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DOCTORAL SCHOOL

MEDICINE

BUC-API REGISTRY – AN ANALYSIS REGARDING EPIDEMIOLOGY, EVOLUTION AND COSTS IN ACUTE PANCREATITIS

- PHD THESIS SUMMARY -

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LIST OF SCIENTIFIC PUBLICATIONS

1. **MR Pahomeanu***, D Ojog, DT Nițu, IȘ Diaconu, H Nayyerani, L Negreanu – Acute Pancreatitis and Type 2 Diabetes Mellitus: the Chicken–Egg Paradox — a Seven-Year Experience of a Large Tertiary Center – Journal of Clinical Medicine, 13(5), 1213, 2024. https://doi.org/10.3390/jcm13051213
   (Capitolul 5)
   Articol original, ISI, Q2 – Medicine, General & Internal, IF = 3,9
2. **MR Pahomeanu***, DI Constantinescu, IȘ Diaconu, DG Corbu, L Negreanu -Acute Pancreatitis—Drivers of Hospitalisation Cost—A Seven-Year Retrospective Study from a Large Tertiary Center – Healthcare, 11 (18), 2482, 2023. https://doi.org/10.3390/healthcare11182482
   (Capitolul 6)
   Articol original, ISI, Q2 – Public Health, IF = 2,8
3. AI Ghiță, **MR Pahomeanu***, L Negreanu – Epidemiological trends in acute pancreatitis: A retrospective cohort in a tertiary center over a seven year period, World Journal of Methodology, 13 (3), pg. 118-126, 2023 https://doi.org/10.5662/wjm.v13.i3.118
   (Capitolul 7)
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4. AI Ghiță, M Olteanu, AE Debelka, OM Cîlțea, **MR Pahomeanu*** - Unveiling the Unexpected: Co-occurrence of Acute Pancreatitis and Riedel's Lobe, Cureus 16 (1), 2024. https://doi.org/10.7759/cureus.52325
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   Prezentare de caz, ISI, Q4 – Medicine, General & Internal, IF = 1,2
5. **MR Pahomeanu**, RB Mateescu, B Dorobăț, L Negreanu* – An Angiographic Treatment for a Pancreatic Pseudoaneurysm, Medicina Modernă, 27 (1), 70, 2020. https://doi.org/10.31689/rmm.2020.27.1.69
   (Capitolul 9)
   Prezentare de caz, BDI – Scopus

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INTRODUCTION

Acute pancreatitis represents a commonly encountered pathology in gastroenterological and surgical services worldwide. In 2018, AF Perry and others estimated a number of 626,769 diagnoses of acute pancreatitis in the United States [1]. Particularly for Romania, a study published in 2021 [2] based on data from the Global Burden of Disease Study 2019 estimated a number of approximately 14,000 cases and 1,042 annual deaths.

Acute pancreatitis is an appealing topic for research, presenting regional variations regarding etiology, costs, case evolution, and a wide heterogeneity concerning therapeutic protocols. The scarcity of data in Romania regarding simple but fundamental topics for describing any pathological phenomenon, such as epidemiology, evolution, and hospitalization costs, has inspired us in choosing the doctoral theme. We consider the data we will present throughout this thesis as a cornerstone for further in-depth research into this pathology.

Medical data of interest were obtained from the electronic archiving system of SUUB and were indexed for statistical analysis in the Bucharest Acute Pancreatitis Index (BUC-API) registry. After the general description of the population and cost analysis, we sought to categorize patients into groups sorted by etiology, precisely to observe phenomena associated with etiology. Regarding epidemiology, we observed that patients in gastroenterology and internal medicine services had alcohol as the predominant etiology (45.7%); the median length of hospitalization is 7 days; severe forms (according to the Revised Atlanta Classification [3]) represented 11.1%; in-hospital mortality rate: 5.5%. Based on the number of cases admitted to SUUB and the population served by this hospital, we estimated an incidence of 29.2 cases/100,000 persons.

Cost analysis estimated a total cost of hospitalizations caused by acute pancreatitis in Romania of approximately 19 million USD. Those of biliary cause required significantly more material resources. Comparing cases where diabetes coexisted, we observed a higher probability of developing severe forms of the disease and consequently a higher risk of admission to intensive care services.

The main limitation of the studies conducted within this doctoral thesis is represented by its retrospective nature; however, we consider the large number of analyzed patients a strong point. Prospective studies and/or international meta-analyses are necessary for validating the obtained results.

I. GENERAL PART

1. Acute pancreatitis

1.1. Pancreas – generalities

The pancreas, a retroperitoneal organ, is a gland with a mixed function (endocrine and exocrine), embryologically originating from the endoderm and composed of two buds, dorsal and ventral [4], which fuse in the seventh week of intrauterine life. It represents a key organ both in the assimilation of food principles and subsequently in the regulation of carbohydrate metabolism. It consists of: head and uncinate process, body, tail.

The head of the pancreas, with a relatively circular shape, is the most voluminous part of the gland and is located to the right of the median line, in the curve formed by the duodenal frame. Its upper part is anteriorly related to the duodenal bulb, and through the concavity of its duodenal margin, it will come into close relation with the descending portion, being almost adherent to its wall. Its lower margin will be superior to the horizontal part of the duodenum and will continue caudally and to the left with the uncinate process.

The body is similar to an elongated triangular prism. This segment gradually narrows towards the lateral part, where it continues with the tail of the gland. The body has three margins - anterior, superior, and inferior - which delimit three distinct faces. The tail, the only intraperitoneal component, is located within the splenorenal ligament and is the most lateral portion of the pancreas, reaching in many cases up to the splenic hilum. [5]

The pancreatic ductal system consists of the main duct (Wirsung) and the accessory duct (Santorini), through which the exocrine substance is collected from the lobular ducts and transported to be emptied into the second segment of the duodenum. These ducts together form a dilation called the Vater's ampulla, which closes through the Oddi sphincter. This ampulla opens obliquely into the duodenum, forming a prominence called the major duodenal papilla. The accessory canal may be absent, occurring in about 20% of people.

From an arterial vascularization perspective, the head and neck of the pancreas are mainly supplied by the two pancreaticoduodenal arcades, each formed by the superior and inferior pancreaticoduodenal arteries. In turn, the inferior artery originates from the superior mesenteric artery and the superior one being a branch of the common hepatic artery via the gastroduodenal artery. Essentially, the cephalo-pancreatic vascularization represents a system of anastomoses between two large arterial systems, the mesenteric and celiac. However, the body and tail are supplied by branches of the splenic artery, part of the celiac artery basin. [6]

Venous drainage is predominantly provided by tributaries of the portal vein, specifically cephalic through the superior and inferior pancreaticoduodenal veins. Although paradoxically the splenic vein passes posterior-inferiorly through the tail and body of the pancreas, it mostly lies within a fibrous capsule and thus drains through few tributaries (between 5 and 12), partially of the tail and body. Lymphatic drainage anatomically resembles arterial distribution, so the body and tail drain into retro-pancreatic nodes, while the head drains into celiac and superior mesenteric nodes. [6]

Histologically, the pancreas presents two types of arrangements: the Langerhans [7] islets (endocrine pancreas) and the pancreatic acini (exocrine pancreas).

As an exocrine gland, the pancreas secretes the following compounds: $NaHCO_3$ (for neutralizing gastric acid secretion) and enzymes necessary for facilitating the absorption and chemical digestion of all food principles, namely:

- Proteins: chymotrypsin (subsequently activated to trypsin) and carboxypolypeptidase;

- Carbohydrates: pancreatic amylase;

- Lipids: pancreatic lipase, cholesterol esterase, phospholipase.

