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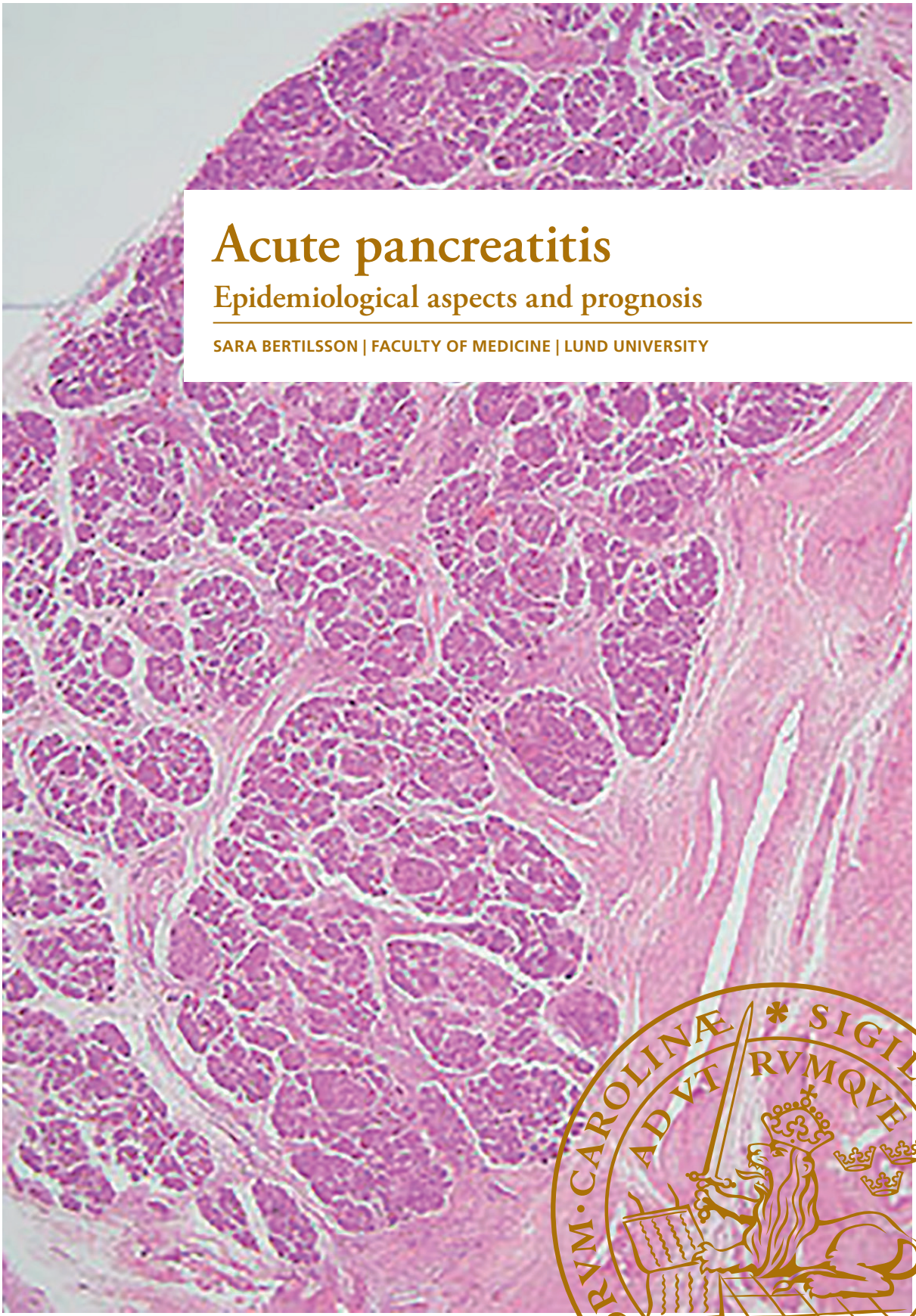

Acute pancreatitis

Epidemiological aspects and prognosis

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Abstract

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In a retrospective part, 1457 patients with first-time AP, between 2003 and 2012, were included. The main AP etiology was gallstone disease, followed by alcohol. In all, 23% experienced one or more recurrent AP (RAP) episode, and 5% developed chronic pancreatitis. Severity of first-time AP, alcoholic etiology and smoking predicted RAP as well as chronic pancreatitis ($p<0.05$), and RAP was the strongest predictor for development of chronic pancreatitis (HR 6.7; 95% CI, 4-11.3, $p<0.01$). The incidence of AP (in particular biliary AP) showed increasing time-trends, while the incidence of alcoholic AP remained stable. Users of AP-associated drugs increased from 32% in 2003 to 51% in 2012 ($p<0.05$), reflective of increasing user rates in the general population, but was not related to AP incidence nor severity ($p>0.05$). Alcohol sales and consumption decreased, in the general population, and did not correlate to the incidence of (alcoholic or non-alcoholic) AP ($p>0.05$).

The prospective part comprised 92 AP patients. The urine α1-microglobulin-, albumin-, and IgG/creatinine ratios were significantly higher in patients with vs. without organ failure ($p<0.05$, for all). In particular, the α1-microglobulin/creatinine upon admission predicted organ failure (OR 1.29; 95% CI, 1.02-1.61) with an AUROC of 0.81 (95% CI, 0.69-0.94), making it a promising marker for early prediction of AP severity.

Key words: acute pancreatitis; recurrent acute pancreatitis; chronic pancreatitis; incidence; drug-induced pancreatitis; alcoholic pancreatitis severity classification; organ failure; seasonal variations; microproteinuria

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This thesis is dedicated to
Alexander, Ella,
Melvin & Milla
My amazing children

Content

Summary

Acute pancreatitis (AP) is an increasingly common gastroenterological disease. Most cases are mild and self-limiting, although 10-20% of patients suffer a more severe disease course, associated with organ failure and complications. It is not fully elucidated, why and in which patients, severe AP develops, or what factors impact the natural history of AP. The aims of the papers included in this thesis were to evaluate the natural history of AP, to study the potential relation of the incidence of AP with the use and sales of certain AP-associated drugs as well as with alcohol sales and consumption. In addition, we aimed to investigate the value of microproteinuria in prediction of organ failure in AP patients.

In a retrospective part, 1457 patients with first-time AP, between 2003 and 2012, were included. The main AP etiology was gallstone disease, followed by alcohol. In all, 23% experienced one or more recurrent AP (RAP) episode, and 5% developed chronic pancreatitis. Severity of first-time AP, alcoholic etiology and smoking predicted RAP as well as chronic pancreatitis ($p<0.05$), and RAP was the strongest predictor for development of chronic pancreatitis (HR 6.7, 95% CI 4-11.3, $p<0.01$). The incidence of AP (in particular biliary AP) showed increasing time-trends, while the incidence of alcoholic AP remained stable. Users of AP-associated drugs increased from 32% in 2003 to 51% in 2012 ($p<0.05$), reflective of increasing user rates in the general population, but was not related to AP incidence nor severity ($p>0.05$). Alcohol sales and consumption decreased, in the general population, and did not correlate to the incidence of (alcoholic or non-alcoholic) AP ($p>0.05$).

The prospective part comprised 92 AP patients. The urine α1-microglobulin-, albumin-, and IgG/creatinine ratios were significantly higher in patients with vs. without organ failure ($p<0.05$, for all). In particular, the α1-microglobulin/creatinine upon admission predicted organ failure (OR 1.29, 95% CI 1.02-1.61) with an AUROC of 0.81 (95% CI 0.69-0.94), making it a promising marker for early prediction of AP severity.

Populärvetenskaplig sammanfattning (Swedish summary)

Akut pankreatit (bukspottkörtelinflammation) är en vanlig åkomma och rapporter visar att antalet sjukdomsfall per år ökar på flera ställen i världen. De vanligaste orsakerna till akut pankreatit är gallstenssjukdom samt överkonsumtion av alkohol. Det förekommer även en mängd andra, mindre vanliga orsaker, såsom läkemedel, ärftliga faktorer, trauma, förhöjda blodfetter samt orsaker relaterade till vissa undersökningar och behandlingar. I vissa fall är orsaken dock okänd (idiopatisk pankreatit). I de flesta fall är förloppet av akut pankreatit lindrigt och komplikationsfritt, men upp till 20% av patienterna får ett svårare sjukdomsförlopp, vilket kan leda till organsvikt och komplikationer. Det är inte helt klarlagt varför eller hos vilka patienter det finns en ökad risk för svår pankreatit. Tidig bedömning av svårighetsgraden är av avgörande betydelse för ett adekvat omhändertagande, men trots flertalet bedömningsverktyg och tester för svårighetsgrad saknas det fortfarande kliniskt användbara och tillförlitliga metoder för att förutspå ett mer komplicerat sjukdomsförlopp. Utsöndring av proteiner i urinen (mikroproteinuri) har i tidigare studier visat sig ha samband med graden av inflammation samt förloppet vid till exempel hjärtinfarkt och blodförgiftning. Sambanden mellan mikroproteinuri och akut pankreatit är däremot inte välkänt.

Efter en första episod av akut pankreatit får upp till 30% en eller flera återkommande episoder av akut pankreatit och ungefär 5% utvecklar kronisk pankreatit. Alkohol och rökning har identifierats som huvudsakliga riskfaktorer för såväl återkommande akut som kronisk pankreatit, även om tidigare studier inte är enhetliga beträffande hur naturalförloppet av akut pankreatit ser ut eller vilka faktorer som påverkar det.

Det finns ett stort antal olika läkemedel, som har associerats med akut pankreatit, men trots det anses läkemedelsorsakad pankreatit vara ovanligt och utgör endast 0.1-5% av samtliga fall. Enstaka rapporter indikerar att förekomsten av läkemedelsorsakad akut pankreatit ökar samt att läkemedel även skulle kunna fungera som bidragande orsaker i vissa fall då en annan känd pankreatitorsak förekommer. Däremot saknas det populations-baserade studier på eventuella samband mellan försäljning och användning av pankreatitassocierade läkemedel och förekomsten av akut pankreatit.

Trots att alkohol är en av de vanligaste orsakerna till akut pankreatit finns det endast ett fåtal studier som har undersökt relationen mellan försäljning och konsumtion av

alkohol i befolkningen och förekomsten av akut pankreatit. Resultaten av dessa studier har dessutom, till viss del, varit motstridiga. Vidare är det känt att alkoholkonsumtionen är högre under vissa perioder, såsom vid helger och högtider, men det är oklart om även förekomsten av akut pankreatit är förhöjd i samband med dessa perioder.

Syftet med delarbete I var att beskriva det långsiktiga förloppet av akut pankreatit, i en befolknings-baserad kohort av patienter med en första episod av akut pankreatit, mellan 2003 och 2012. Totalt inkluderades 1457 patienter. Samtliga journaler granskades och data beträffande orsak, svårighetsgrad, återkommande episoder av akut pankreatit, utvecklande av kronisk pankreatit samt dödlighet registrerades. Vi fann att den vanligaste orsaken till akut pankreatit var gallstenssjukdom, följt av alkohol, hos kvinnor såväl som hos män. Återkommande pankreatitepisoder förekom hos 23% av patienterna och hade tydliga samband med alkohol och ökad svårighetsgrad vid första episoden av akut pankreatit samt med rökning. Hos patienter med gallstensorsakad förstagångs-pankreatit var återkommande pankreatitepisoder relaterade till väntetiden på galloperation. Kronisk pankreatit utvecklades hos 5% av patienterna och den största andelen av dessa patienter (74%) hade tidigare haft en eller flera återkommande episoder av akut pankreatit. Dessutom var alkohol, rökning och svårighetsgraden av första pankreatitepisoden även relaterade till utvecklingen av kronisk pankreatit. Totalt avled 41 patienter (2.8%) i samband med första episoden av akut pankreatit. Bland patienter med gallstenspankreatit var andelen dödsfall vid återkommande pankreatit högre (5.9%) än vid första pankreatitepisoden (2%), vilket framhåller betydelsen av tidig operation för dessa patienter.

I delarbete II beräknades den årliga, åldersstandardiserade förekomsten av akut pankreatit, mellan åren 2003 och 2012, i ett upptagningsområde på 600 000 invånare. Den totala förekomsten av akut pankreatit ökade under studieperioden, för både män och kvinnor, framförallt beroende på en markant ökning av antalet fall av gallstenspankreatit. Förekomsten av läkemedelsorsakad pankreatit var i genomsnitt 2%, men ökade under den studerade 10-årsperioden. Andelen patienter med akut pankreatit, som använde ett eller flera pankreatitassocierade läkemedel steg från 32% 2003 till 51% 2012. Motsvarande ökning sågs dock även i den totala befolkningen och användningen av dessa läkemedel verkade inte ha någon påverkan på de epidemiologiska förändringarna beträffande förekomst, svårighetsgrad eller återinsjuknande i akut pankreatit.

I delarbete IV ämnade vi undersöka eventuella samband mellan försäljning och konsumtion av alkohol med förekomsten av (alkoholrelaterad och icke-alkoholrelaterad) akut pankreatit. Vi ville dessutom undersöka om förekomsten av akut pankreatit uppvisade några säsongsrelaterade mönster och framförallt om pankreatitförekomsten ökade i samband med perioder associerade med högre alkoholkonsumtion. Mellan åren 2003 och 2012 minskade såväl alkoholförsäljningen

som den självrapporterade alkoholkonsumtionen. Under samma period ökade den totala förekomsten av akut pankreatit, som tidigare beskrivits. Däremot var förekomsten av alkoholrelaterad akut pankreatit oförändrad under perioden och varken alkoholrelaterad eller icke-alkoholrelaterad pankreatit uppvisade några tydliga samband med alkoholkonsumtion och försäljning. I Sverige är framförallt perioderna kring jul och nyår samt midsommar, enligt Systembolagets försäljningsstatistik, förknippade med ökad alkoholkonsumtion. Vi fann dock ingen ökning i förekomsten av akut pankreatit under dessa perioder, jämfört med veckorna före respektive efter.

I delarbete III var syftet att undersöka om mikroproteinuri kunde förutspå risken för organsvikt hos patienter med akut pankreatit. Totalt inkluderades 92 patienter med akut pankreatit och blod- och urinprover togs vid ankomst till vårdavdelning, dagen efter ankomst samt vid uppföljning 3 månader efter utskrivning. Förekomsten av proteinerna α1-microglobulin, albumin, och IgG i urin uppvisade samband med parametrar för inflammation samt med förekomsten av organsvikt. Framförallt visade nivåerna av α1-microglobulin i urinprover god förmåga att kunna förutspå organsvikt.

