknown)	Medical treatment for AIP (prednisone, rituximab, azathioprine, 6-mercaptopurine, methotrexate, mycophenolate mofetil, other)	
	Interventional treatment for AIP (partial pancreatectomy, biliary stent placement, other)	
	AIP relapse (no relapse, 1–2 relapse(s), 3–4 relapses, >5 relapses, unknown)	
	AIP-related complications (no, diabetes mellitus, pancreatic exocrine insufficiency, other)	
	Month and year of last contact	

AIP, autoimmune pancreatitis; AIPPEAR, autoimmune pancreatitis, pancreatic and extrapancreatic cancer; HISORT, Histology, Imaging, Serology, Other organ invovlment, Respond to steroid therapy; IBD, inflammatory bowel disease; ICDC, international consensus diagnostic criteria; IgG4, immunoglobulin G4; NOS, not-otherwise-specified.

Statistical methods

Patients with insufficient data on diagnostic variables regarding the diagnosis of AIP will be excluded from the final analysis. Other missing data will be addressed by multiple imputation techniques.

Continuous variables will be presented as mean ± SD or median IQR, depending on normality, which will be tested using the Shapiro-Wilk test. Counted data will be presented as absolute counts and proportions.

The primary endpoint for the study will be the SIR for the incidence of any cancer and specific subtypes of cancer in AIP patients. SIR will be calculated between the observed and the expected number of cancers. The expected number of cancers will be determined using the 'Cancer Incidence in Five Continents Volume XI' registry.[14] Given the Poisson distribution, the probability mass function test will be calculated (× = patientyears in the AIP group, λ = patient years from the registry database) for any cancer and for specific subtypes of cancer. Sensitivity analyses will exclude patients diagnosed with pancreatic cancer within 12 and 24 months after AIP diagnosis, respectively. SIR will be adjusted for potential confounding factors (age, sex, geography).

The secondary endpoint is the prevalence of any cancer in patients with AIP. Also, the OR for cancer incidence will be calculated to assess the association of AIP patient

characteristics with different clinical subgroupings (eg, type 1 vs type 2, seropositive type 1 vs seronegative type 2, focal pancreatic enlargement on imaging vs no pancreatic enlargement on imaging, post-pancreatitis diabetes mellitus (DM) vs no DM, pancreatic exocrine insufficiency (PEI) vs no PEI, maintenance treatment vs no maintenance treatment, relapse vs no relapse). ORs and corresponding 95% CI will be illustrated in a forest plot. All statistical calculations will be conducted in R V.4.2 or greater.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination of this study.

ETHICS AND DISSEMINATION

Research ethics approval

This study was reviewed and approved by the ethics committees of the centres within the AIPPEAR core group, including the University Hospital Halle (Saale) (Germany), The North Denmark Region Aalborg University Hospital (Denmark), Tartu University Hospital (Estonia), LMU University Hospital Munich (Germany), University Medical Center Göttingen (Germany) and University Medical Centre Maribor (Slovenia), under the following reference numbers: 2023–204, 2023–0 29 953, 382/T-3, 24–0768, 9/7/23 and UKC-MB-KME 59/23, respectively. Furthermore, the study protocol will be reviewed and approved by the respective ethics committees at participating centres in accordance with their local regulatory requirements. Initial local ethical approval was obtained from University Medical Center Göttingen, Germany.

Confidentiality

Prior to data analysis, all data will be anonymised, and any identifying information will be removed. Sensitive information about subjects in the study will be kept securely locally at each site under the responsibility of the primary investigator.

Declaration of interests

The entire AIPPEAR core group declares no conflicts of interest.

Access to data

Each site will have access to its own data, but the entire dataset will be accessible to the AIPPEAR core group only. In this context, the AIPPEAR group will have joint responsibility for the data, and thus, all six centres have entered into a collaboration agreement and a joint responsibility agreement prior to the onset of the study. The Data Transfer Agreement will be signed by the participating centres, if required (online supplemental appendix 1).

Dissemination policy

All results from this study will be disseminated through publication in international, peer-reviewed journals and presentations at international conferences. Coauthorships will be assigned to collaborators according to the rules defined in the AIPPEAR Study Group Agreement (online supplemental appendix 2).

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