1.2. Patogenesis

Acute pancreatitis develops when the factors that maintain cellular homeostasis become imbalanced. The precipitating event can refer, without limitation, to: alcohol abuse, biliary pathologies, medications, metabolic imbalances, etc. Currently, the pathogenetic trigger is uncertain, and theories are based on animal models [8]. It is presumed that both extracellular and intracellular factors collaborate in the onset of the pathology. Cellular injury leads to the activation of zymogens with the transformation of trypsinogen into trypsin, the release of intracellular calcium, and the activation of the pro-inflammatory cascade. Neutrophil recruitment to the focus leads to their degranulation and the release of superoxide and proteolytic enzymes (cathepsins, collagenases, and elastases).

1.3. Clinical presentation

The cardinal symptom that prompts the patient to seek medical attention is represented by the "bar-like" pain (supramesocolic, with the main location in the epigastrium but variable depending on the affected segment) radiating towards the right hypochondrium, left hypochondrium, and posteriorly towards the loins. The pain is predominantly early

postprandial, with the activation of the cephalic phase of digestion, constant in nature, and with slow improvement (days) [9]. The classic antalgic position described in acute pancreatitis is that of the trunk bent over the abdomen and the associated psychomotor agitation due to minor alleviation of painful phenomena. Pancreatitis pain has also been described as very intense and constrictive in character.

During clinical evaluation, the patient may present the following signs: fever; tachycardia and arterial hypotension (secondary to dehydration due to fluid losses in the extracellular space), abdominal pain with muscular defense, decreased bowel sounds down to intestinal silence, scleroicterus (if there is cephalopancreatic involvement), muscle spasms (secondary to hypocalcemia). Clinical signs of severity may include: Cullen's sign (peri-umbilical skin discoloration) and Grey-Turner's sign. [10]

1.4. Differential diagnosis

Table 1 – Summary of diferential diagnosis

Pathology	Differential characteristics
Perforated peptic disease	Abdominal plain X-ray will show pneumoperitoneum
Biliary pain	Main location: right hipocondrum, limited to several hours and repeated; US signs.
Intestinal obstruction	Colicky pain; persistent vomiting (possibly faecal)
Mesenteric infrarction	Bloody diarheea
Duodenal diverticulitis	CT scan
Lower lobar pneumonia	Presence of respiratory symptoms
Myocardial infraction	Electrocardiogram; elevated levels of troponins I and T and creatine-kinase
Renal/ureteral colic	Intermittent lumbar pain radiating to the groin

1.5. Laboratory

The serum activity of amylase presents significant limitations in both sensitivity and specificity. Amylase activity is highly volatile, increasing several hours after the onset of pancreatic cytolysis syndrome and normalizing around 72 hours. Serum lipase appears to be more specific for pancreatic-origin cytolysis and has better persistence than amylase. Its limitations, however, lie in the lack of a positive predictive value and increases associated with pathologies from other systems or organs such as acute cholecystitis, appendicitis, and false elevation due to chronic kidney disease through decreased urinary excretion. [11]

Abdominal imaging can represent a method of confirming the diagnosis. While abdominal ultrasound may be useful primarily in describing the biliary system and excluding or confirming a biliary cause, its sensitivity for pancreatic description decreases due to anatomical or functional considerations [12]. The current gold standard in pancreatic imaging is considered to be abdominal CT with contrast, which has a sensitivity of over 90% [13]. However, current guidelines recommend postponing CT examination to approximately 72 hours from the onset of symptoms to accurately describe the evolution of pancreatic parenchyma. EUS, although cited in the literature [14] as an imaging investigation method of the pancreas with potential applicability in acute pancreatitis, remains rarely used in the aforementioned pathology but represents an extremely efficient tool in managing its local complications.

The Bedside Index for Severity in Acute Pancreatitis (BiSAP) [15] is a score developed in 2008 by a group of researchers from the USA. The score takes into account: serum urea level (above 25mg/dL); mental status (evaluated by the Glasgow score, below 15 points); presence of SIRS; age over 60 years; presence of pleural effusions on imaging investigations. Each of the above criteria is scored with one point. Stratification was based on the risk of mortality, namely a result greater than or equal to 3 points indicating a case with a higher probability of mortality (over 15%). As observed, the score is easy to perform even under conditions with relatively limited resources, easy to learn, and has better prediction rates than Ranson and similar to APACHE-II according to a prospective study published in 2018. [16]

1.6. Positive diagnosis

According to the American Gastroenterological Association Guidelines [13], to diagnose acute pancreatitis, we need a minimum of 2 out of the following 3 criteria:

1. Clinical criterion: Supramesocolic "bar-like" pain, usually located in the epigastric region and radiating to both hypochondria and posteriorly to the loins. Violent, continuous character, precipitated postprandially.

2. Biological criterion: Serum amylase activity, or preferably serum lipase activity, at least 3 times above the maximum reference value.

3. Imaging criterion: Evidence of acute pancreatitis on ultrasound, CT, or MRI.

1.7. Complications

According to the revised Atlanta criteria, the local complications of acute pancreatitis (AP) can be of two types: fluid (acute peripancreatic collections or pseudocysts) and necrotic (acute necrotic collection, delimited necrosis). Necrotic collections can be complicated by bacterial superinfection leading to pancreatic abscess formation. Pancreatic pseudocysts can, in turn, be complicated by pseudoaneurysms when they erode into a vascular structure, most commonly the splenic artery. Pseudoaneurysms can further complicate matters by causing hemosuccus pancreaticus and upper gastrointestinal bleeding [17]. Other less common complications include abdominal compartment syndrome, metabolic acidosis, acute kidney injury due to hypovolemia, ARDS, ascites, mesenteric infarction, disseminated intravascular coagulation, gastric varices, paralytic ileus, and thrombosis of the mesenteric and splenic veins. [18]

1.8. Treatment

According to the AGA [19] guideline for the management of acute pancreatitis (AP) in the early phase, volume repletion is recommended to avoid hypovolemia due to fluid losses in the retroperitoneal space, guided by: blood pressure, serum urea, diuresis, and heart rate. Despite the guideline not differentiating between normal saline and Ringer's lactate, a recent meta-analysis [20] suggests the superiority of Ringer's lactate in reducing the incidence of SIRS at 24 hours and shortening the duration of hospitalization. To maintain volume, the guideline advises against the use of plasma expander solutions. In the absence of evidence regarding the superinfection of necrosis, regardless of severity, the use of prophylactic antibiotics is contraindicated. Supportive treatment includes: analgesic therapy, which can be escalated to opioids, antipyretic therapy, gastric prokinetic agents to counteract the emetic syndrome, and

eventual vitamin therapy (B complex) to alleviate the symptoms of alcohol withdrawal if the etiology is alcoholic.

2. Epidemiology of acute pancreatitis

2.1. Etiology in acute pancreatitis

In Table 2, I will summarize the etiologies as they were described in the 10th edition of the gastroenterology treatise "Sleisenger and Fordtran's Gastrointestinal and Liver Disease" [21] and how they were used for stratification in the BUC-API registry.

Table 2 - Etiologies of acute pancreatitis

Obstruction	Gallstones
	Tumors
	Parasites
	Duodenal diverticula
	Annular pancreas
	Choledochocele
Toxins	Ethyl alcohol
	Methyl alcohol
	Scorpion venom
	Organophosphorous insecticides
	Drugs
Metabolic abnormalities	Hypertriglyceridemia
	Diabetes mellitus
	Hypercalcemia
Infection	CMV, EBV, HSV, SARS-CoV2 etc.
Vascular disorders	Vasculitis
	Emboli to pancreatic blood vessels
	Hypotension/ischemia
Trauma	Abdominal trauma
	Postoperative state
Post-ERCP	
Hereditary/familial/genetic	
Controversial	Pancreas divisum

	SOD
Idiopathic	

2.2. Severity in acute pancreatitis

At present, the gold standard in classifying the severity of acute pancreatitis (AP) is represented by the one proposed in 2013 by the revised Atlanta criteria [3]. Please see Table 3 in full. Although very clear and reliably associated with the risk of mortality, the mentioned classification can only be performed retrospectively and cannot prevent the augmentation of severity class. For this reason, numerous prediction systems have been devised. According to a systematic review from 2020 [21], none of the currently widely accepted scoring systems provide satisfactory sensitivity and specificity.