Sammanfattningsvis visar resultaten av denna avhandling att svårighetsgraden av första episoden av akut pankreatit, alkohol samt rökning ökar risken för såväl återkommande akut pankreatit som kronisk pankreatit. Hos patienter med gallstenspankreatit är risken för återinsjuknande i pankreatit relaterad till väntetiden för operation och dödligheten vid återkommande episoder av akut pankreatit är högre hos dessa patienter. Förekomsten av akut pankreatit ökar, främst beroende på ökad förekomst av gallstenspankreatit. Däremot verkar varken användningen av pankreatitassocierade läkemedel eller konsumtionen av alkohol, i den generella befolkningen, ha någon påverkan på pankreatitförekomsten. Slutligen har vi funnit att proteinet α1-microglobulin i urin verkar vara en lovande tidig markör för organsvikt hos patienter med akut pankreatit.

Abbreviations

ACE	Angiotensin Converting Enzyme
AP	Acute Pancreatitis
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARB	Angiotensin Receptor Blockers
AUROC	Area Under the Receiver Operating Characteristics Curve
BISAP	Bedside Index of Severity in Acute Pancreatitis
BUN	Blood Urea Nitrogen
CAN	Swedish Council for Information on Alcohol and Other Drugs
CARS	Compensatory Anti-inflammatory Response Syndrome
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CRP	C-reactive Protein
CT	Computed Tomography
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme Linked Immunosorbent Assay
ERCP	Endoscopic Retrograde Colangiopancreatography
GFB	Glomerular Filtration Barrier
HR	Hazard Ratio
ICD	International Classification of Diseases
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IQR	Interquartile Range
MODS	Multiple Organ Dysfunction Syndrome
NSAID	Non-steroidal Anti-inflammatory Drugs
OR	Odds Ratio
PPI	Proton Pump Inhibitors
RAP	Recurrent Acute Pancreatitis
ROC	Receiver Operating Characteristics
ROS	Reactive Oxygen Species
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
TAP	Trypsinogen Activation Peptide
Å	Ångström

List of publications

I . Bertilsson S., Swärd P., & Kalaitzakis E. Factors that affect disease progression after first attack of acute pancreatitis. Clinical Gastroenterology and Hepatology 2015: 13(9); 1662-1669.

II. Bertilsson S., & Kalaitzakis E. Acute pancreatitis and use of pancreatitis-associated drugs: A 10-year population-based cohort study. Pancreas 2015: 44 (7); 1096-1104.

III. Bertilsson S., Swärd P., Håkansson A., Tofik R., Rippe B., & Kalaitzakis E. Microproteinuria predicts organ failure in patients presenting with acute pancreatitis. Digestive Diseases and Sciences 2016: 61(12); 3592-3601.

IV. Bertilsson S., Håkansson A., & Kalaitzakis E. Acute pancreatitis: Impact of alcohol consumption and seasonal factors. Alcohol and Alcoholism 2017: 31; 1-7.

Reprints of the papers are enclosed at the end of the thesis with permission from the publishers.

Introduction

The pancreas and acute pancreatitis

The pancreas is a glandular organ consisting of an endocrine and an exocrine part (figure 1). The endocrine part (islet cells) is involved in the blood glucose regulation, mainly by secretion of hormones like insulin and glucagon. The exocrine part, consisting of clusters of acinar and ductal cells, constitutes the largest part of the gland. The acinar cells produce, store and secrete digestive enzymes, in the form of inactive proenzymes (zymogens), including trypsinogen, proelastase and phospholipase A_2. These enzymes are secreted together with bicarbonate, from ductal cells, and activated in the duodenum, where they contribute in the digestion of proteins, carbohydrates and fats. The enzymes lipase and amylase do not need activation (1).

Acute pancreatitis (AP) is a common gastroenterological condition. The onset of the disease is typically characterized by sudden and intense upper abdominal pain, often with a radiation to the back, and occasionally associated with local peritonitis. The complete mechanisms behind the development of AP are not fully understood. The inflammation presumably starts in the acinar cells, through premature activation of trypsinogen to trypsin, which in turn activates other pancreatic proenzymes, causing autodigestion of the pancreas (2-4), although several other mechanisms are probably involved to further mediate the intrapancreatic inflammatory process. Activated pancreatic enzymes stimulate the production of pro-inflammatory mediators, such as cytokines, chemokines, adhesion molecules, platelet activating factor and reactive oxygen species (ROS), which in turn activates leukocytes that migrate into the pancreatic interstitial space. This infiltration of inflammatory cells mediates further upregulation of cytokines and chemokines, inducing an inflammatory cascade. The peripancreatic inflammation can progress to systemic inflammatory response syndrome (SIRS), potentially causing multiple organ dysfunction syndrome (MODS), including respiratory, renal, and circulatory failure. In turn, the inflammatory process leads to a compensatory anti-inflammatory response syndrome (CARS). If this anti-inflammatory response is sufficient, the inflammation is controlled and the AP patient recovers, while inadequate control promotes organ dysfunction as well as later local complications and infections (5-9).

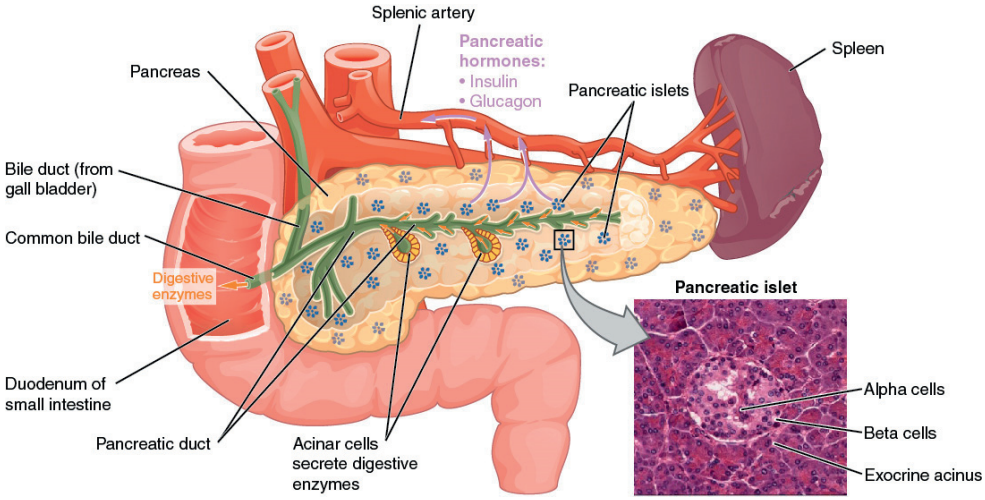

Figure 1. Anatomy of the pancreas. (https://commons.wikimedia.org)

Biliary acute pancreatitis

Gallstone disease is an increasingly common problem throughout the world and gallstone-related (biliary) AP represents the most common AP etiology in several countries, comprising 28-42 % of all AP cases (10-12), and with reports of increasing incidence time-trends (13, 14). Female gender and older age increase the risk for biliary AP (13, 15, 16). The exact mechanisms behind biliary pancreatitis are still not fully elucidated. Migrating gallstones are thought to cause a transient obstruction of the pancreatic duct, leading to increased pancreatic pressure and enzyme activation in the pancreas, causing autodigestion and inducing the inflammatory process, as previously described (17).

Alcoholic acute pancreatitis

Alcohol-related AP accounts for about 20-40% of all AP cases (14, 18). The pathogenesis is complex and probably includes both direct alcoholic toxicity and immunologic mechanisms (19). Even if a dose-response relationship between alcohol consumption and AP has been suggested (20), there are no universally established values on amounts and frequency of alcohol consumption considered necessary to cause AP. In previous reports, consumption of 50 to 80 grams of alcohol per day has been proposed as threshold amounts for pancreatitis (10, 14, 21), and different types of beverages and drinking patterns have been associated to the development of AP to different degrees (22, 23). It has been reported that only 2-5% of heavy drinkers

(defined as ≥ 60 grams of alcohol per day) develop (acute or chronic) pancreatitis (16, 24), and it has therefore been suggested that alcohol may represent a cofactor, sensitizing the pancreas to injury and that additional factors, or genetic variants (25), may trigger the development of AP (19, 26).

Drug-induced acute pancreatitis

A large number of frequently used drugs have been associated with AP (27). Although some medications have been found related to AP in epidemiological studies (28-30) most of our knowledge of drug-induced pancreatitis derives from single case reports. The most frequently reported AP-associated drugs include azathioprine, angiotensin converting enzyme (ACE) inhibitors, antidiabetics, non-steroidal anti-inflammatory drugs (NSAID), proton pump inhibitors (PPI) and medications used in cancer and HIV therapy (31, 32). Additionally, certain commonly prescribed drugs, like omeprazole and sertraline, have been associated with a more severe AP disease course (27). Different classification systems of drug-induced AP have been proposed over the last decades. In 1980 a system, including drugs classified as having a definite, probable or possible association with pancreatitis, was published (33). This system was later revised, whereas more weight was put on the number of reported cases and if there was a positive rechallenge. The latest classification to date was published by Badalov et al. It includes 120 different drugs, classified into 5 classes, based on the weight of evidence for causing AP (27).

Many drugs identified to induce AP are common drugs, frequently prescribed and used in the general population. In a recent Dutch prospective study a substantial proportion (42%) of patients with AP, with different etiologies, were using one or more AP-associated drugs, leading to the suggestion that drugs might act as cofactors or disease modifiers in the development of AP (34). However, it is still uncertain as to what extent different drugs are related to the incidence of AP and drug-induced pancreatitis is considered to be rare, occurring in only 0.1-5 % of pancreatitis cases (35-39).

Other causes of acute pancreatitis

A large number of other, yet rare, causes of AP include hypertriglyceridemia, hypercalcemia, endoscopic retrograde cholangiopancreatography (ERCP), hereditary conditions, trauma, tumors and infections (12, 17). Still, in a substantial proportion of patients (10-36%) the etiology cannot be ascertained (10, 14, 40). Some reports suggest that the majority of these idiopathic AP cases actually are caused by microlithiasis (41, 42), although others have questioned this (43, 44).

Natural course of acute pancreatitis

Population-based data on the natural course of AP are limited, and with somewhat contradictory results regarding risk factors for recurrence of AP and progression to chronic pancreatitis (10, 11, 45, 46). In addition, the potential relation between severity of first time AP and the natural course of the disease is sparsely studied (10, 46).

Severity of acute pancreatitis

In most cases, AP attacks are mild and self-limiting, although up to 20% of the patients experience a more severe clinical course (10, 11, 47, 48). The local inflammation of the pancreas can lead to SIRS, potentially progressing to failure of one or more distant organs, MODS. According to the revised Atlanta classification of AP (49), organ failure includes respiratory, cardiovascular and renal dysfunction. In addition, systemic and local complications are included in the severity classification. It is not clear why, and in which patients, a severe disease course develops. Etiology of AP has not been found to have an impact on the severity, except for the presentation of local complications, more frequently observed in patients with alcoholic AP (50, 51). Clinical parameters associated with a higher risk for a more severe AP course are older age, comorbid conditions, and obesity, although results from different studies on their impact are not unanimous (16, 52-55).

Recurrent acute pancreatitis

After a first attack of AP a substantial proportion of patients (17-30%) suffer one or more recurrent acute pancreatitis (RAP) episodes (10, 11, 45, 46). RAP is more common after alcohol induced first-time AP compared to other known etiologies and idiopathic AP, with proportions of up to 45% of the patients experiencing RAP following an alcoholic first-time AP episode (56, 57). RAP has further been found related to smoking (11, 58). In patients with biliary AP the risk of recurrence is associated with cholecystectomy being delayed compared to the recommendations in guidelines (11, 50, 53, 59-63). While recurrence is less common in patients with biliary compared to alcoholic AP, it seems to occur after a shorter time interval, stressing the importance of early cholecystectomy (11, 64-66). Every recurrent episode of AP is associated with a risk for complications and mortality. While some reports have proposed that RAP episodes are generally less severe and have lower mortality rates compared to incident AP attacks (15, 67), others have found similar mortality rates among first and recurrent AP episodes (68-70).

Development of chronic pancreatitis

The mechanisms behind the progression from acute to chronic pancreatitis are not fully understood, and it has been argued that acute and chronic pancreatitis are two separate diseases, with AP rarely progressing to the chronic form (71). This has, however, been questioned by Klöppel and Maillet, who described the "Necrosis-fibrosis sequence hypothesis" as a possible pathogenesis of chronic pancreatitis (72). They suggested that the damage of the pancreas during AP leads to obstruction of pancreatic ducts and development of fibrotic tissue. Yadav and Whitcomb have suggested a "two-hit hypothesis", with the first attack of AP representing the "first hit" and continued exposure to the inducing risk factor (i.e. alcohol) or genetic factors representing the "second hit" (73).

Previous studies are, however, not unanimous according to how often, and in which patients AP progresses to chronic pancreatitis. Lankisch et al. reported a proportion of 4% of patients developing chronic pancreatitis and exclusively among those with alcoholic first-time AP (10), while others have reported progression in 15-24%, and in patients of different etiologies (45, 46). These discrepancies may be due to differences in follow-up periods as well as to different diagnosis criteria for chronic pancreatitis. In addition to alcohol, smoking has been recognized as an important risk factor for development of chronic pancreatitis, often under-recognized by clinicians (10, 19, 74-77), while in 10 to 30% of the patients the cause is unknown (78).

Mortality

The overall mortality rate due to AP has been reported to be 5-15% (10, 62, 79). However, among severe cases, particularly in those with necrotizing AP, death rates are significantly higher (14, 80). The presence of (persistent) organ failure is strongly associated with poor outcome and mortality (49, 81, 82), and patients with both persistent organ failure and infected necrosis experience the highest mortality risk (83). There are, however, discrepancies in published data on potential predictors of short and long-term mortality after first and subsequent AP episodes (47, 54, 62, 69, 84, 85).

Trends in incidence of acute pancreatitis

Several studies show increasing incidence rates of AP over the last decades, in Sweden (13, 65) as well as internationally (15, 86-88). In a population-based report from Malmö, Sweden between 1985 and 1999, the observed increasing time-trends of AP were found to be mainly due to a significant increase in the incidence of biliary AP, while the incidence of alcoholic AP decreased (13). Other reports have shown increasing (65, 88, 89) or stable incidence of alcoholic AP (90) over the last years.