Table 3 - Revised Atlanta criteria for severity stratification

Mild	Moderately-Severe	Severe
		Persistent organ failure (>48h), together with the following:
No organ failure	Transitory organ failure (<48h)	Unique organ failure
No local or systemic complications	Local or systemic complications without persistent organ failure	Multiple organ failure

2.3. Hospital mortality in acute pancreatitis

Based on an international, prospective study [23] that included patients from Romania and was conducted under the auspices of the APPRENTICE registry (University of Pittsburgh, USA), large transcontinental variations in mortality rates are observed. Mortality rates range from 0.6% in North America to 5.7% in Europe. In Europe, particularly in Romania, the highest mortality rate was reported in this study, namely 8.6%. However, a recent prospective study from Poland [24] suggests an in-hospital mortality rate similar to that predicted for Romania, at 7.1%.

The excessive variability in in-hospital mortality rates in AP may primarily stem from environmental and/or genetic factors that each population faces at any given time. Considering

that there is little variability regarding the definition of mortality and it represents a major event, I thus consider methodological differences less relevant in this particular aspect.

2.4. Costs of acute pancreatitis

The main sources of data regarding the cost of hospitalizations for patients with acute pancreatitis (AP) come from North America. In 2007, a study conducted by Fagenholz et al. [25] estimated the total cost of hospital care associated with AP in the USA at 2.2 billion USD in 2003, with an average total hospitalization cost of approximately 9870 USD and an average daily cost of around 1670 USD. The aforementioned study identifies potential risk factors for increased costs: advanced age, hospitalization in an urban university hospital, and prolonged length of stay.

At the time of writing this doctoral thesis, except for the results obtained from it, we have not been able to identify in the specialized literature written in English, French, or Romanian any published studies discussing the cost situation of AP cases in Romania. However, we do not completely exclude the existence of such studies.

II. PERSONAL CONTRIBUTIONS

3. Hypothesis and main objectives

3.1. Hypothesis

Within this doctoral thesis, we have theorized the existence of significant epidemiological differences among hospitalized patients with acute pancreatitis (AP) in Romania compared to other countries. The heterogeneity of epidemiological results across retrospective cohorts from different regions/states is a consequence of a dynamic interaction between environmental, cultural, and dietary factors. The interaction of these factors with other elements, such as genetic background (relatively similar at the continental level but strongly different in transcontinental analyses) and/or the organization of the medical system (which not only influences costs but also health-promoting habits for primary prevention purposes), leads to the emergence of particular national profiles in many other studied cases.

The different national profiles of the same disease suggest a close interrelationship between causal and potential aggravating factors of AP and the aforementioned elements. Therefore, we consider that the specific profile of AP in Romania must also be identified.

3.2. Main and secondary objectives

The main objective of this doctoral research was to identify the general profile of the population affected by acute pancreatitis (AP) in Romania and compare it with similar data from other regions. Achieving the aforementioned goal was accomplished through a series of secondary objectives, namely:

1. Estimating the financial burden caused by AP on the national healthcare system in Romania;

2. Estimating the hospitalization costs of AP in our center, including: average daily cost, average total cost;

3. Identifying factors that may lead to increased hospitalization costs;

4. Establishing the proportion of each etiology in the study cohort;

5. Estimating the rate of local complications in the study cohort;

6. Estimating the incidence rate in the region served by our center;

7. Identifying the severity profile of the pathology in the study cohort;

8. Identifying the transfer rate to the Intensive Care Unit (ICU) in the study cohort;

9. Establishing the proportions of discharge outcomes, including: improvement/healing rate and in-hospital mortality rate;

10. Estimating the in-hospital mortality rate of patients with AP associated with diabetes mellitus (DM);

11. Identifying the severity profile of AP associated with DM and comparing it with the rest of the AP cases;

12. Publishing specific cases of AP to increase the data available in the literature.

4. General research methodology

4.1. Approach of the theme

For this doctoral research, the BUC-API (Bucharest Acute Pancreatitis Index) registry was established to organize patient data. The establishment of the registry was initially based on identifying all consecutive discharges from SUUB (University Emergency Hospital

Bucharest) coded with the following ICD-10 codes: K85, B26.3, B25.2, during the period from June 1, 2015, to April 1, 2022. We strictly processed the discharge documents of the captured cases. Thus, 2470 consecutively discharged cases were identified from the following Clinics of SUUB: Gastroenterology II, Gastroenterology I, Internal Medicine II, General Surgery I, General Surgery II, General Surgery III, General Surgery IV, and the former Internal Medicine III Clinic. The BUC-API registry obtained approval from the SUUB Ethics Committee in 2021.

4.2. Patients and methodology

For inclusion in the BUC-API registry and subsequent statistical analysis of cases, we used the following inclusion criteria, necessary criteria for the positive diagnosis of AP according to the current guidelines mentioned in section 1.6., namely a minimum of two of the following three criteria:

1. Clinical criterion - epigastric pain radiating to the back and loins, worsened postprandially at around 1-2 hours and potentially accompanied by phenomena such as nausea, vomiting, anorexia, Cullen and Grey-Turner signs;

2. Biological criterion - elevation of serum lipase and/or amylase activity to more than 3 times the maximum reference value;

3. Imaging criterion - imaging evidence of AP obtained by the following methods: ultrasonography, computed tomography, magnetic resonance imaging.

For refining cases and data, we used the following exclusion criteria:

1. Age under 18;

2. Imaging signs of chronic pancreatitis - pancreatic duct dilation and/or pancreatic or peripancreatic calcifications;

3. Explicit documentation of chronic pancreatitis in the medical history or current episode;

4. Lack of sufficient data in the extracted documents to establish the diagnosis of AP according to the inclusion criteria;

5. Lack of results from biological investigations performed during hospitalization in the extracted documents.

4.3. Software processing and statistical analysis regarding BUC-API registry

For retrieving data from the electronic database of SUUB, we used the following software: InfoWorld (Infoworld SRL, Romania, European Union) version 2021 and subsequent versions (the electronic database manager of SUUB) and Adobe Acrobat (Adobe Inc., California, USA) versions: 21.007.20099 (until January 11, 2022), later version 21.011.20039. Subsequently, for establishing the registry, we used Google Docs (Alphabet Inc., California, USA) and Microsoft Excel (Microsoft Inc., Washington, USA) version 2019. To protect the database against cyber-attacks and electronic fraud, we used Bitdefender Total Security (Bitdefender SRL, Romania, European Union) versions available after January 1, 2021.

For the statistical analysis of the present studies, we exclusively used SPSS (IBM Inc., New York, USA) version 29.0.1.0. No general statistical studies at the registry level were employed. The statistical studies used were customized for each study according to needs and are described in detail in the following chapters.

5. Acute Pancreatitis and Type 2 Diabetes Mellitus: the Chicken–Egg Paradox — a Seven-Year Experience of a Large Tertiary Center

5.1. Introduction

Two very common diseases, type 2 diabetes (T2D) with a global prevalence estimated at 538 million people in 2021 [26], of which 96% are represented by type 2 diabetes, and acute pancreatitis (AP), which has a global estimated incidence between 2.71 cases per year and 134.9 cases per year per 100,000 people in 2021 [27], present an interrelationship highlighted by multiple studies.

Currently, there is a heated debate in the literature regarding the relationship between AP and T2D. On the one hand, there is evidence that presents AP as a risk factor for T2D [28], while on the other hand, there is evidence that has shown the exact opposite [21,29].