Alcohol consumption and incidence of acute pancreatitis

Overall changes in alcohol consumption over time as well as certain periods with higher alcohol consumption in a calendar year have been found to have an impact on the occurrence of various alcohol-related harmful events and diseases (91-93). Reports from Finland have shown that fatal alcohol poisoning significantly increased during periods of increased alcohol sales and consumption as well as after raised alcohol import quotas in 2004 (92-94). Following an increase in per capita quotas of alcohol import to Sweden, the frequency of acute alcohol intoxication increased, although the number of violent assaults and drunk driving did not change (95). However, the potential relations between the incidence of alcoholic or (presumed) non-alcoholic AP, and the sales and consumption of alcohol in the general population are scarcely studied and with contradictory results. Studies from Ireland, Wales, and Finland have shown increasing trends in alcoholic AP admissions, associated with increasing per capita alcohol consumption (18, 89, 96). In contrast, a later Finnish report failed to show any correlation between alcohol consumption in the general population and the occurrence of AP (88).

It is, furthermore, well known that alcohol consumption in the general population is highly event specific, and more heavy drinking occurs in weekends, summer months, and on national public holidays (92, 97). An increased occurrence of AP during periods associated with excessive alcohol consumption has been reported by a couple of studies (18, 98), although others have not found such variations (99, 100). In Sweden the Midsummer Eve, Christmas and New Year's Eve are holidays particularly related to a higher alcohol consumption (101), although it is not clear whether the occurrence of AP in Sweden is increased in relation to these holidays.

Pancreatitis-associated drugs and incidence of acute pancreatitis

The proportion of AP cases caused by different drugs is reported low (37, 39), although some evidence indicates an increase in the incidence of drug-induced AP (31, 35). Drug-induced AP is, however, challenging to diagnose and its true incidence has been proposed both to be underestimated and overestimated (102). Only a few epidemiological reports have studied the incidence and presentation of AP caused by drugs. Vinklerova et al. retrospectively investigated the incidence and disease course of drug-induced AP. Drugs were found to represent the third most common cause of AP and the incidence seemed to be underestimated (39). In a previous Swedish population-based, case-control study, several drugs were found to be associated to AP, although in a large proportion of patients, more than one possible etiologic cause of AP were identified (28). While a large number of drugs have been associated with AP, it is unknown whether changes in the sales and use of these drugs, in the general population, could have any impact on the incidence of AP.

Prediction of severity in acute pancreatitis

Early prediction of AP severity is crucial, in order to offer the patients sufficient and timely treatment. Despite several attempts to develop useful and reliable methods to identify patients at risk of developing severe AP, there is at present, no universally accepted severity prediction system (103, 104).

Prognostic scoring systems

Various specific and non-specific scoring systems for AP severity have been developed. The first one was the Ranson criteria, including 5 prognostic variables measured at the time of admission, and another 6 criteria registered within 48 hours after admission (105). The modified Glasgow (Imrie) criteria (106) include 8 of the original 11 Ranson variables. The Ranson as well as the Imrie scores have been found to accurately predict AP severity (107, 108), although they both have the disadvantage of requiring assessment 48 hours after admission. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score (109) has been proposed to be the best scoring system for AP severity (110), although due to its complexity, it has not been frequently used in clinical practice. The Bedside Index of Severity in Acute Pancreatitis (BISAP) was developed as a simple scoring system, applicable in clinical practice. It has shown similar prognostic accuracy compared to more complex scoring systems, although it has been criticized as it may not distinguish transient organ failure from persistent (111-113). Despite extensive efforts to develop valid and reliable methods for AP severity

prediction, existing scoring systems are often impractical or insufficient (108, 111) and have been proposed to have reached their maximal efficacy (104, 111).

Inflammatory markers

A number of single inflammatory markers have been suggested to have a prognostic value in predicting AP severity (114-116), with C-reactive protein (CRP) representing the most widely used and "gold standard", although with the disadvantage of reaching its maximum value up to 72 hours after onset of symptoms (110). Several pro-inflammatory cytokines, such as interleukin-6, interleukin-8, hepatocyte growth factor and tumor necrosis factor-α have shown good prognostic values in early prediction of AP severity (117-120), yet they have the disadvantage of being unavailable or too expensive for routine clinical practice. Blood urea nitrogen (BUN) is a routine laboratory test that reflects renal function and indicates changes in the intravascular volume. It has been incorporated in different AP severity scoring systems, like the Ranson score (105). Wu et al. evaluated the accuracy of BUN for prediction of mortality, in a large hospital-based cohort of AP patients. They found that elevated BUN upon admission as well as a rise in BUN within the first 24 hours were associated with increased in-hospital mortality (121).

Another promising early marker is trypsinogen activation peptide (TAP). TAP is released from the acinar cells during the activation of trypsinogen to trypsin and appears early after onset of AP in blood and urine. Elevated plasma and urine levels of TAP, within the first 48 hours after onset of symptoms, have been found to significantly correlate with AP severity (122-125).

Microproteinuria and urinary biomarkers in acute pancreatitis

Renal impairment associated with AP is a common and severe complication. The pathogenic mechanisms are complex and include several factors. Multiple inflammatory mediators are involved, and pro-inflammatory cytokines can promote SIRS and affect glomeruli and renal tubule capillaries, leading to increased glomerular permeability (126) as well as ischemia and necrosis of the renal tubular cells (127). Hypoxemia, impaired renal microcirculation and decrease in renal perfusion as well as ROS are further associated with renal dysfunction in patients with a severe AP course (127, 128). The systemic inflammation in AP leads to endothelial dysfunction and capillary leakage of proteins and plasma water from the bloodstream. **Albumin** is the main protein in plasma and a daily urinary excretion <30 mg is normal, while an excretion of 30-300 mg/day or an albumin/creatinine ratio >3 mg/mmol is defined as microalbuminuria, which has been proposed an indicator of the degree of systemic

endothelial dysfunction (129). The small protein **α1-microglobulin** is, in normal conditions, filtered freely at the glomeruli and is increased in serum as well as in urine upon SIRS and trauma (130). Increased urinary excretion of α1-microglobulin strongly indicates tubular damage and/or tubular overload (130). **Immunoglobulin G (IgG)** is a large protein, accounting for 80% of antibodies in the body. Like albumin, IgG can cross the glomerular filtration barrier (GFB) only through "large pores" (131). **Immunoglobulin M (IgM)** represents the largest antibody molecule and cannot cross the GFB unless the barrier is damaged (132). It is still unknown, whether urinary excretion of very large proteins, such as IgM, increases upon SIRS.

Microalbuminuria is common in several acute conditions and has been shown to predict the outcome after myocardial infarction and severe burn injury (133, 134). Albuminuria has been found to independently predict mortality associated with cardiovascular disease (135), and IgM-uria has been related to the risk of coronary artery disease and long-term cardiovascular complications in patients presenting with chest pain (136). Since microalbuminuria has been suggested to reflect the degree of systemic endothelial dysfunction (129), urinary excretion of albumin and other proteins could represent interesting candidate markers of severity in AP. Only few, and small, studies have evaluated microproteinuria as a predictor of AP outcome, and the findings from these studies are conflicting (137, 138).

Aims of the thesis

The aims of the papers included in this thesis were:

Paper I – To evaluate the natural history of AP in a population based cohort of patients with first-time AP.

Paper II – To study the use of pancreatitis-associated drugs in patients with first-time AP and the potential relation between the incidence of AP and sales and use of these drugs in a well-defined geographical area in Sweden. In addition, to investigate the potential impact of the use of pancreatitis-associated drugs on AP severity and recurrence.

Paper III – To investigate the value of the urinary excretion of differently sized proteins (microproteinuria) at clinical presentation to predict development of organ failure in patients with AP.

Paper IV – To evaluate the potential relation between the incidence of AP, of alcoholic and non-alcoholic etiology, and alcohol consumption in a well-defined geographical area, and to study whether the occurrence of AP shows any seasonal variation, particularly in relation to periods with an expected increase in alcohol consumption.

Subjects and methods

All studies included in this thesis were performed in accordance with the Declaration of Helsinki, and were approved by the local Ethics Committee.

Subjects

Paper I, II and IV

Skåne University Hospital in Sweden serves a primary population of 600,000 inhabitants and is the only medical institution providing acute hospital care in this area. While patients may be transferred to the hospital from elsewhere there are no referrals of patients with AP from this hospital. Thus, all patients with incident AP, residing in the catchment area, could be included in the studies.

All adult patients (≥18years) with AP admitted to the hospital, between 2003 and 2012 were identified through the computerized discharge diagnosis register, on International Classification of Diseases, 10th revision (ICD-10) codes (K85.0-K85.3, K85.8, K85.9, B25.2, B26.3). Autopsy and forensic diagnosis records were searched for the same diagnosis codes. All medical records of all patients identified were scrutinized and patients with incident AP attacks during the study period were included. Inclusion and exclusion of patients is illustrated in figure 2.

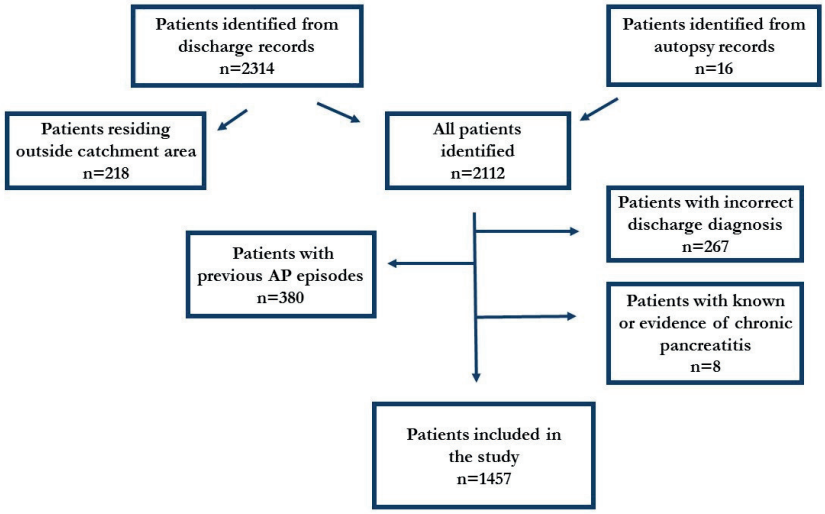

Figure 2. Flowchart of patient inclusion and exclusion

AP attacks were considered to be incident in the absence of evidence of previous AP in medical records. Patients with known, or evidence of, chronic pancreatitis, according to the Lüneburg scoring system (table 1) (10), at first-time AP attack as well as patients residing outside the primary catchment area of the institution, were excluded. Patients were followed until death or the end of 2013.

Tabel 1 Lüneburg scoring for chronic pancreatitis (10)

Parameters	Scoring points
Morphological examinations	
Postmortem diagnosis of chronic pancreatitis	4
Histology	4
Intra-operative findings, characteristic of chronic pancreatitis	4
Pancreatic calcifications, shown on imaging procedure	4
Exocrine pancreatic function tests	
Abnormal secretin pancreozymin test	3
Abnormal pancreolauryl test	2
Abnormal fecal chymotrypsin level	2
Abnormal fecal elastase 1 level	2
Steatorrhea	1
Imaging procedures	
Abnormal ultrasound	3
Abnormal endoscopic ultrasound	3
Abnormal computed tomography	3
Abnormal ERCP	3

ERCP, endoscopic retrograde cholangiopancreatography. Greater than or equal to 4 points, proven chronic pancreatitis

Computerized medical records in our institution include clinician and nurse notes, laboratory tests, imaging exams, and histopathology results. Relevant data from the records, regarding demographics, etiology, comorbid conditions, medications and available information on smoking habits, as well as the occurrence of RAP and chronic pancreatitis were extracted.

Paper III

Consecutive adult patients (≥18 years) with AP, admitted to an acute surgical ward at Skåne University Hospital in Lund, Sweden were prospectively enrolled in the study. Only the first AP episode of each patient during the study period (April 2012 to June 2014) was included. Patients with known chronic kidney disease were excluded. All patients gave written informed consent.

Data regarding demographics, etiology, comorbid illness and medications, in particular those known to affect renal function (NSAIDs, ACE-inhibitors and angiotensin receptor blockers (ARB)), were registered.

Blood and urine samples

Blood and urine samples were collected upon admission to hospital, 12-24 hours after admission, and 3 months after discharge. Serum levels of creatinine, albumin, IgG, and IgM upon presentation and high-sensitivity CRP (upon presentation and 48h after admission), were analysed at an accredited clinical laboratory (the Central Clinical Chemistry Laboratory at Skåne University Hospital in Lund).

Urinary α-1-microglobulin, albumin, and IgG were measured using turbidimetry with a Cobas system, and urinary creatinine was measured by an enzymatic colorimetric method (Roche Inc.), on fresh urine. Urine samples were stored at -20^0 C until analysis for IgM concentrations, that were measured by an enzyme-linked immunosorbent assay (ELISA) technique, as previously described in detail (139). The ratios of α1-microglobulin/creatinine, albumin/creatinine, IgG/creatinine, and IgM/creatinine, as well as the estimated glomerular filtration rate (eGFR) (140) were calculated.

Definitions

Acute pancreatitis diagnosis

AP diagnosis was based on the presence of at least 2 out of 3 of the following criteria: abdominal pain, serum amylase > x3 the upper limit of normal, and/or characteristic findings on computed tomography (CT). In papers I, II and IV, evidence of AP at autopsy was also accepted for diagnosis.

Etiology classification

The etiology of AP was classified as:

biliary, when gallstones were detected in the gallbladder or bile ducts by any imaging procedure.

alcoholic, when the patient or the patient´s family reported a high regular alcohol intake, and/or an alcoholic bout before the onset of the attack.

drug-induced, when the patient, in the absence of other etiological factors, received an AP-associated drug, previously reported to have caused AP, which, according to the treating clinician, was likely to explain the AP, and with no recurrent episodes of AP after discontinuation of the drug (paper II).

other known etiologies, in patients with AP due to causes such as ERCP, hyperlipidemia, and trauma.

idiopathic, when no cause could be ascertained.

Definition of outcome variables

Severity classification

Severity of AP was classified according to the revised Atlanta criteria (49), as:

mild, in the absence of organ failure and local or systemic complications

moderately severe, in the presence of transient (<48 h) organ failure and/or local or systemic complications

severe, characterized by persistent (>48 h) organ failure.

Organ failure was defined according to the Modified Marshall scoring system (141) (table 2).