In this study, we present epidemiological data regarding admission to intensive care units and the severity of AP, as described by the revised Atlanta classification (3), in relation to T2D.

5.2. Patients and methods

For ease of statistical analysis, we considered only the first six most common causes of AP, as detailed in Table 2. Wherever we encountered a mix of etiologies, we reported the case as monoe tiological based on the consensus of the authors of the present study. We considered type 2 diabetes (T2D) as a cause of AP if at any time during hospitalization there were biological

signs of decompensated T2D or poorly controlled T2D and no other obvious causes of AP were detected. We used the criteria issued by the American Diabetes Association in 2011 for the de novo diagnosis of T2D [30], namely: HbA1C > 6.5% and/or any random blood glucose determination >200mg/dL. Cases documented to suffer from type 1 diabetes prior to hospitalization were excluded from the study.

The data for this study were organized using Microsoft Office Excel 2019 and Google Docs. The general characteristics presented in Table 5.1 were analyzed using frequency tests. Pearson chi-square, Phi, and Cramer's V tests were used to examine correlations between categorical variables. Additionally, the Mann-Whitney U test was used to check the correlation between categorical and continuous variables. All statistical analyses were performed using IBM SPSS Statistics version 29.0.0.0.

5.3. Results

Cases of male gender were predominant in the studied population (n = 954, 60.7%). The median age of all cases was 57 years, and the median length of hospital stay was 7 days (IQR = 6.0). The median daily cost of hospitalization was 920.9 RON (IQR = 432.5). The majority (82.8%) of the studied cases represented first episodes of AP. Cases of AP associated with type 2 diabetes (T2D) accounted for 3.0% (n = 55) of the total study population. Most of our cases (51.4%) had a mild course of the disease, and the majority presented pancreatic interstitial changes (38.5%). The admission rate to the Intensive Care Unit (ICU) was 9.6%.

The chi-square test used showed a statistically significant association between etiology and severity $X2(df=2) = 20.9$, $p< 0.01$. To verify the strength of the association, we calculated Cramer's V, obtaining a value of +0.12, suggesting a low-strength association between the two variables. Considering that we had a severity classification stratified into 3 levels, we also conducted post-hoc analyses using standardized adjusted residuals (SAR). We thus obtained a SAR of +4.2 in the case of AP-T2D II with severe forms, compared to a SAR of -3.2 in the case of AP-T2D II with mild forms, showing a significant difference compared to the expected frequencies.

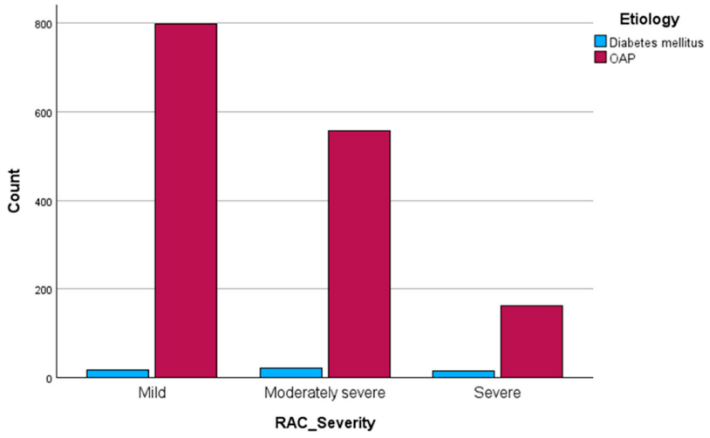

Figure 1 – Comparation of case regarding severity

Table 4 – Clinical and demographical characteristics of T2DM associated cases – only statistically significant situations are presented

	T2DM (n = 55)	Other causes (n = 1517)	p-value
Severity			
Mild	17 (30,9%)	798 (52,6%)	p < 0,01
Moderately-severe	22 (40,0%)	557 (36,7%)	
Severe	16 (29,1%)	162 (10,7%)	
ICU			
No	43 (78,2%)	1394 (91,9%)	p < 0,01
Yes	12 (21,8%)	123 (8,1%)	

A chi-square test was conducted to determine a potential association between etiology and admission to the Intensive Care Unit (ICU). A suggestive association was observed (X^2 (df = 1) = 12.7, $p < 0.01$). To assess the strength of the association, we used Cramer's V test, obtaining a value of +0.09, indicating a weak association between the two variables. To further investigate the nature of the association, we examined the SAR result through post-hoc tests. For admission to the ICU, a SAR of +3.6 was obtained for cases associated with type 2 diabetes (T2D), significantly deviating from the expected frequencies. Using the Mann-Whitney U test, we failed to obtain significant differences in terms of ICU length of stay between the two groups (U = 655.0, Z = -0.6, p = 0.52).

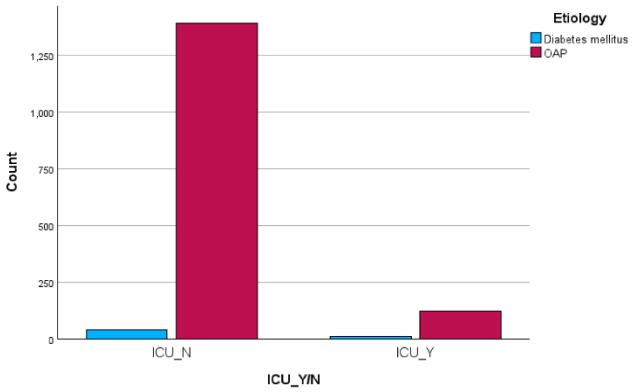

Figure 2 – Case comparison regarding ICU admission

5.4. Conclusions

In this retrospective cohort study based on registry data, we observed a statistically significant association between cases of type 2 diabetes (T2D) associated with poor control and more severe forms of pancreatitis, plus an increased risk of admission to intensive care units (ICUs). The association between diabetes and pancreatitis remains a paradoxical topic, akin to a "chicken-and-egg" scenario. Future studies investigating this type of relationship, likely bidirectional, are warranted.

6. Acute Pancreatitis - Drivers of Hospitalisation Cost - A Seven-Year Retrospective Study from a Large Tertiary Center

6.1. Introduction

AP represents a major burden for all healthcare services globally. The Global Burden of Diseases study estimated in 2019 2.8 million cases of AP annually worldwide, and nationally around 14,000 cases per year, with a calculated incidence of 50.8 cases per 100,000 persons [2]. Regarding the analysis of hospitalization costs, there is a high level of heterogeneity in North American studies and a relative shortage of data in European and Asian regions. In the English and Romanian literature, we have not been able to identify previous studies on the same subject regarding the situation in Romania.

There are significant discrepancies in the estimated cost of hospitalizations for AP in the literature. Variability may stem from multiple sources, among which the most significant may lie in differences in the organization of the healthcare system and/or health insurers. However, regarding Eastern Europe and especially Romania, there is a lack of data, which is why fellow researchers such as Li et al. [2] have issued a call.

In this study, the main target was to estimate the median daily cost (MDC) of hospitalizations related to AP in a large tertiary center in southern Romania, namely SUUB. As secondary targets, we list: the total median cost (TMC), estimating the total cost of hospital care related to AP nationwide, and testing possible associations between MDC and other independent factors such as: the care department, sex, admission to intensive care, discharge outcome, severity, pancreatic morphology, etiology, duration of hospitalization, and age.

6.2. Patients and methods

The costs were extracted from the discharge tickets available in the electronic registry of SUUB as they were calculated at discharge by the financial department. The costs represent the sum of the following factors: hospitalization costs (length of stay multiplied by SUUB's fixed rate), food costs (duration of hospitalization multiplied by the daily allocated food cost), cost of prescribed medications, cost of medical materials, cost of paraclinical and imaging investigations. It is essential to mention that all the above factors are regulated by law (Government Decision no. 696/2021) by the healthcare insurance monopoly (CNAS) and the Ministry of Health. Regulation takes into account multiple factors specific to each tertiary center, such as the number of beds and the medical complexity index of the previous year. Considering that most cost studies in AP originate in the USA and costs are reported in USD, we also decided to report the cost results in the same currency.

From the SUUB electronic records, we obtained values in RON, which were converted to USD at the exchange rate published by the National Bank of Romania on April 1, 2022, namely 1 USD = 4.47 RON. Due to a wide diversity regarding the discharge date, we could not adjust the cost for inflation. For references (31–34) that used EUR to report cost values, we used the EUR – USD exchange rate on the date the manuscripts were submitted to the journals, namely: August 15, 2013, April 7, 2018, March 8, 2008, and March 17, 2014. The MDC was calculated by dividing the total median cost by the number of days of hospitalization.

The data were organized using Microsoft Office Excel 2019 and Google Docs. Frequency tests were performed to analyze the general characteristics of the cohort. To evaluate the homogeneity of the case distribution, the Kolmogorov-Smirnov test was used. In case of a non-normal distribution of the population for comparing the medians, the Kruskal-Wallis test was used, and post-hoc analysis was performed using the Dunn-Bonferroni test to analyze differences between groups when analyzing more than two continuous variables. The Pearson correlation test (two-tailed) was run to observe potential associations between two continuous

variables. All statistical tests were run using IBM SPSS Statistics version 29.0.0.0. For statistical significance, we considered only results associated with a p-value < 0.05. We reported the third decimal of the previous value only when it was close to 0.05. All values in the figures are presented in the original currency, RON.

6.3. Results

In the cohort, the majority of cases were: in males (n = 911, 61.8%), cared for in a gastroenterological profile department (n = 860, 58.4%), presented mild forms of the disease (n = 758, 51.8%), and were discharged as healed or improved (n = 1234, 83.8%). A total of 816 cases (55.4%) presented local complications, with the majority of cases being of alcoholic (n = 517, 35.1%) and biliary (n = 509, 34.6%) causes. 125 cases (8.5%) required intensive care therapy. The reported mortality rate was 5.2% (n = 77).

The MDC reported was 203.8 USD (IQR = 95.5) and the median total hospitalization cost was 1360.5 USD (IQR = 1241.6). Based on the Global Burden of Disease 2019 study, as reported by Li et al. (2), which estimated 14037.2 cases-year of AP at the national level and the estimates related to the total hospitalization cost, we managed to calculate an annual total cost of financial burden related to AP hospitalizations in Romania at 19 million USD (19097610.6 USD).

We used the Kolmogorov-Smirnov test to verify the homogeneity of the distribution of the four studied etiological groups. Thus, we observed that none of the groups had a normal distribution regarding the MDC. We obtained the following values: for the alcoholic group D (517) = 0.17, p < 0.01; for the biliary D (509) = 0.48, p < 0.01; for the hypertriglyceridemic D (80) = 0.26, p < 0.01, and for the diabetic D (62) = 0.32, p < 0.01.

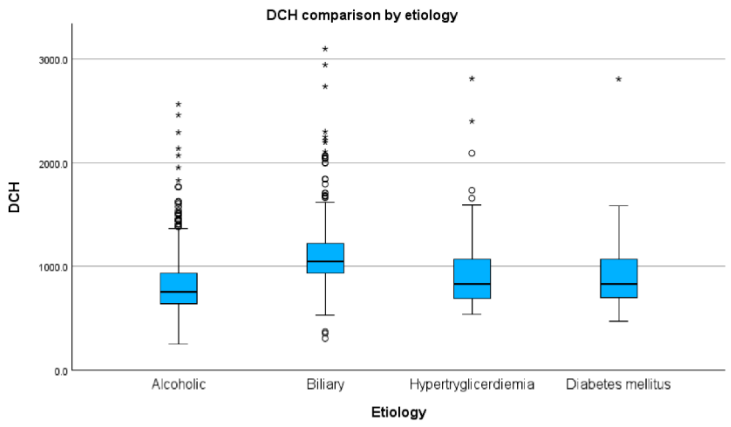

Figure 3 – MDC stratified by etiology

The Kolmogorov-Smirnov test used to assess the heterogeneity of the data distribution revealed a normally distributed population among the pseudocyst group (D (60) = 0.10, p = 0.20) and those with acute necrotizing collections (D (63) = 0.11, p = 0.08). Regarding the other groups, those with: interstitial involvement (D (575) = 0.16, p < 0.01), acute peripancreatic fluid collections (D (114) = 0.21, p < 0.01), and without pancreatic changes (D (210) = 0.50, p < 0.01) exhibited heterogeneity in the distribution of cases regarding the MDC.

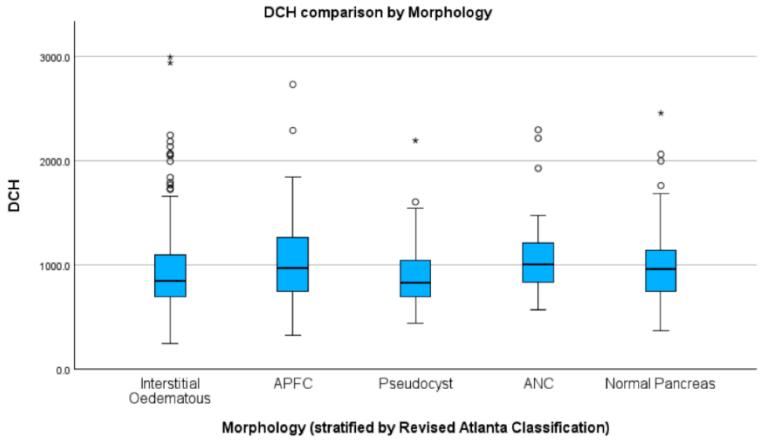

Figure 4 – MDC reported by pancreatic morphology

The tests used to assess the distribution of cases indicated that none of the groups were normally distributed in relation to MDC, obtaining the following values: mild form (D (758) = 0.48, p < 0.01), moderate-severe (D (542) = 0.46, p < 0.01), and severe (D (173) = 0.23, p < 0.01).

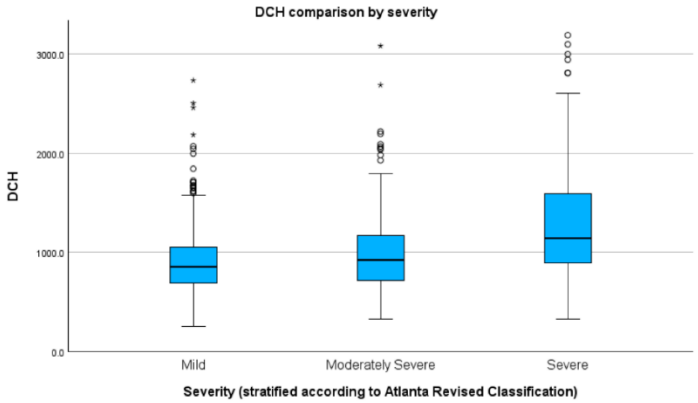

Figure 5 – MDC reported by severity

None of the analyzed groups showed a normal distribution in relation to the MDC mean. Specifically, the Kolmogorov-Smirnov test revealed the following values among the groups: recovered or improved (D(1234) = 0.47, p < 0.01); transferred (D(54) = 0.52, p < 0.01);

discharged at their own request (D(101) = 0.14, p < 0.01); and deceased (D(77) = 0.14, p < 0.01).