Table 2. Modified Marshall scoring system for organ dysfunction (141)

Organ system	Score				
	0	**1**	**2**	**3**	**4**
Respiratory **(PaO2/FiO2)***	>400	301-400	201-300	101-200	≤101
Renal **Serum creatinine (μmol/L)**	≤134	134-169	170-310	311-439	>439
Cardiovascular **Systolic blood pressure (mmHg)**	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2
***Estimated FiO2 for non ventilated patients**	Supplemental oxygen (L/min)		FiO2 (%)		
	Room air		21		
	2		25		
	4		30		
	6-8		40		
	9-10		50		

A score of 2 or more defines the presence of organ failure.

Systemic inflammatory response syndrome

Signs of SIRS were defined by the presence of 2 or more criteria; heart rate >90 beats per minute, core temperature $<36^0$ C or $>38^0$ C, white blood cell count $<4x10^9$/L or $>12x10^9$/L, respiration >20/minute or PCO2 <32 mm Hg.

APACHE II

The APACHE II score (109), which is based upon weighted values of 12 routine physiological measurements, age and previous health status, was used as a measure of disease severity. The APACHE II is considered the most widely accepted scoring system for risk stratification in AP (110, 142, 143). In paper III the APACHE II scores were calculated for all patients. In papers I, II and IV some patients did not have complete data, and APACHE II scores were generated by treating missing data as normal values (score 0). The cut-off value for the APACHE II was set to ≥ 8 points, as previously applied (111).

Recurrent acute pancreatitis and chronic pancreatitis

Episodes of RAP and development of chronic pancreatitis, during follow-up (papers I, II and IV), were evaluated through a search of the fully computerized medical records of our institution as well as all hospitals in the whole health care region (population 1.3 million). Chronic pancreatitis was defined according to the Lüneburg scoring system (table 1) (10).

Pancreatitis-associated drugs

Drugs were grouped according to the classification of Badalov et al (27), into 5 classes (Ia-IV):

Class Ia, drugs with at least one case report with positive rechallenge, in which all other causes of AP had been ruled out.

Class Ib, drugs with at least one case report with positive rechallenge, in which other causes of AP had not been fully excluded.

Class II, drugs with ≥4 cases in the literature and consistent latency (≥75% of cases).

Class III, drugs with ≥2 documented cases, without rechallenge or consistent latency

Class IV, drugs with single case reports.

Annual sales and use of pancreatitis-associated drugs

Data on annual sales and use of AP-associated drugs, as specified by Badalov et al (27), during the study period, in the primary catchment area of our institution were obtained from the Swedish drug administration service. Data included:

Annual prescription rates, the total number of purchased prescriptions per 100,000 inhabitants per year, of the separate drugs and classes of drugs, for men and women (data available for the whole study period: 2003-2012)

Annual user rates, the number of persons per 100,000 inhabitants, with at least one prescription of these drugs (per class and total) per year, for men and women (data available for the period 2006-2012).

Annual sales and consumption of alcohol

Data on annual sales and consumption of alcohol, by different beverages, in Skåne during the study period; were obtained from the Swedish Council for Information on Alcohol and Other Drugs (CAN, http://www.can.se). Data (in Liter alcohol per inhabitant per year) included:

Annual registered alcohol sale, alcohol sold by the Swedish Alcohol Retail Monopoly (Systembolaget) and by restaurants.

Annual unregistered alcohol sale, traveller´s import and smuggling. Data are retrieved, by CAN, from estimates of self-reported alcohol consumption data (the Monitoring project, (144)), through monthly telephone interviews of 18,000 Swedish residents per year.

Annual alcohol consumption, self-reported alcohol consumption, based on the Monitoring project (144), for men and women separately.

Comorbidity

The Charlson Comorbidity index (CCI) was calculated for all patients, as a measure of comorbid illness. The CCI assigns scores of 1,2,3 or 6 for 22 different comorbid conditions, depending on their mortality risk (145).

Statistics

Statistical analyses were performed using the SPSS statistical package (v.22, SPSS Inc, Chicago, Ill). Data were expressed as mean and standard deviation (SD), as median and inter quartile range (IQR), or as number and percentage as appropriate.
When comparing groups, the chi2 test and Fisher´s exact test were used for categorical variables, and ANOVA and Mann Whitney *U* test for continuous variables. Reported p-values are 2-tailed and level of significance was set at $p<0.05$.

Annual age-standardized incidence rates for AP were calculated, using direct standardization, for all-cause AP as well as for etiology subgroups (paper II), and for alcoholic and non-alcoholic AP (paper IV), in men and women. The total population

of the primary catchment area of our institution in the first study year (2003) was used as standard. Exact data on the size, age and gender constitution of the population of our institution's primary catchment area, for every year of the study period, were obtained from the Central Bureau of Statistics.

Paper I

Survival analysis (Kaplan-Meier) was used to estimate the risk of RAP, chronic pancreatitis, and mortality during follow-up, and groups were compared with the log-rank test. Multivariate logistic regression analysis was applied to identify independent predictors of inhospital mortality. Cox regression analysis was used to identify independent predictors of the parameters RAP, chronic pancreatitis, and mortality during follow up, after first-time AP, using a staged approach. In the first stage, variables available in all patients that were univariately related with the outcome parameters at $p<0.05$ were entered into forward conditional analysis. Subsequent stages added smoking and local complications separately (data available in 63% and 49% of patients, respectively). In order to evaluate the potentially differential impact of local and systemic complications, or organ failure (parameters included in the revised Atlanta classification of AP severity), on the occurrence of RAP, chronic pancreatitis, and mortality, these components were entered separately in multivariate analyses, instead of the severity grade (mild, moderate, severe) (49). In analysis on inhospital mortality following RAP, all RAP episodes occurring after a diagnosis of chronic pancreatitis were excluded.

Paper II

Time trends on the annual incidence of AP and prescription/user rates of AP-associated drugs were evaluated by means of the Pearson´s correlation coefficient.
The potential relation between the prescription/use of AP-associated drugs and AP recurrence was estimated in survival analysis (Kaplan-Meier) and groups were compared with the log-rank test. In order to adjust for AP etiology, age, and smoking status in the potential relation between recurrent AP and use of AP-associated drugs, multivariate Cox regression analysis was used. Logistic regression analysis was performed, for adjustment of confounding comorbid illness and age on the potential relationship between AP severity and use of AP-associated drugs.

Paper III

The Spearman´s rank coefficient was used for correlation analysis, and the Wilcoxon signed rank test was used to investigate longitudinal changes of microproteinuria biomarker levels on admission, 12-24 hours after admission, and 3 months after hospitalization. The predictive value of the urinary excretion of different proteins on organ failure was explored by means of the area under the receiver operating characteristics curve (AUROC). Receiver operating characteristics (ROC) data were used to identify cut-off values, for the separate microproteinuria ratios, with optimal operating characteristics. Statistical comparisons of AUROCs were performed with the MedCalc® Statistical Software, using the method of DeLong et al.(146). Multivariate logistic regression analysis, with adjustment for confounders, was performed in order to evaluate whether microproteinuria biomarkers could represent independent predictors of organ failure. Parameters significantly ($p<0.05$) correlated to the presence of organ failure in univariate analysis were entered into the model.

Paper IV

Time trends of the annual incidence of AP and annual sales/consumption of alcohol were assessed by means of the Pearson´s correlation coefficient. The same test was used for the evaluation of potential correlations between the annual incidence of AP and alcohol sales/consumption.

Seasonal as well as monthly variations in first-time AP were analyzed with the Chi2 goodness-of-fit test. Two periods with high alcohol consumption in Sweden (101) i.e. the two weeks around Christmas and New Year´s Eve (last week in December and first in January), and the two weeks around the occurrence of summer solstice (midsummer; last week in June and first in July), were compared with two 2-week periods after and prior to it. These comparisons were also performed using the Chi2 goodness-of-fit test.

Results

In papers I, II and IV the study cohort comprised 1457 patients with first-time AP during the study period, 2003-2012. Patient characteristics are described in table 3.

Table 3. **Patient characteristics (papers I, II and IV) (n=1457)**

	Biliary (n=704)	Alcoholic (n=249)	Other known etiology (n=72)	Idiopathic (n=432)
Age, mean (SD), yr	64 (19)	55 (13)	53 (20)	62 (19)
Female (%)	56	22**	53	45
Follow-up, patient-years	38079	15009	3507	24508
Median (IQR), yr	4.0 (2.17-6.49)	4.6 (2.73-7.11)	3.5 (2.16-5.44)	4.5 (2.11-7.57)
Charlson comorbidity index >1 (%)	25.1	8.9**	18.1	25.6
Local complications (%)[1]	14.7	31.7**	19.4	19.5
Local complications (%)[2]	33.9	49.6**	33.3	31.3
Systemic complications (%)	6.3	5.4	2.8	5.1
Organ failure (%)	10.1	16.1	16.7	12.3
RAP (%)	17.4	36.5**	19.4	23.5
Time to first RAP, median (IQR), mo	2.6* (1.0-11.4)	7.6 (2.2-16.6)	5.3 (3.0-11.2)	5.7 (1.6-19.5)
Chronic pancreatitis (%)	0.6	17.3**	5.6	5.8
Time to chronic pancreatitis, median (IQR), mo	17 (4.4-34.6)	9 (1.4-21.6)	0.2 (0.1-0.5)	7.5 (1.5-32.9)
Inpatient mortality during first-time AP (%)	2	3.6	2.8	3.7

SD, standard deviation; CRP, C-reactive protein; RAP, recurrent acute pancreatitis; IQR, interquartile range; AP, acute pancreatitis

[1] The proportions of patients with local complications calculated in all patients

[2] The proportions of patients with local complications calculated in patients with CT scans. At least one CT scan was performed in 39% of patients with biliary AP, 59% of those with alcoholic AP, 56% with AP of other known etiology and 59% with idiopathic AP.

* p<0.05 compared to all other etiologies

**p<0.01 compared to all other etiologies

Natural course of acute pancreatitis (paper I)

In men as well as in women, gallstone disease was the most common etiology, followed by alcohol. In all, 73% of the patients experienced mild, 17% moderately severe and 10% severe AP. Systemic complications occurred in 5.6% and organ failure in 12% of the patients, and did not differ significantly between etiology groups, while local complications were significantly more common in alcoholic AP compared to other etiologies (table 3). Thus, the proportion of patients with moderately severe or severe AP was significantly higher in the group of alcoholic AP compared to the other etiology groups.

Recurrent episodes of acute pancreatitis

Among patients surviving incident AP, 329/1416 (23%) experienced one or more RAP episodes during the follow-up period, whereas 63.5% had one and 36.5% had two or more RAP episodes. In multivariate analysis, the risk for recurrence was related to alcoholic AP etiology and smoking, as well as to the presence of organ failure, and systemic or local complications at first-time AP (table 4).

Table 4. Independent predictors of recurrent acute pancreatitis after incident acute pancreatitis

	Stage 1 (all patients, n=1457)		Stage 2 (63% of patients)		Stage 3 (49 % of patients)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR(95% CI)	p-value
Etiology (vs. alcoholic)						
Biliary	0.43 (0.33-0.57)	**<0.01**	0.56 (0.39-0.80)	**<0.01**	0.52 (0.37-0.73)	**<0.01**
Other	0.51 (0.29-0.90)	**0.02**	0.54 (0.26-1.13)	0.10	0.59 (0.30-1.15)	0.12
Idiopathic	0.62 (0.47-0.82)	**<0.01**	0.61 (0.43-0.88)	**<0.01**	0.73 (0.52-1.03)	0.07
Systemic complications at index AP (vs. no)	1.88 (1.27-2.79)	**<0.01**	1.13 (0.67-1.91)	0.66	1.43 (0.88-2.32)	0.15
Organ failure at index AP (vs. no)	1.46 (1.05-2.03)	**0.02**	1.58 (1.07-2.32)	**0.02**	1.01 (0.68-1.50)	0.95
Smoking (vs. no)			1.42 (1.03-1.95)	**0.03**		
Local complications at index AP (vs. no)					1.66 (1.22-2.27)	**<0.01**

AP, acute pancreatitis; HR, hazard ratio; CI, confidence interval

Recurrent acute pancreatitis in patients with biliary acute pancreatitis

While recurrent episodes of AP were more common among patients with alcoholic etiology, they occurred after a shorter time-interval following biliary AP (median 2.6 vs 7.6 months, p<0.05, table 3). Among biliary AP patients without previous cholecystectomy (n=676/704), 22% underwent cholecystectomy during index admission, 12% within 2 weeks, 7% within 2-4 weeks, 22% after 4 weeks following discharge for first-time AP, and 37% did not undergo cholecystectomy during follow up. Recurrence in biliary AP patients was significantly correlated to delayed cholecystectomy (figure 3). In Cox regression analysis, after adjustment for predictors of RAP in the whole cohort, the time from first-time AP to interval cholecystectomy independently predicted RAP among patients with biliary AP (Hazard ratio (HR) 1.02 per month, 95% confidence interval (CI) 1.01-1.04, p<0.05).

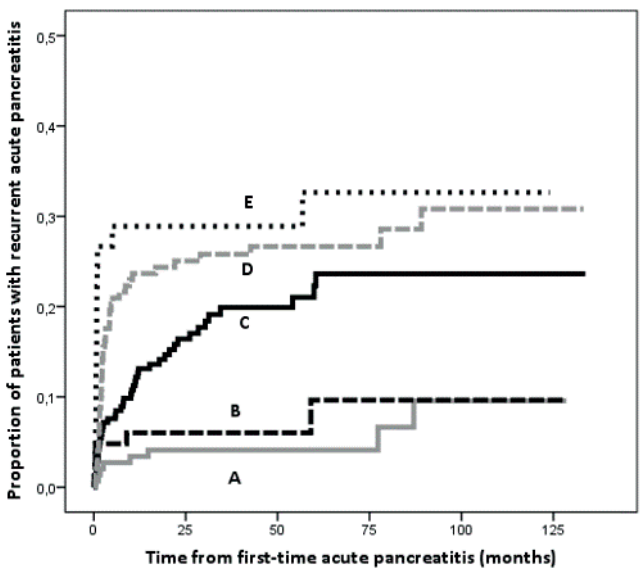

Figure 3. Development of recurrent acute pancreatitis among patients with first-time biliary acute pancreatitis in relation to timing of cholecystectomy

A- cholecystectomy during admission for first-time AP; B - cholecystectomy within 2 weeks following admission for first-time AP; C- no cholecystectomy during follow-up; D- cholecystectomy after 4 weeks following admission for first-time AP; E- cholecystectomy between 2 - 4 weeks following admission for first-time acute pancreatitis.