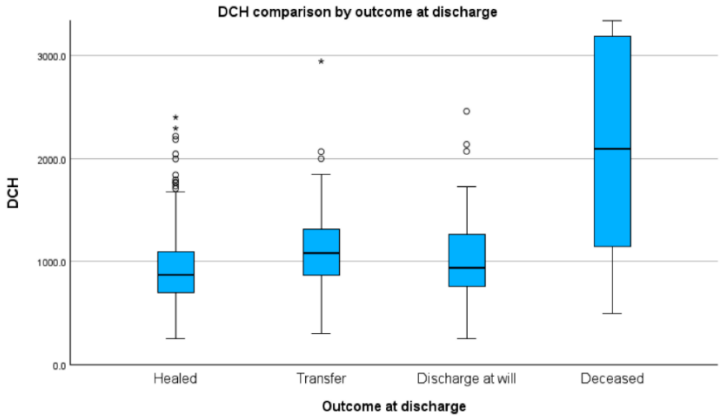

Figure 6 – MDC reported by outcome at discharge

Regarding admission to the intensive care unit, we found that both compared groups exhibited a heterogeneous distribution of cases. The specific values obtained using the Kolmogorov-Smirnov test were D(1348) = 0.47, p < 0.01 for those who did not require intensive care and D(125) = 0.24, p < 0.01 for those who did.

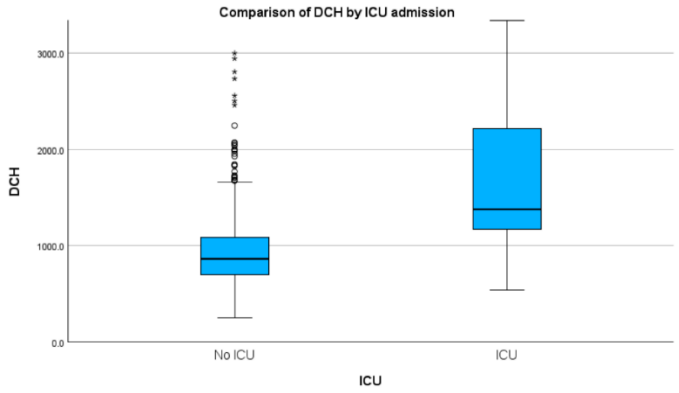

Figure 7 – MDC reported by ICU admission

Regarding MDC stratified by sex, both groups were not normally distributed, as follows: males (D(911) = 0.19, p < 0.01) and females (D(562) = 0.47, p < 0.01). A significant difference was identified between the two analyzed groups (H(1) = 54.53, p < 0.01), with medical care for females requiring more extensive material resources in terms of CMZ (223 USD versus 188.7 USD).

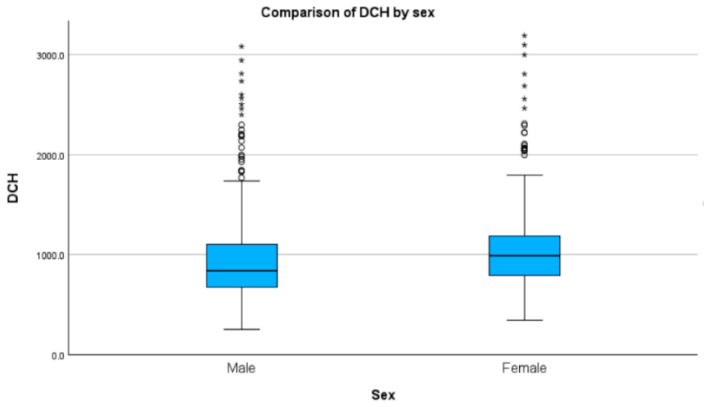

Figure 8 – MDC reported by gender

A heterogeneous distribution of cases was identified in the two groups based on MDC. Specifically, for gastroenterological cases, the following values were obtained: $D(860) = 0.22$, $p < 0.01$), while for those cared for in surgical profile sections: $D(613) = 0.47$, $p < 0.01$).

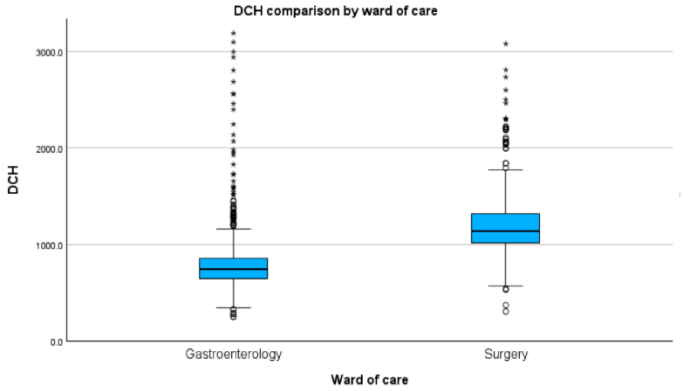

Figure 9 – MDC reported by ward of care

6.4. Conclusions

We noticed that the MDC in AP hospitalized in southern Romania is 203.8 USD, while the median total hospitalization cost is 1360.5 USD. An estimate of the total annual cost of hospitalizations related to AP in Romania would be around 19 million USD. To the best of our knowledge at the time of publication, this represents the first cost study in AP conducted at a national level and likely one of the few originating in Eastern Europe.

7. Epidemiological Trends in Acute Pancreatitis: A Retrospective Cohort in a Tertiary Center Over a Seven Year Period

7.1. Introduction

AP remains one of the main pathologies treated in gastroenterological departments worldwide and a frequent cause of hospitalization. The estimated incidence ranges from 3.8 to 74.8 cases per 100,000 inhabitants in Europe [27]. AP remains a burden for healthcare systems even though 75-80% of patients will develop mild forms of the disease [35]. Recent population studies in Romania are lacking. Our aim was to evaluate data related to AP from a large tertiary center in Bucharest. The objective of this study is to estimate local incidence, costs, and smoking prevalence among the studied population.

7.2. Patients and methods

For this retrospective observational cohort study, we accessed the electronic database of SUUB searching for cases of AP based on the discharge codes ICD-10: K85, B25.2, and B26.3. All discharged cases from gastroenterological departments between June 1, 2015, and April 1, 2022, were considered.

Querying the database resulted in a total of 1074 consecutive cases (Table 1). All cases were evaluated by the authors to exclude incorrectly coded ones, revealing that all 1074 obtained cases met at least two out of three diagnostic criteria for AP. Among these, we found that 126 actually represented cases of acute exacerbated chronic pancreatitis and therefore excluded them from the study. We collected data regarding: sex, month of admission, length of hospital stay, number of days spent in the intensive care unit (if applicable), discharge outcome, severity type according to revised Atlanta criteria, pancreatic morphology type according to revised Atlanta criteria, probable etiology, origin environment (urban/rural), county of residence, previous history of AP, smoking status, and hospitalization cost.

The database was organized using Microsoft Excel 2019. For statistical data analysis, we employed tabular analysis, frequency analysis, linear regression, ANOVA, chi-square test, Fisher's exact test, and goodness of fit test. All statistical tests were conducted using IBM SPSS Statistics version 29.0.0.0.

7.3. Results

Our hospital is a tertiary center serving a population of approximately 950,000 inhabitants, with gastroenterological departments admitting about half of the AP cases, while the other half is attributed to surgical departments. Our search identified 1074 cases, out of which 126 were actually acute exacerbated chronic pancreatitis cases. The remaining 974 consecutive cases represent the total number of hospitalized AP cases over 6 years and 10

months in gastroenterological departments. Based on these data, we estimated an incidence of AP in southern Romania at 29.2 episodes per 100,000 inhabitants. This incidence translates to approximately 5900 annual hospitalizations nationwide.

In total, 68.88% (n = 652) of cases were represented by males, and the median age in our population was 54 years (IQR = 15.9). Regarding the environment of origin, 73.1% (n = 692) of cases came from urban areas, 25.4% (n = 241) from rural areas, and the remaining 1.4% (n = 14) did not have a fixed residence in Romania.

Table 5 - Etiology Frequency

Cause	Number of cases	Percent (%)
Ethylic	433	45,7
Idiopathic	155	16,4
Gallstones	144	15,2
Hypertriglyceridemia	33	3,5
T2DM-associated	28	3,0
Drugs	25	2,6
Ethylic & gallstones	21	2,2
Ethylic & T2DM	21	2,2
Ethylic & Hypertriglyceridemic	18	1,9
Hypertriglyceridemic & T2DM	17	1,8
Ischemia	14	1,5
Extrapancreatic anomalies	13	1,4
Others (< 1 %)	25	2,6

We found that 54.4% of cases (n = 515) developed a mild form, 34.5% (n = 327) a moderate-severe form, and the remaining 11.1% (n = 105) a severe form of AP. 4.6% (n = 44) of cases required admission to the intensive care unit (ICU), with a mortality rate among them of 38.6% (n = 17), and an average length of stay in the ICU of 4 days (+- 0.8). Reported across the entire study population, the mortality rate was 5.5% (n = 52), with a rate of recovery/improvement of 83.2% (n = 788).

Regarding pancreatic morphology, we were able to identify relevant information in 73.4% of cases. The most commonly encountered form of morphology was interstitial involvement, present in 45.3% (n = 429) of cases, followed by 11.3% with a normal pancreatic

morphology. Necrosis, understood as acute necrotic collections or encapsulated necrosis, was identified in 3.9% of cases.

7.4. Conclusions

We estimated an incidence of hospitalized AP cases of 29.2 cases per 100,000 inhabitants per year. The majority of our cases were represented by men (68.9%) and were caused by alcohol abuse (45.7%). Among the cases where we identified smoking data, a large majority were active smokers (68.5%). Most of our patients suffered from a mild form of the disease (54.4%), and the overall mortality rate was 5.5%. Interstitial pancreatic changes (45.3%) predominated in the study population. The median daily hospitalization cost was reported at 748.0 RON. The main strengths of the study are the large number of cases included and a low risk of bias considering that these were consecutive discharges. The limitations of this study are represented by its retrospective structure and the single-center origin of the cases. There is a need for further profiling studies extending to patients hospitalized in surgical services to obtain a complete picture of the phenomenon.

8. Unveiling the Unexpected: Co-occurrence of Acute Pancreatitis and Riedel's Lobe

8.1. Introduction

The Riedel lobe, named after a German surgeon who discovered it in 1888, represents a rare anatomical variation of the liver, often described as an inferior extension of the right hepatic lobe [36]. AP is one of the most common causes of hospitalization in gastroenterological services worldwide, with an estimated mortality rate of 5.5% [37]. In this scientific report, we present a case of incidental diagnosis of the Riedel lobe in a 47-year-old patient diagnosed with alcoholic AP.

8.2. Case presentation

A 47-year-old patient, with no medical history, active smoker (30 pack-years) and chronic drinker (5-10 alcohol units daily), presents with epigastric pain radiating to the right hypochondrium and posteriorly, exacerbated approximately 1 hour after meals and accompanied by nausea. Clinical symptoms started 12 hours prior to presentation to the Emergency Department. The patient denies fever and chills.

The patient was afebrile, presented with ethylic tremor in the upper limbs, normal-colored skin and mucous membranes. Abdominal examination revealed distended abdomen due to meteorism, spontaneous pain in the supramesocolic region, and muscle guarding in the

epigastric area. The liver was palpable 5 cm below the costal margin, firm in consistency, with a smooth inferior edge.

Laboratory tests revealed non-specific inflammatory syndrome (leukocytosis, elevated C-reactive protein, prolonged erythrocyte sedimentation rate, increased fibrinogen), macrocytosis in the red blood cell line, pancreatic cytolysis syndrome (increased serum lipase and amylase activity), hepatic cytolysis syndrome (elevated transaminases, cholestasis), mild hypertriglyceridemia, and decreased total iron-binding capacity.

Abdominal ultrasound performed at the Emergency Department showed a gallbladder of normal size, without stones; intrahepatic bile ducts were not dilated, common bile duct was not dilated; pancreas was heterogeneous, hyperechoic, without visible collections or fluid accumulations in the pancreatic region; no free intraperitoneal fluid was observed.

Abdominopelvic CT scan, both native and post-contrast, indicated an enlarged liver (cranio-caudal diameter of the right lobe 230 mm) with homogeneous steatosis, along with the presence of a Riedel lobe.

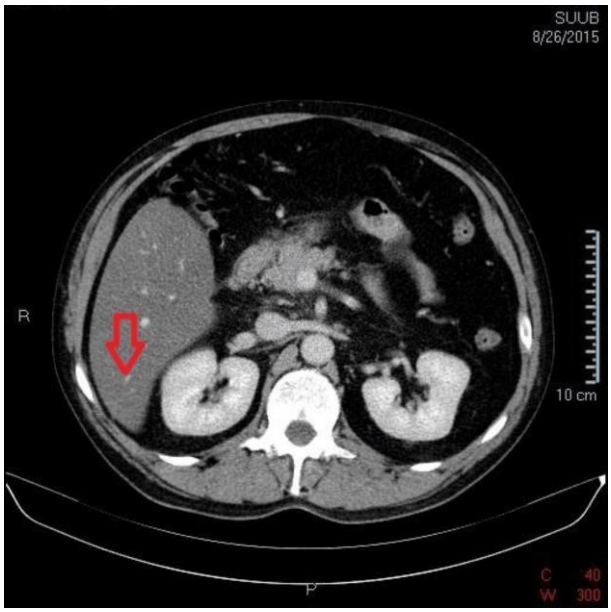

Figure 10 – Riedel's lobe marked with a red arrow

The pancreas showed enlarged dimensions along with a diffuse contrast area in the cephalopancreatic region, with significant thickening of peripancreatic fat associated with effusions and the presence of a 5 mm fluid layer near the anterior renal fascia. Furthermore, the duodenum (segments II and III) presented thickened walls with edema. The gallbladder was

distended with supple walls, apparently without stones, and the intrahepatic bile ducts, common bile duct, and Wirsung duct were not dilated.

After reviewing the results, the patient was diagnosed with alcoholic edematous pancreatitis along with the following secondary diagnoses: Riedel lobe, hypertriglyceridemia, alcoholic hepatitis, and alcohol withdrawal syndrome, which developed within 0-72 hours of admission, with the following clinical picture: ethylic tremor, profuse sweating, tachycardia, psychomotor agitation.

During hospitalization, the patient received the following treatments: 24-hour digestive rest and parenteral nutrition with 10% glucose 500 mL every 12 hours, as the patient could not tolerate nasojejunal tube, followed by progressive diet. For hydro-electrolytic balance re-equilibration, Ringer's solution was administered at a rate of 1.5 mL/kg/h, with de-escalation according to the evolution of heart rate, diuresis, and blood pressure. For pain management, Paracetamol 500 mg every 8 hours i.v. was administered. Digestive symptoms (nausea, vomiting) were managed with Metoclopramide 10 mg every 8 hours i.v. Omeprazole 40 mg every 24 hours was used for stress gastritis prevention. To control alcohol withdrawal syndrome, Diazepam 10 mg every 12 hours i.m. was used for the first 72 hours of hospitalization along with Thiamine 200 mg every 8 hours and Metoprolol Succinate 50 mg every 24 hours orally for heart rate control.

Under the aforementioned treatment, a favorable evolution of the patient was observed with remission of digestive, painful, and alcohol withdrawal syndrome symptoms.

8.3. Conclusions

In this case presentation, the Riedel's lobe represented an unexpected imaging finding, similar to most situations reported in the specialized literature. It is not clear whether the Riedel's lobe played any role in promoting the pathogenesis of AP. Although unlikely, we cannot entirely exclude the possibility that the anatomical modification represented by the presence of Riedel's lobe did not promote an increase in pressure in the biliary-pancreatic tree, which could have had a role in promoting the pathogenic mechanisms of AP. Further research is needed to better understand the implications of this discussed anatomical variation on other pathologies. In summary, the synchronous presence of the two medical conditions is most likely a coincidence.