Chronic pancreatitis

In all, 5% of patients surviving first-time AP developed chronic pancreatitis, which was significantly more common in patients with incident alcoholic AP ($p<0.01$ compared to all other etiologies, table 3). Among patients who developed chronic pancreatitis, 74% had previously experienced one or more RAP episodes. The strongest predictor for progression to chronic pancreatitis, in multivariate Cox-regression analysis, was RAP (HR 6.7, 95% CI 4.0-11.3, $p<0.01$). Furthermore, alcoholic etiology, smoking, and systemic as well as local complications (in particular pancreatic necrosis) at first-time AP, independently predicted progression to chronic pancreatitis.

Among all patients with alcoholic first-time AP, 20% were offered some kind of alcohol misuse counselling or treatment. This had, however, no significant impact on either the risk of RAP or the development of chronic pancreatitis (figure 4).

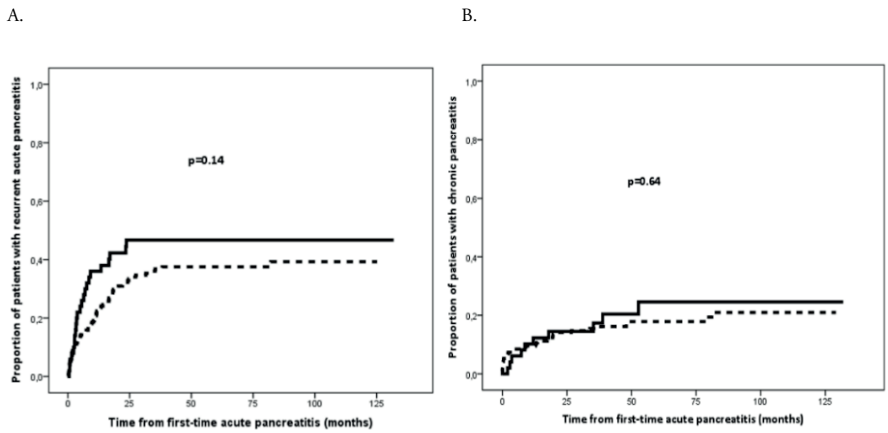

Figure 4. Alcohol misuse counseling during index alcoholic acute pancreatitis and risk of (A) recurrent acute pancreatitis and (B) chronic pancreatitis

Dotted line, no counseling; continous line, counseling

Mortality

During the study period, 318/1457 patients (21.9%) died, whereas 41 (2.8%) during the index admission. In logistic regression analysis, the only independent predictor of inhospital mortality at first-time AP, was organ failure (Odds Ratio (OR) 71.2, 95% CI 21.1-239.6, $p<0.01$), but neither pancreatitis etiology, patient age, local nor systemic complications ($p>0.05$ for all). However, older age (OR 2.1, 95% CI 1.0-4.2 (age 49-62years), OR 3.3, 95% CI 1.7-6.2 (age 63-76years), OR 6.0, 95% CI 3.2-11.1

(age 77-100years) vs. age<49 years, p<0.01 for all) and pancreatic necrosis (OR 29.8, 95% CI 15.5-57.1, p<0.01) were independent predictors of organ failure.

Mortality during recurrent acute pancreatitis

Out of the patients surviving incident AP, 15 (1.1%) died during RAP. Of these, 10/15 (67%) died during their first RAP, 8 of which had biliary AP. Even though the 8 biliary AP patients, who died upon RAP, were older than biliary AP patients surviving RAP, and had experienced a more severe index AP, the groups did not differ significantly according to gender, comorbidity or body mass index. Among these 8 patients, 5 were not planned for cholecystectomy due to significant comorbidity, one had opted out of cholecystectomy, and two were awaiting cholecystectomy (both for >1 year). Only two of the patients underwent ERCP with sphincterotomy. There were, however, no significant differences in mortality among biliary AP patients with RAP who underwent ERCP compared to those who did not (p>0.05). Inhospital mortality at first-time RAP was slightly higher compared to first-time AP (3.1% vs. 2.8%, p=0.81) in the whole study cohort, although this difference was statistically significant only among patients with biliary AP (5.9% vs. 2%, p=0.01). Hence, biliary AP etiology was more common among patients who died during first RAP compared to those who died upon first-time AP (70% vs. 34%, p=0.03).

Acute pancreatitis and use of pancreatitis-associated drugs (paper II)

Incidence of acute pancreatitis

During the study period, the annual age-standardized incidence of AP increased significantly in women as well as in men (p<0.05) (figure 5), mainly due to an increase of biliary AP in both genders (p<0.05), while the incidences of alcoholic AP, AP of other known etiologies, and of idiopathic AP did not change significantly (p>0.05 for all, in both genders). The annual age-standardized incidence of drug-induced AP did, however, increase in men by 6.5% (95% CI 0.2-12.7) per year and in women by 7% (95% CI 1.7-12.4) per year (p<0.05 for both).

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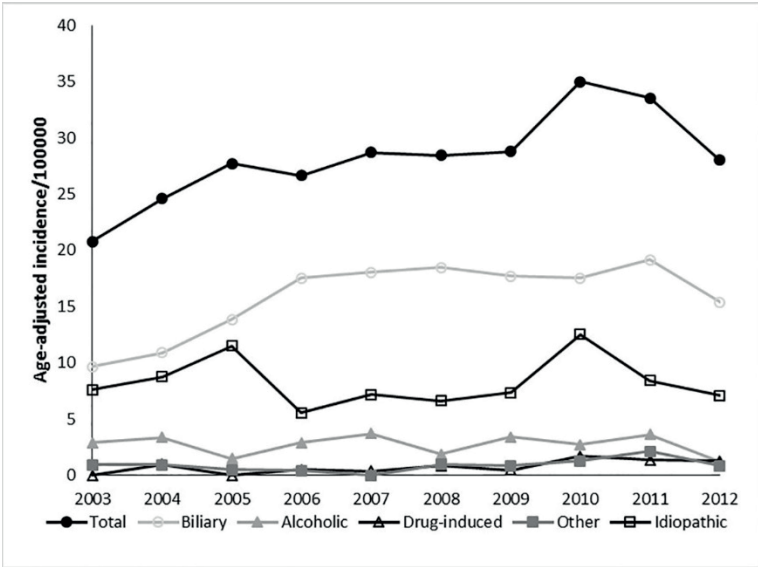

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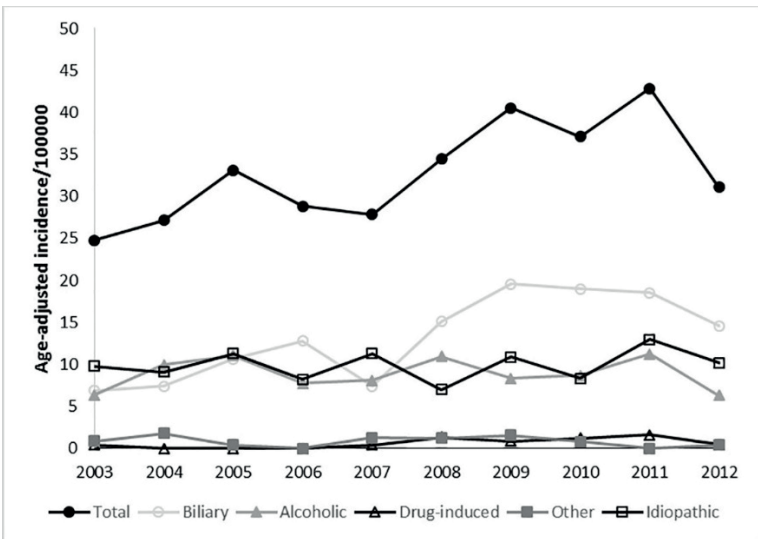

Figure 5. Incidence of acute pancreatitis from 2003 to 2012 in women (A) and men (B)

Use of pancreatitis-associated drugs

The proportion of patients with first-time AP, who were using one or more AP-associated drugs increased significantly from 32% in 2003 to 51% in 2012 ($p<0.05$ for men and women). Overall, 23% were using ≥1 Class Ia, 17% ≥1 Class Ib, 14% ≥1 Class II, 20% ≥1 Class III, and 16% ≥1 Class IV drugs. The most frequently used AP-associated drugs are listed in table 5. The use of AP-associated drugs was common in both men and women with first-time AP of all etiologies. However, in women, there was a significantly higher proportion of patients using class Ia drugs among patients with idiopathic AP compared to those with alcoholic or other known etiologies ($p<0.05$), but not compared to those with biliary AP ($p>0.05$), while the proportion of class II drug users was higher among idiopathic AP patients compared to the biliary and alcoholic groups ($p<0.05$), but not compared to patients with other known AP etiologies ($p>0.05$). In men, the use of class III drugs was significantly higher in patients with other known AP etiologies compared to all other etiology subgroups ($p<0.05$ for all).

Table 5. Pancreatitis-associated drugs most frequently used in the study cohort

Class Ia	Class Ib	Class II	Class III	Class IV
Simvastatin	Omeprazol	Acetaminophen	Metformin	Ramipril
Furosemide	Losartan	Estrogen	Atorvostatin	Bendroflumethiazide
Enalapril	Azathioprin	Tamoxifen	Claritromycin	Diclofenac
Mesalamine	Mercaptupurin		Prednisolone	Sertaline
Valproic acid			Carbamazepine	Ranitidine
			Hydrochlorotiazide	Propoxiphene

Incidence of acute pancreatitis in relation to prescription and user rates of pancreatitis-associated drugs

The annual prescription rates of AP-associated drugs (of all classes) increased, in the catchment area of our institution, during the study period ($p<0.05$ for all classes; for men and women). Similarly, the annual user rates of class Ia, Ib, II and III drugs increased significantly ($p<0.05$ for all classes; for men and women), although the user rates of class IV drugs remained unchanged ($p>0.05$; for men and women).

The annual age-adjusted incidence of AP in total correlated to the annual prescription rates of AP-associated drugs ($p<0.05$ for all classes, in men and women). This was, however, not true for the incidence of idiopathic AP ($p>0.05$, in men and women). Furthermore, the annual age-adjusted incidence of AP (total and etiology subgroups) did not correlate to the annual user rates of AP-associated drugs in either gender, although, there was a trend between the user rates of class Ia drugs and incidence of drug-induced AP ($p=0.08$) (table 6).

Table 6. Correlation between the annual age-adjusted AP incidence rate with prescription and user rates of AP-associated drugs in the catchment area of our institution during the study period (2003-2012) in (A) women and (B) men

A. Age-adjusted incidence	Women	Total AP	Biliary AP	Alcoholic AP	Drug-induced AP	Other AP	Idiopathic AP
		r (p)	r (p)	r (p)	r (p)	r (p)	r (p)
Class Ia	Prescription rate	0.81 (**<0.01**)	0.86 (**<0.01**)	-0.01 (0.99)	0.64 (0.05)	0.38 (0.29)	-0.07 (0.86)
	User rate	0.66 (0.11)	0.83 (0.86)	-0.14 (0.76)	0.7 (0.08)	0.75 (0.06)	0.55 (0.2)
Class Ib	Prescription rate	0.78 (**<0.01**)	0.85 (**<0.01**)	-0.07 (0.84)	0.64 (0.05)	0.33 (0.35)	-0.12 (0.74)
	User rate	0.31 (0.5)	-0.08 (0.87)	-0.4 (0.38)	0.66 (0.11)	0.6 (0.16)	0.04 (0.94)
Class II	Prescription rate	0.8 (**<0.01**)	0.8 (**<0.01**)	-0.13 (0.71)	0.68 (**0.03**)	0.41 (0.24)	-0.04 (0.91)
	User rate	0.33 (0.48)	-0.32 (0.49)	-0.4 (0.37)	0.72 (0.07)	0.48 (0.28)	0.19 (0.69)
Class III	Prescription rate	0.8 (**<0.01**)	0.84 (**<0.01**)	-0.09 (0.81)	0.66 (**0.04**)	0.35 (0.32)	-0.07 (0.84)
	User rate	0.18 (0.7)	-0.25 (0.58)	-0.46 (0.3)	0.57 (0.18)	0.4 (0.38)	0.00 (0.99)
Class IV	Prescription rate	0.66 (**0.04**)	0.7 (**0.03**)	0.06 (0.87)	0.67 (**0.03**)	0.45 (0.91)	-0.18 (0.63)
	User rate	-0.04 (0.94)	0.24 (0.6)	0.32 (0.48)	-0.09 (0.85)	-0.1 (0.83)	-0.31 (0.51)

B. Age-adjusted incidence	Men	Total AP	Biliary AP	Alcoholic AP	Drug-induced AP	Other AP	Idiopathic AP
		r (p)	r (p)	r (p)	r (p)	r (p)	r (p)
Class Ia	Prescription rate	0.78 (**<0.01**)	0.87 (**<0.01**)	0.1 (0.78)	0.72 (**0.02**)	-0.17 (0.63)	0.13 (0.72)
	User rate	0.73 (0.06)	0.73 (0.06)	0.19 (0.68)	0.7 (0.08)	0.04 (0.93)	0.32 (0.48)
Class Ib	Prescription rate	0.71 (**0.02**)	0.8 (**<0.01**)	0.04 (0.91)	0.69 (**0.03**)	-0.21 (0.55)	0.17 (0.65)
	User rate	0.5 (0.25)	0.51 (0.24)	0.03 (0.96)	0.5 (0.26)	-0.23 (0.62)	0.42 (0.35)
Class II	Prescription rate	0.75 (**0.01**)	0.85 (**<0.01**)	0.06 (0.88)	0.68 (**0.03**)	-0.23 (0.52)	0.14 (0.7)
	User rate	0.56 (0.19)	0.63 (0.13)	-0.05 (0.92)	0.42 (0.35)	-0.4 (0.37)	0.42 (0.35)
Class III	Prescription rate	0.68 (**0.03**)	0.78 (**<0.01**)	0.03 (0.95)	0.64 (0.05)	-0.21 (0.56)	0.16 (0.67)
	User rate	0.32 (0.48)	0.37 (0.42)	-0.15 (0.75)	0.32 (0.48)	-0.17 (0.71)	0.35 (0.44)
Class IV	Prescription rate	0.68 (**0.03**)	0.77 (**<0.01**)	0.01 (0.99)	0.71 (**0.02**)	-0.31 (0.39)	0.2 (0.58)
	User rate	-0.19 (0.68)	-0.32 (0.49)	0.15 (0.75)	-0.09 (0.85)	-0.87 (**0.01**)	0.28 (0.55)

AP, acute pancreatitis; Prescription rate, n of purchased prescription/100,000/yr; User rate, n of persons/100000/yr with ≥1 prescription; r, Pearson´s coefficient; p, p-value

The severity of first-time acute pancreatitis and the recurrence of pancreatitis episodes are not related to the use of pancreatitis-associated drugs

Most cases (90%) of drug-induced AP were mild, although in the rest of the cohort, patients who used class Ia, II and III drugs, experienced severe AP and systemic complications significantly more often compared to the rest of the patients ($p<0.05$). However, in logistic regression analysis, after adjustment for the confounders age and comorbid illness (CCI (145)), the relation between AP severity and use of AP-associated drugs, by any class and in total, was no longer significant ($p>0.05$ for all). Furthermore, the use of certain drugs, previously implicated in severe AP (27) was, in our study cohort, more common among patients with severe AP compared to patients with mild or moderately severe AP (51% vs. 38%, $p<0.01$). However, after adjustment for age and comorbidity, by means of logistic regression analysis, the relation between these drugs and AP severity was no longer significant ($p>0.05$).

During follow up, 163 (22%) of AP patients using AP-associated drugs experienced one or more RAP episodes, 23% for class Ia, 19% for class Ib, 25% for class II, 24% for class III, and 23% for class IV drug users. The occurrence of RAP episodes, did however, not differ significantly between patients with vs. those without AP-associated drugs ($p>0.05$ for all classes, in men and women). In Cox regression analysis, after adjustment for confounding AP etiology (alcoholic vs. other), age, and smoking, the use of AP-associated drugs was still not significantly correlated to RAP ($p>0.05$ for all classes).

Impact of Alcohol Consumption and Seasonal Factors on acute pancreatitis (paper IV)

Incidence of acute pancreatitis in relation to alcohol sales and consumption

Total annual alcohol sales (registered and unregistered) decreased during the study period, from 11.21 L/capita in 2003 to 7.96 L/capita in 2012 ($p=0.002$), mainly due to decreased sales of spirits ($p=0.001$) and beer ($p=0.002$) (figure 6). There were no correlations between the annual age-adjusted incidence of AP (alcoholic, non-alcoholic or total) in women and alcohol sales ($p>0.05$ for all kinds of alcohol beverages and total alcohol sales). The overall age-adjusted AP incidence in men was significantly related to the sale of cider ($p=0.045$). In addition, the incidence of non-alcoholic AP in men showed a significant, positive correlation to the sales of cider ($p=0.008$) and a negative correlation to the sales of spirits ($p=0.036$). There were no significant correlations

between the incidence of alcoholic and idiopathic AP and the sales of alcohol, of any beverage or in total ($p>0.05$ for all, in men and women).

Self-reported alcohol consumption decreased during the study period. Women reported decreased consumption of spirits and beer ($p<0.05$ for both), but unchanged consumption of alcohol in total and of wine ($p>0.05$ for both, figure 6). Alcohol consumption among men decreased during the study period ($p=0.022$), mainly due to decreased consumption of spirits ($p=0.012$), while consumption of beer and wine remained unchanged ($p>0.05$ for both, figure 6). In women, there were no significant correlations between the incidence of alcoholic, non-alcoholic, or total AP and self-reported alcohol consumption. There was, however, a significant correlation between the incidence of idiopathic AP in women and the consumption of wine ($r=0.71$, $p=0.021$), but not to total alcohol consumption or consumption of any other alcoholic beverage ($p>0.05$ for all). The self-reported consumption of alcohol in total, and spirits in particular, among men was negatively correlated to the non-alcoholic AP incidence ($p<0.05$, for both). There were no significant correlations between alcohol consumption in men and the incidence of total or alcoholic AP ($p>0.05$, for both).

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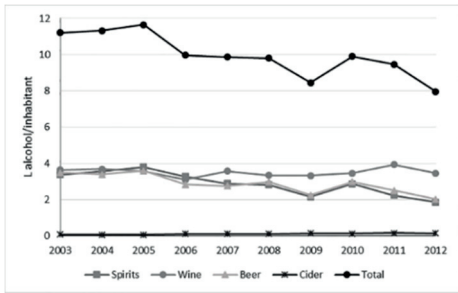

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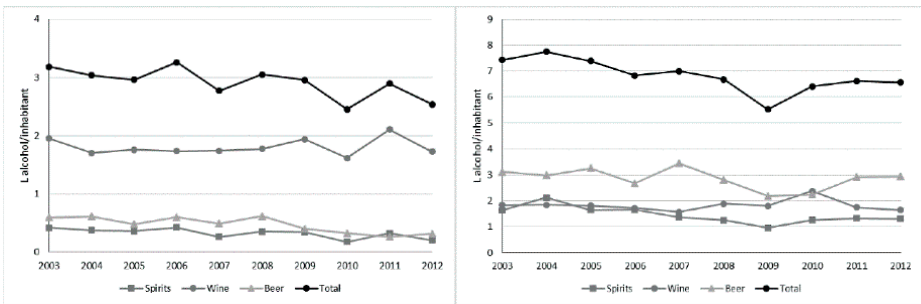


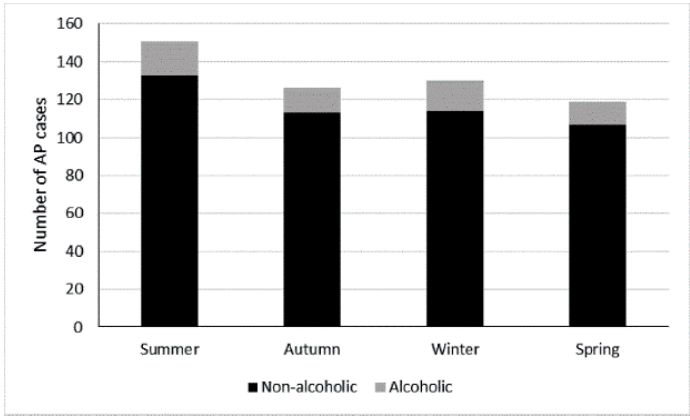
Figure 6. Annual alcohol sales (A), and self-reported alcohol consumption for women (B) and men (C), in the general population during the study period

(A)Decreasing time trends for total alcohol, spirits, and beer (r=-0.84 to -0.89, p<0.001). Increasing time trend for cider (r=0.92, p<0.001). No significant change for wine (r=-0.00, p=0.991). (B)Decreasing time trends for spirits and beer (r=-0.70 to -0.83, p < 0.05). No significant changes for wine and total alcohol consumption (r=-0.54 to 0.38, p > 0.05).(C)Decreasing time trends for total alcohol consumption and spirits (r= -0.71 to -0.75, p < 0.05). No significant changes for beer and wine (r= -0.29 to 0.16, p > 0.05)
r, Pearson´s correlation coefficient

Seasonal variations in the occurrence of first-time acute pancreatitis

The occurrence of first-time AP, among women and men, did not vary significantly during different seasons of the calendar year (winter, spring, summer, autumn; p>0.05 for all, figure 7). Furthermore, there were no significant differences in AP occurrence between calendar months within each season, except for admissions among women, with non-alcoholic AP being significantly lower in April compared to March and May (p=0.042), and the number of admissions for alcoholic AP, in men, being significantly lower in June compared to July and August (p=0.010).

A.



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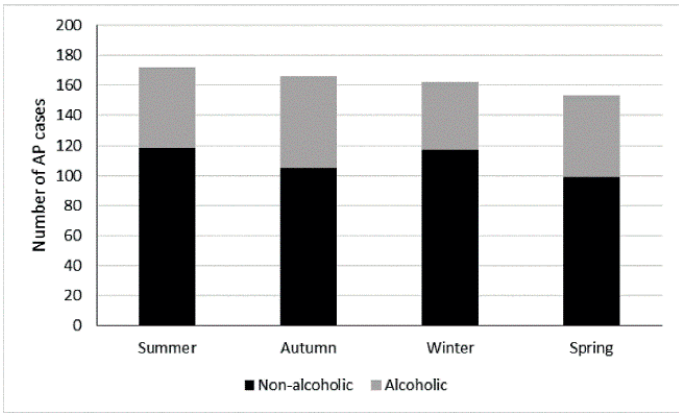

Figure 7. Variation in the occurrence of first-time acute pancreatitis during different seasons in women (A) and men (B)
No significant differences in the occurrence of AP during different seasons (p>0.05 for women and men). AP, acute pancreatitis

Holidays particularly associated with increased alcohol consumption in Sweden, are Christmas/New Year´s Eve and Midsummer. The occurrence of AP (alcoholic and non-alcoholic, in men and women) during these holidays was, however, similar to the weeks before and after the holidays (p>0.05 for all, table 7).

Table 7. Variation in the occurrence of first-time acute pancreatitis during holidays with increased alcohol consumption

	Women			Men		
	Alcoholic AP (n)	Non-alcoholic AP (n)	Total AP (n)	Alcoholic AP (n)	Non-alcoholic AP (n)	Total AP (n)
Christmas/New Year´s Eve	3	27	30	10	30	40
2 wks before Christmas	2	16	18	10	16	26
2 wks after New Year´s Eve	1	15	16	10	24	34
Chi2 (p-value)	1.0 (0.607)	4.59 (0.101)	5.38 (0.068)	NA	4.23 (0.121)	2.96 (0.228)
Midsummer	2	22	24	10	15	25
2 wks before Midsummer	4	22	26	0	29	29
2 wks after Midsummer	5	25	30	12	19	31
Chi2 (p-value)	1.27 (0.529)	0.26 (0.878)	0.70 (0.705)	0.18 (0.672)	4.95 (0.084)	0.66 (0.719)

AP, acute pancreatitis. Christmas/New Year´s Eve (December 24 to January 7), Midsummer (June 22 to July 7)

Microproteinuria predicts organ failure in acute pancreatitis (paper III)

In paper III, 94 consecutive patients with AP were prospectively screened, and agreed to participate in the study. However, two patients had a history of chronic kidney disease and were therefore excluded. The characteristics of the 92 patients included in the study are shown in table 8. The most common AP etiology was biliary, followed by alcoholic. Moderately severe or severe AP was significantly more common in patients with alcoholic AP compared to other etiology groups, mainly due to an increased occurrence of local complications in the former. Among patients who developed organ failure (n=13), 10 experienced respiratory, one experienced renal and two experienced multiorgan failure. In patients with organ failure, 7 (54%) had transient and 6 (46%) had persistent organ failure.

Table 8. Patient characteristics

	All patients (n=92)	No organ failure (n=79)	Organ failure (n=13)	p-value
Women, n(%)	41 (44.6)	37 (46.8)	4 (30.8)	0.372
Age, median (IQR), yr	61 (25)	60 (26)	63 (16)	0.292
Etiology, n(%)				0.580
Alcoholic	23 (25.0)	20 (25.3)	3 (23.1)	
Biliary	44 (47.8)	36 (45.6)	8 (61.5)	
Other cause	5 (5.4)	5 (6.3)	0	
Idiopathic	20 (21.7)	18 (22.8)	2 (15.4)	
Diabetes, n(%)	7 (7.6)	5 (6.3)	2 (15.4)	0.257
Onset of symptoms prior to admission, median (IQR), h	24 (38)	24 (38)	24 (19)	0.320
Potentially nephrotoxic drugs*, n(%)	27 (29.3)	22 (27.8)	5 (38.5)	0.514
hsCRP upon admission, median (IQR), mg/L	38 (74)	31 (58)	98 (248)	**0.013**
hsCRP 48 hours after admission, median (IQR), mg/L	110 (152)	101 (123)	223 (221)	**<0.001**
eGFR,median (IQR) ml/min per 1.73m^2	80.8 (42.1)	81.2 (38.4)	78.0 (47.7)	0.590

IQR, interquartile range, *Non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers

Predictors of increased levels of microproteinuria biomarkers

The levels of microproteinuria biomarkers did not differ significantly between admission and 12-24 hours after admission ($p>0.05$, for all), while the levels from 3-months follow-up measurements were significantly lower ($p<0.05$, for all) (figure 8).

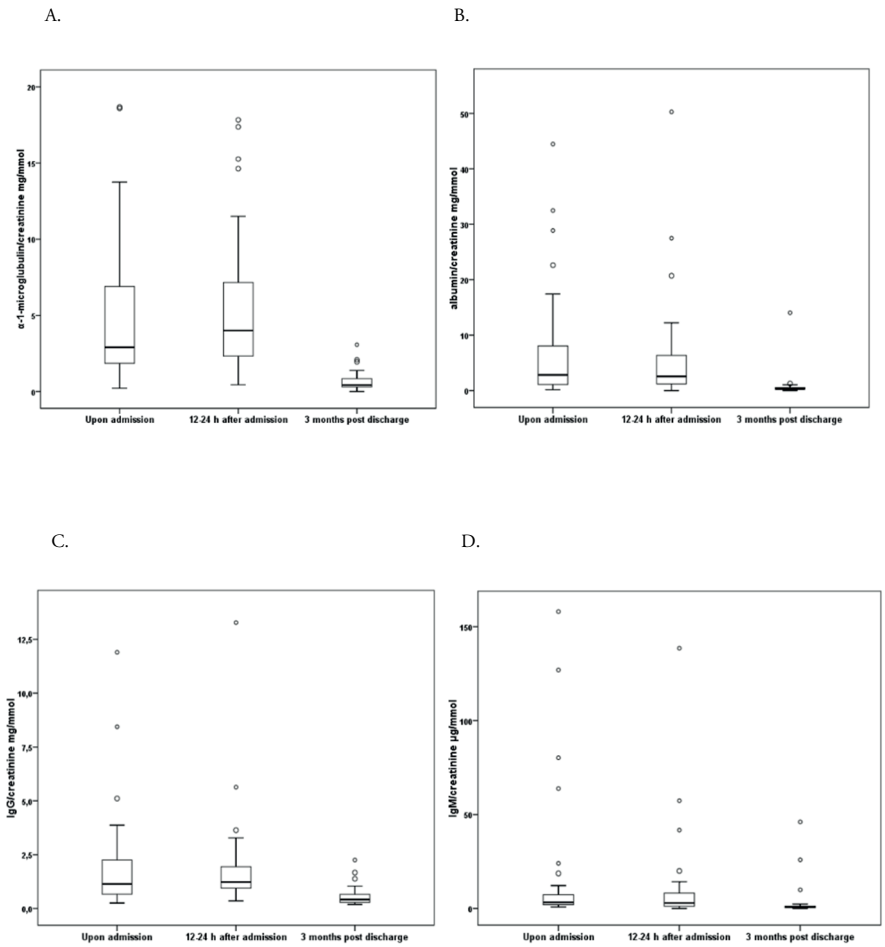

Figure 8. Biomarkers of microproteinuria upon admission, 12 to 24 hours after admission and 3 months after hospitalization. A. α-1-microglubulin/creatinine ratio, B. albumin/creatinine ratio, C. IgG/creatinine ratio, and D. IgM/creatinine ratio

Data available for n=92 patients upon admission, n=59 patients 12-24 h after admission, n=48 patients 3 months post discharge.
o, Outliers representing values ≥ 1.5 interquartile range

There were no significant differences in microproteinuria values between alcoholic vs. non-alcoholic AP etiologies, between patients with vs. without diabetes, or in patients with vs. without potentially nephrotoxic medications ($p>0.05$ for all), and microproteinuria levels were not related to patient age ($r=-0.04$-0.12, $p>0.05$). Men had significantly higher α1-microglobulin/creatinine ratios upon admission compared to women (4.1 (6.2) mg/mmol vs. 2.6 (3.7) mg/mmol, $p<0.01$), although there were no gender differences in any other microproteinuria biomarker ($p>0.05$ for all).

Microproteinuria is related to organ failure and severity in acute pancreatitis

Significantly higher α1-microglobulin-, albumin-, IgG-, and IgM/creatinine ratios, upon admission, were found among patients who developed organ failure compared to those who did not (table 9). Similar relations were found for AP severity, except for the IgM/creatinine ratio (table 9). The CRP-values upon admission and 48 h after admission correlated to the α1-microglobulin/creatinine ratios ($r=0.54$, $p<0.01$ and $r=0.61$, $p<0.001$) as well as to the albumin/creatinine ratios ($r=0.43$, $p=0.001$ and $r=0.47$, $p<0.001$). The APACHE II scores were weakly correlated to α1-microglobulin/creatinine ($r=0.41$, $p<0.001$), albumin/creatinine ($r=0.30$, $p=0.006$) and to IgG/creatinine ($r=0.22$, $p=0.043$) upon admission, although not to the IgM/creatinine scores ($r=0.08$, $p=0.564$).

In logistic regression analysis, organ failure was found to be independently related to the α1-microglobulin/creatinine ratio upon admission (OR 1.29, 95% CI 1.02-1.61, $p=0.03$) and to the APACHE II score (OR 1.45, 95% CI 1.02-2.06, $p=0.04$) but not to any other parameter ($p>0.05$ for all).

Table 9. Relation of biomarkers of microproteinuria with organ failure and severity of acute pancreatitis

	All patients	Mild AP	Moderate/severe AP	p-value	No organ failure	Organ failure	p-value
Upon admission, median (IQR)	**n=92**	**n=67**	**n=25**		**n=79**	**n=13**	
α-1-microglobulin/creatinine, mg/mmol	3 (4.6)	2.81 (3.3)	7.42 (9.6)	**<0.001**	2.84 (3.6)	9.22 (6.7)	**<0.001**
Albumin/creatinine, mg/mmol	2.37 (5,6)	1.76 (4.8)	4.9 (8.5)	**0.004**	1.98 (5.1)	5.13 (4.4)	**0.007**
IgG/creatinine, mg/mmol	1.3 (1.29)	1.15 (1.12)	1.71 (2.49)	**0.016**	1.2 (1.1)	1.89 (2.2)	**0.007**
IgM/creatinine, µg/mmol	4.39 (15.8)	2.75 (17.2)	5.01 (9.5)	0.075	3.87 (11.9)	6.55 (23.6)	**0.045**
12-24h after admission, median (IQR)	**n=59**	**n=42**	**n=17**		**n=51**	**n=8**	
α-1-microglobulin/creatinine, mg/mmol	3.93 (5.7)	3.09 (3.2)	8.53 (4.4)	**<0.001**	3.42 (3.8)	9.3 (6.9)	**<0.001**
Albumin/creatinine, mg/mmol	2.23 (4.4)	1.52 (3.7)	3.79 (3.2)	**0.031**	1.67 (4.2)	3.66 (2.5)	0.071
IgG/creatinine, mg/mmol	1.15 (1)	1.03 (1)	1.62 (1)	0.273	1.13 (1.1)	1.62 (1)	0.938
IgM/creatinine, µg/mmol	3.14 (7.6)	2.93 (6.8)	5.67 (10.1)	0.153	3.04 (7.1)	6.69 (7)	0.361

AP, acute pancreatitis; IQR, interquartile range

The highest AUROC values among the evaluated microproteinuria biomarkers were found for α1-microglobulin/creatinine ratio upon admission, and 12-24 hours after admission, and were similar to that of the admission APACHE II score (figure 9, table 10). At cut-off values of 3 and 7.2 mg/mmol, respectively, the sensitivity was 85% and 89% whereas specificity was 61% and 82% for the prediction of organ failure.

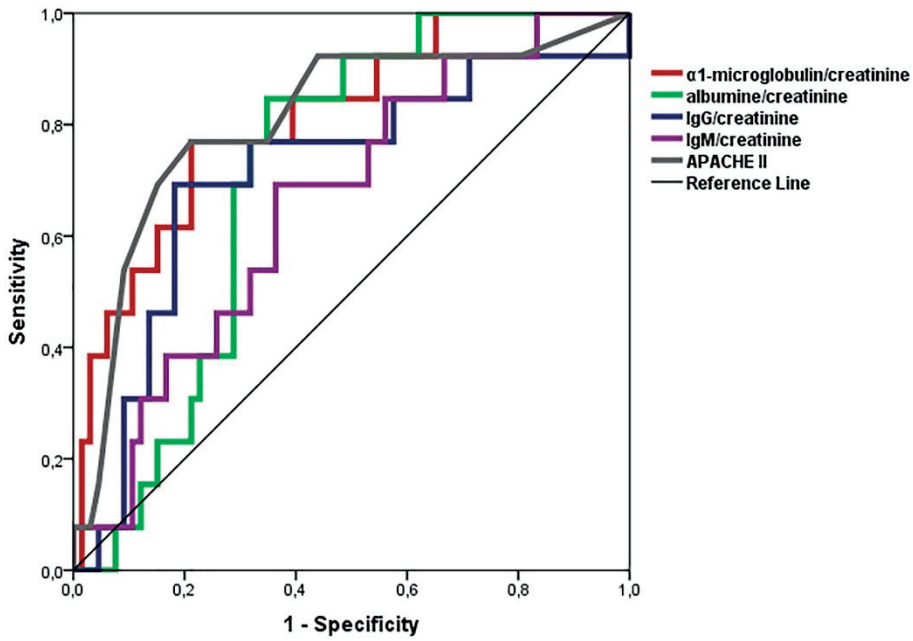

Figure 9. The receiver operating characteristics (ROC)-curve for microproteinuria biomarkers, upon admission, and APACHE II scores, for the prediction of organ failure

Table 10. The utility of biomarkers of microproteinuria in predicting organ failure

Microproteinuria biomarker	AUROC	95% CI		p-value
Upon admission, n=92				
α-1-microglubulin/creatinine	0.81	0.69	0.94	**<0.001**
Albumin/creatinine	0.74	0.62	0.85	**0.007**
IgG/creatinine	0.74	0.60	0.87	**0.007**
IgM/creatinine	0.66	0.50	0.82	0.065
hs-CRP	0.74	0.58	0.89	**0.013**
APACHE II score	0.86	0.70	1	**0.001**
SIRS	0.77	0.68	0.88	**0.001**
12-24h after admission, n=59				
α-1-microglubulin/creatinine	0.88	0.80	0.97	**0.001**
Albumin/creatinine	0.65	0.52	0.79	0.170
IgG/creatinine	0.51	0.32	0.69	0.938
IgM/creatinine	0.60	0.32	0.69	0.364
hsCRP	0.76	0.63	0.88	**0.001**

AUROC, area under the receiver operating characteristics curve; CI, confidence interval; hsCRP, high sensitivity-C-reactive protein; APACHE II, Acute Physiology and Chronic Health Evaluation II; SIRS, systemic inflammatory response syndrome

Discussion

Factors affecting the natural course of acute pancreatitis

AP is an increasingly common gastroenterological condition and despite extensive research efforts, data regarding the natural history of AP, and factors impacting the disease course are scarce. In our 10-year population-based cohort of patients with first-time AP, alcoholic etiology, smoking, and severity of the index AP episode were related to an increased risk of RAP as well as chronic pancreatitis (paper I).While, systemic and local complications (in particular pancreatic necrosis) predicted RAP as well as chronic pancreatitis, organ failure at first-time AP also predicted RAP. The potential role of the severity of the first-time episode of AP on the natural course of the disease has previously been evaluated only by a few studies (10, 46, 57, 147, 148), and with contradictory results. Our findings appear to be in line with recently published results by Ahmed Ali et al. (149). Contradictory to this, RAP episodes have been found less common following severe, than mild or moderately severe AP, in patients with alcoholic AP (57), as well as after AP of various etiologies (46). However, when comparing results from different studies, discrepancies in severity classification, according to different criteria and/or scoring systems, as well as different diagnosis criteria for etiology and for chronic pancreatitis need to be taken into consideration. In a recent prospective study, AP severity, according to the revised Atlanta criteria (49), as in the papers included in this thesis, was related to the development of chronic pancreatitis (148). In contrast, results from other studies, have shown no association between severity of incident AP, assessed with the APACHE II, the Ranson (10) or the Japanese severity scores (46), and the progression to chronic pancreatitis.

Prediction of recurrent acute pancreatitis and chronic pancreatitis

After a first episode of AP, we found that 23% of the patients experienced one or more RAP episodes, most frequently after alcoholic index AP. This is in line with the results from previous population-based studies (10, 11, 46), as well as with a more recent review of 14 studies on the progression from acute to chronic pancreatitis. The prevalence of chronic pancreatitis after an incident AP episode was, however, 10% in this meta-analysis, which is somewhat higher than in our series (150). It has been

argued that acute and chronic pancreatitis are two separate diseases and that AP rarely progresses to chronic pancreatitis (71, 151). However, our findings, that increased severity of first-time AP (in particular with pancreatic necrosis) and attacks of RAP, are both associated with the development of chronic pancreatitis during follow-up, indicates that AP can progress to chronic disease. These results appear to be in line with the necrosis-fibrosis sequence hypothesis for the pathogenesis of chronic pancreatitis (72, 152), and with recently reported data from a prospective Dutch study (149).

The cause of RAP is, in most cases, similar to the cause of first-time AP. Therefore, in order to prevent RAP, the factor causing the incident AP episode needs to be identified and corrected (153, 154). However, despite advances in imaging procedures and laboratory tests, there is still a substantial proportion of patients where no cause of AP can be established, while multiple etiologies or various cofactors have been proposed to be present in some cases (25, 155). In patients with alcoholic AP, extensive alcohol counselling is considered an important intervention in order to reduce the risk of RAP episodes (156). Alcohol counselling in our study cohort (paper I), did not appear to have any impact on either RAP episodes or progression to chronic pancreatitis, in line with results from an Irish study (157). Our results might, however, be due to the limited number of cases, whereas only 20% of alcoholic first-time AP patients, were offered misuse counselling during hospitalization. In addition, we have only limited information about the number of patients who actually underwent the interventions recommended after index admission. Nevertheless, alcohol counselling or treatment for patients with alcoholic AP should be emphasized and included in AP guidelines.

In addition to alcohol, smoking has been identified as an independent and dose-dependent risk factor for acute (58, 158) as well as chronic pancreatitis (10, 150, 159). In paper I, smoking was a predictor of RAP and chronic pancreatitis, in line with previously published data (160). However, we could not find any documentation, in any medical files, regarding counselling or recommendations on smoking cessation, from the treating clinicians, neither at incident nor recurrent AP episodes. While it has been proposed that smoking is still under recognized as a risk factor for acute and chronic pancreatitis (75), our findings further implicate that more efforts are needed to establish clinical routines for identification of smoking habits as well as for counselling on smoking cessation.

In patients with mild biliary AP, early cholecystectomy (during index admission for AP) is recommended (59, 60), in order to prevent recurrent biliary events, including AP. Nevertheless, previous studies have shown low adherence to guidelines on the timing of cholecystectomy following biliary AP (161, 162) and in keeping with this, we found that only about 20% of the patients with biliary AP, and no prior cholecystectomy, were operated during index admission, which is lower than the rate from a previous meta-analysis (63), although somewhat higher than that from an older Swedish study (65). Furthermore, our findings support previous results, showing that

delayed cholecystectomy following biliary AP is associated to increased risk of RAP (63, 161). While recurrent episodes of AP have been proposed, by some researchers, to be less severe and to have lower mortality rates compared to first-time AP (16, 85, 148), this has been questioned by others (68-70). We found that inhospital mortality upon RAP was similar to the inhospital mortality upon first-time AP, although in patients with biliary AP, mortality was significantly higher during RAP than during index AP. Among the biliary AP patients who died during RAP some had significant comorbidity, and were therefore not planned for surgery. However, some died after awaiting cholecystectomy, for unacceptably long time, after a severe index AP episode, and only a couple had undergone prophylactic endoscopic sphincterotomy. These findings further stress the importance of early cholecystectomy for patients with biliary AP as well as, in selected cases, endoscopic sphincterotomy, as widely recommended (63, 64, 162).

The role of pancreatitis-associated drugs on acute pancreatitis

In paper II, we found, similar to the results by Vinklerová et al. (39), that drug-induced AP represented the third most common etiology (after gallstones and alcohol). Furthermore, in the catchment area of our study, the incidence of drug-induced AP increased during the study period, which has also been reported by a previous Danish study (35). Whether this represents a true increase or merely reflects improvements in identification and reporting of drug-related AP cases remains however unknown.

Pancreatic toxicity due to drug use is a well-established cause of AP (27), although most of our knowledge about drug-induced AP is based merely on data from case-reports of various quality. The validity of these data have been questioned for several reasons. Besides the problem that only a small number of adverse drug reactions are reported, it is likely that AP cases due to drugs previously associated with AP are more frequently recognised. In addition, new drugs are more carefully monitored, while older drugs might be considered to be "safe" (31). The use of some drugs, such as PPIs, systemic antibacterials, and azathioprine, have been reported to be used more frequently in patients with AP compared to the general population (28-30, 34, 163), and patients using multiple drugs have been overrepresented among idiopathic AP cases (164). Recently, a Swedish population-based case control study showed a dose-response relation between polypharmacy and the risk of AP (165). In paper II, almost half of the AP patients used one or more pancreatitis-associated drugs, which is in line with the results from a Dutch report (34). However, the frequent use of AP-associated drugs in patients with various AP etiologies, along with the fact that other risk factors for AP, such as comorbid illness (like inflammatory bowel disease or diabetes) and smoking,

are often present, makes causality assessment of drug-induced AP difficult (28, 29, 31, 166, 167). There are discrepancies between epidemiological data and adverse reaction case reports (30, 168-171), as well as between different epidemiological studies (28-30, 36), on the potential role of AP-associated drugs.

In addition to previously described difficulties to ascertain causality relations between drugs and AP, a couple of frequently used drugs, like simvastatin (170, 172-174) and NSAIDs (27, 38, 175), have been reported to induce as well as to protect from AP. Similarly, ARBs are included in the classification by Badalov et al. (27), although a recent Swedish case-control study found that the use of ARBs lowered the risk for developing AP (176). Furthermore, while azathioprine is one of the most frequently reported drugs implied to cause AP, this seems to apply only to patients with inflammatory bowel diseases, in particular Crohn´s disease. Patients treated with azathioprine for autoimmune hepatitis, or after renal or liver transplantation do not experience AP to the same extent (177, 178).

The use of AP-associated drugs in the general population, appeared to be unrelated to the age-adjusted incidence of AP, in our study cohort, with the exception of drug-induced AP, which correlated with class Ia drug user rates in both genders. Although we have identified significant increases in the user rates of AP-associated drugs in AP patients, as well as in the general population, the age-adjusted incidence rate of idiopathic AP has remained unchanged during the 10-year study period. It has, further, been proposed that AP-associated drugs might modify the clinical course of AP and to possibly have an impact on its severity (34). In a previous Danish study, drug-induced AP cases were more often severe compared to AP cases of other etiologies, however this might have been due to reporting biases or to confounders, like comorbid illness (35). We found the cases of drug-induced AP, in our cohort, generally presenting with a mild disease course, in line with other reports (34, 37, 39). After adjusting for confounders, i.e. comorbidity and older age, use of AP-associated drugs was not found to have any impact on severity of first-time AP. In addition, while certain drugs have been related to severe AP (27), the use of these drugs were not more common in patients with severe compared to mild or moderate AP in our study population.

The role of alcohol consumption on acute pancreatitis

During the 10-year period of our studies, overall alcohol sales and consumption decreased, which is in accordance with previous reports from Sweden (179). In particular, alcohol consumption among young Swedish residents has decreased and the proportion of non-drinkers has doubled during the last decades (180, 181). In paper IV, we found that the incidence of alcoholic first-time AP remained fairly unchanged during the study period, and was unrelated to the changes in alcohol sales and

consumption. The relation between the occurrence of AP and alcohol sales or consumption is not well studied, and the results from previous studies are conflicting. According to one report, on data from 14 different countries, the overall changes in alcohol sales correlated to changes in the mortality rate due to pancreatitis, although this included mortality due to AP as well as chronic pancreatitis (182). A few studies have reported increasing trends of admissions for alcoholic AP, in correlation with increased per capita alcohol consumption (18, 89, 96, 183). In contrast, Sand et al. found no correlation between hospitalizations for alcoholic AP and alcohol consumption in the general Finish population (88), which is in line with our results. The potential effects on the occurrence of alcohol-associated conditions and events, due to changes in alcohol consumption in the general population, are challenging to estimate. Furthermore, it is not clear whether overall mean changes in alcohol consumption, or rather the patterns of drinking have the biggest impact on various forms of alcohol-related harm (181, 184, 185). Heavy episodic drinking is associated with alcohol-related violence, while long-term alcohol abuse rather increases the risk for alcohol-related diseases (186, 187). Associations between periods of higher alcohol consumption and the number of alcohol-related intoxications (93) and road accidents (188) have previously been reported, although it is not clear whether alcohol-related diseases, i.e. AP, follow the same pattern. The occurrence of AP (alcoholic or non-alcoholic), in our study cohort, did not show any significant fluctuations over the seasons of the year or in association to certain holidays with higher alcohol consumption in Sweden. Our results are in keeping with the results of a German study that did not find any increase in the occurrence of AP during the Octoberfest (100). This may be explained by that a long-term period of high alcohol consumption represents a higher risk for AP than occasional episodes of binge drinking (189). On the contrary, other reports have found elevated rates of alcoholic AP associated to certain calendar months with higher alcohol consumption (98), during Christmas and New Year's Eve (18), and in association with national festivals (190).

Similar to drug-induced AP, alcoholic AP is often associated with several confounding factors. Epidemiological studies have previously shown that only a minority of heavy drinkers develop acute pancreatitis (22, 24) and it has been suggested that additional factors (i.e. genetic variations, smoking or dietary factors) triggers the inflammation in alcoholic pancreatitis (19, 25, 191, 192). Gallstone disease represents another confounding factor and it is conceivable, although not well studied, that there might be an overlap between gallstones and a high alcohol intake in some AP patients. On the other hand, there is also some evidence supporting that a moderate alcohol intake is associated with lower risk of gallstone disease (193) as well as AP (194), and that the relation between alcohol intake and risk for AP might differ between men and women (194, 195).

Prediction of severity in acute pancreatitis

Rigorous efforts have been made in order to find reliable and clinically applicable methods, to identify patients at risk of experiencing a severe AP course. Despite the development of several scoring systems as well as the evaluation of numerous biomarkers, no accurate and universally accepted clinical predictor of AP severity exists.

Only a few previous studies have evaluated the predictive value of microproteinuria on AP severity (137, 138). These included small study samples and the results were not unanimous. The first study, with a sample of 20 AP patients, found that higher levels of albumin and IgG in urine correlated to a more severe AP course (137). Contradictory to this, and to our results in paper III, a more recent study could not demonstrate any relation between total urinary protein excretion and AP severity (138). It is, however, worth to consider that urinary excretion of total protein represents a non-specific marker, and that the results from this study may have been confounded by a high degree of urinary amylase excretion (196). Injury to the glomerular filtration barrier can, furthermore, lead to different types of microproteinuria (132), which was not evaluated in this study. Our study (paper III) was, to our knowledge, the first to investigate the value of the urinary excretion of several proteins, widely varying in size, to predict organ failure in patients with AP. In line with the "two pore theory" (197, 198), small proteins, such as α1-microglobulin (28.5 Å) are filtered through "small pores", at the GFB, while larger proteins, including albumin (36 Å) and IgG (55 Å), pass the GFB only through "large pores" (131). The IgM molecule (110-120 Å) is much larger than both the IgG and albumin molecules and can cross the GFB only if it is more severely damaged (132).

We found that biomarkers of microproteinuria, in particular urine α1-microglobulin-, albumin- and IgG/creatinine, were related to parameters of inflammation as well as to severity of AP. The α1-microglobulin/creatinine ratio was an independent predictor of organ failure, showing similar accuracy as the APACHE II score, which makes it a potential early biomarker for prediction of AP severity. Furthermore, even though the urinary IgM/creatinine ratios were increased during the AP episode compared to follow-up, no correlations were observed between the urinary IgM/creatinine ratios and the α-1-microglobulin/creatinine ratios or any marker of systemic inflammation. This suggests that, compared to the excretion of smaller proteins, the urinary IgM excretion is less affected by vascular inflammatory and hormonal conditions (136).

Limitations

In papers I, II and IV all data were retrospectively collected, and ICD-10 discharge codes were used for patient identification. The accuracy of discharge codes in AP studies have been previously investigated. In a systematic review on studies identifying AP patients from administrative data, predictive values for ICD-9 codes showed a broad variation from 40-97 % (199). A Swedish study found that discharge codes for AP were mostly correct, while there was a substantial proportion of false-negative cases of AP, mainly among patients with a diagnosis code of chronic pancreatitis (200). In our papers, the patient records of all cases of AP identified from discharge ICD-10 codes were scrutinized to ascertain a correct diagnosis. We found that 13% of the AP discharge codes were incorrect, and those cases were hence excluded. According to this, there is a possibility that patients with AP have not received a correct AP discharge code and have, therefor not been included in our study population. Furthermore, the patients included in paper I, II and IV have been treated over a 10-year period. During this period the management of AP patients may have changed, which could have had an impact on our results. In addition, some data, such as smoking status, were not available for all patients.

Paper II focused on the potential role of AP-associated medications on a group level and not on single drugs, and no reliable data on the duration of treatment were available. We cannot exclude that certain individual drugs, might have had an impact on the development of AP, in particular among individual patients with idiopathic AP. In addition, although we believe that we have included all first-time AP patients with an AP discharge code, we could perhaps have drawn more firm conclusions on the role of AP-associated drugs, if we had included a matched control group of patients without AP. Furthermore, several new drugs have been developed after the publication of Badalov´s (27) classification and a number of case reports on drug-induced AP have been published. We have not been able to systematically evaluate these new drugs and studies, and it is possible that this might have influenced our results.

In paper IV, alcohol consumption data were based on self-reported estimates and it has previously been suggested that there might be a discrepancy between the self-reported alcohol consumption and alcohol sale statistics (144), although previous methodological studies have confirmed that self-reported data on alcohol consumption could be considered valid and reliable (201-203). The data on alcohol sales and consumption, used in paper IV, showed equal trends. Furthermore, the kind of data used in our paper, have been collected in the same manner, and by the same institution, for more than 15 years, and the trends of alcohol consumption have been rather stable, throughout these years (179). Nevertheless, our results may not be applicable to other areas or populations, in other countries or even to other parts of Sweden. We have studied an area in the south of Sweden, geographically close to Denmark and Germany,

from where a substantial proportion of the unregistered alcohol sales, in Sweden, derive. While the data on alcohol sales and consumption, used in the paper includes registered as well as unregistered sales data, we cannot assure that they are comparable to other regions.

In paper III, our study sample was somewhat small, leading to a small number of patients with organ failure and complications due to AP. Although our results indicated a significant relation between the urinary excretion of various proteins (in particular the α1-microglobulin) and the development of organ failure, this needs to be further evaluated in larger study samples. Furthermore, urine samples on admission were obtained from all patients, while samples 12-24 hours after admission as well as from follow-up, were not collected from all patients.

Finally, it cannot be ascertained that statistically significant correlations in the papers included in this thesis, represent causal relations. There might have been confounders or certain characteristics in our study population, which we have not identified, and that could have influenced or results. Further population-based studies from different geographical areas are needed in order to confirm our findings.

Conclusions

The major conclusions that could be drawn from the papers included in this thesis were:

I. Severity of first-time AP, smoking and alcoholic etiology predict the occurrence of RAP as well as the development of chronic pancreatitis. RAP is also an independent predictor of progression to chronic pancreatitis. Furthermore, mortality during RAP does not appear to be lower than that at first-time AP, and biliary patients appear to be overrepresented among patients dying during RAP. This, along with the increased occurrence of RAP in relation to delayed interval cholecystectomy, stresses the importance of early cholecystectomy, in accordance with international guidelines.

II. The use of AP-associated drugs is increasingly frequent among AP patients, as well as in the general population. However, the use of these drugs do not seem to have any major impact on the observed epidemiological changes in the incidence of AP, except for a possible relation with the increased incidence of drug-induced AP. Although a large proportion of patients with AP (of known etiology or idiopathic), are using AP-associated medications this do not appear to have a significant effect on the severity of the first-time AP episode or on the occurrence of RAP attacks.

III. Different biomarkers of microproteinuria, in particular urine α1-microglobulin-, albumin- and IgG/creatinine, correlates to parameters of inflammation, as well as to organ failure in AP. Furthermore, the α1-microglobulin/creatinine ratio seems to predict organ failure with similar accuracy as the more complex APACHE II score, and might be a promising early marker of AP severity.

IV. Changes in alcohol consumption, in the general population, do not appear to be related to the incidence of first-time (alcoholic or non-alcoholic) AP. In addition, while certain periods are associated with higher alcohol consumption in Sweden, the occurrence of AP during these periods do not appear to be higher.

Future perspectives

Rigorous research efforts on AP have resulted in advances in our understanding of the disease, and improved clinical management of the patients, although there is still a lot to learn about the pathophysiology and natural course of AP. Early prediction of AP severity is of great clinical importance and the search for an applicable and valid assessment method continuous. We have found that the α1-microglobulin/creatinine ratio correlated to organ failure in patients with AP, and it is conceivable that microproteinuria biomarkers, in particular α1-microglobulin, may develop into promising and clinically applicable early predictors of AP severity. These findings need, however, to be confirmed in larger prospective, multi-center studies including more patients with organ failure and severe AP.

Alcohol is a well-known risk factor for AP, RAP and chronic pancreatitis. However, there are several confounding factors associated with alcohol consumption and pancreatitis. While our results indicate that only a minority of patients with alcoholic AP receive any kind of alcohol misuse counselling, the actual influence by different interventions on the progression and recurrence of AP is scarcely studied. More randomized controlled trials would be needed to evaluate the effect and outcome on alcohol counselling and treatment (including drug therapy) of patients with alcoholic AP. In addition, alcohol and smoking are associated to acute as well as to recurrent and chronic pancreatitis, and smoking has further been identified as one of the main factors impairing the quality of life in patients with chronic pancreatitis (204). Directions and recommendations for clinical interventions and counselling for abstinence, of alcohol and tobacco, are included in recently published guidelines for the diagnosis and therapy of chronic pancreatitis (205), but should also be included in guidelines for AP.

The thorough review and classification of drugs reported to cause AP (27), used in paper II, is to date the latest published classification. However, several new medications have been developed since this publication and some drugs originally not included in the classification have later been reported to have caused AP. An up-dated evidence-based classification, including new drugs, is clearly warranted, as well as larger prospective, multicentre pharmaco-epidemiologic studies in this area.

Finally, there is a paucity of research data regarding patient experiences of AP, as well as the physical and mental recovery, and quality of life after a first and subsequent AP episodes. Anxiety and depression is known to be related to increased alcohol

consumption, although there are no data on the potential role of psychological distress on (alcoholic and non-alcoholic) AP. It is, in particular, unknown if depression might co-occur with AP, or if patients are at risk to develop depression after an AP episode. An elevated risk for psychological distress after AP might in turn increase the risk for alcohol misuse and thereby the risk of recurrent AP episodes. More knowledge in this area is needed in order to implement accurate treatment and follow-up strategies.

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