9. An Angiographic Treatment for a Pancreatic Pseudoaneurysm

9.1. Introduction

Pancreatic pseudoaneurysm (PaP) is a visceral arterial pseudoaneurysm. The estimated prevalence of PaP from several case series ranges from 1.3 to 10% of all AP complications. The most commonly affected arteries for the occurrence of PaP are the splenic artery (50%), gastroduodenal artery (20%), pancreaticoduodenal artery (10%), while the remainder affects the proper hepatic artery and branches of the superior mesenteric artery [38]. The clinical presentation is nonspecific, with most patients being asymptomatic. In cases of rupture, the clinical picture may include: recurrent abdominal pain, gastrointestinal bleeding, obscure anemia, and rapid expansion of a pseudocyst with previously stable dimensions [39]. Angiography is the gold standard for diagnosis and also represents a therapeutic method. CT angiography and MR angiography can be successfully used to localize the lesion.

9.2. Case presentation

A 40-year-old patient, an active drinker and smoker with multiple previous episodes of recurrent AP, presents at Colentina Clinical Hospital with epigastric pain radiating to the back, nausea, and general deterioration of health. Paraclinical examination at admission indicates an increase in serum amylase and lipase activity. During hospitalization, the patient experiences an episode of hemorrhagic shock (hypotension, tachycardia, acute anemia, pallor, etc.). An abdominal CT scan with contrast reveals a pancreatic pseudocyst with hemorrhagic content measuring 51 mm, located adjacent to the inferior pancreaticoduodenal artery.

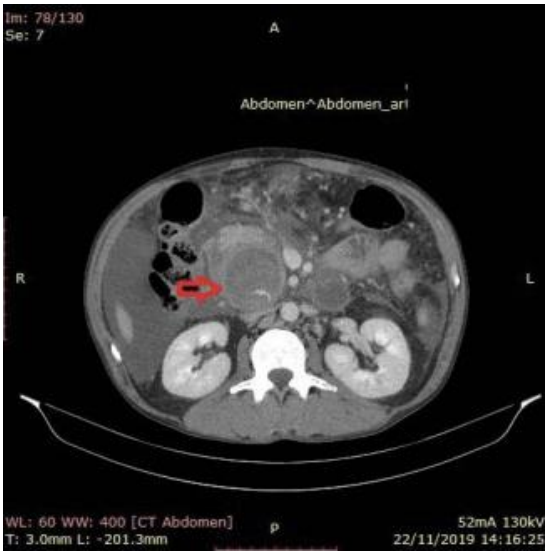

Figure 11 – Pancreatic Pseudoaneurysm. CT section.

Upon admission to SUUB, the patient was cachectic, with mucosal and cutaneous pallor, diffuse abdominal pain with muscular defense sketch in the epigastrium, hypotensive (BP = 90/50 mmHg), tachycardic (heart rate = 120 bpm regular). Laboratory tests revealed: reduced erythrocyte mass (hematocrit = 26.5%), hypochromic anemia (hemoglobin = 8.5 g/dL, MCHC = 32.2 g/dL), thrombocytosis (468,000/mL), hyposideremia (serum iron = 27 mg/dL), increased serum lipase activity (148 U/L, 1.5 times above the reference value) and amylase (200 U/L, 1.5 times above the reference value), low fibrinogen (159.56 mg/dL). Angiographic examination detected, similar to the CT result from the referring hospital, a PaP at the level of the inferior pancreaticoduodenal artery, type IIA2 according to the Pang classification. Angioembolization was performed using a VortX device (Boston Scientific, USA) without peri-procedural complications. Figures 9.2. and 9.3. Complete exclusion of the PaP from the vascular system was achieved. The patient was discharged 48 hours later.

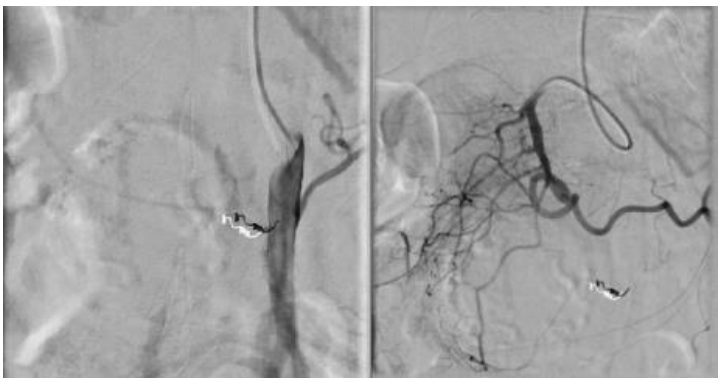

Figure 11 – Angiography after selective endovascular embolization

9.3. Discussion and Conclusions

The gold standard in the curative treatment of ruptured PaP is represented by selective endovascular embolization. In the above scientific report, such a technique was successfully applied to a young patient with recurrent AP.

10. Final conclusions and personal contributions

10.1. Final conclusions

The results of the current doctoral research can be summarized as follows:

1. We estimated the total cost of hospitalizations for AP in Romania at approximately 19 million USD annually.

2. The median daily cost of hospitalization in our center was 203.8 USD. The median total cost of hospitalization in our center was 1360.5 USD.

3. Factors that may promote increased costs include advanced age, admission to the ICU, in-hospital mortality, severity, development of acute necrotic collections, biliary etiology, and female sex.

4. The majority of cases from gastroenterological departments were represented by men (68.9%).

5. The main etiologies of cases from gastroenterological departments were: alcoholic (45.7%), idiopathic (16.4%), biliary (15.2%), hypertriglyceridemic (3.5%), diabetes mellitus (3.0%), and drug-induced (2.6%).

6. The proportion of local complications among cases from gastroenterological departments was: Interstitial (45.3%), No pancreatic changes (11.3%), acute peripancreatic fluid collections (7.4%), pseudocyst (5.5%), acute necrotic collections (3.5%), encapsulated necrosis (0.4%). In 26.6% of cases, local complications could not be identified due to lack of data.

7. Based on available data, we estimated the incidence rate of hospitalized AP in the southern region of Romania at 29.2/100,000 population.

8. Among cases from gastroenterological departments, the proportions of severity according to revised Atlanta criteria were: mild forms (54.4%), moderate-severe forms (34.5%), severe forms (11.1%).

9. Of the gastroenterological cases, 4.6% required admission to the ICU. The median length of ICU stay was 4 days.

10. Regarding discharge outcome, among gastroenterological cases, we note the following proportions: healed or improved (83.2%), discharged at their own request (8.2%), transferred to other medical units (2.7%), stationary (0.3%). Mortality rate: 5.5%.

11. Severity at discharge of cases associated with diabetes mellitus according to revised Atlanta criteria was: mild form (30.9%), moderately severe (40.0%), severe (29.1%). In comparison with other AP cases, a statistically significant association ($p<0.01$) was observed between severe forms of the disease and diabetic etiology.

10.2. Personal contributions

1. Development of a new AP registry with regional coverage at the time of conducting the doctoral research, but with potential for national expansion.

2. Identification of hospitalization costs related to AP at the national level.

3. Highlighting diabetes mellitus as an unfavorable causal factor in AP.

4. Profiling the phenomenon of AP at the regional level.

10.3. Study limits

1. The retrospective nature of the study;

2. The single-center nature of the study;

3. Significant lack of data regarding: smoking history, patient history prior to admission to the SUUB system;

4. Moderate lack of data regarding pancreatic morphology;

5. The limited temporal scope of the source registry;

6. The lack of depth in case data, including missing data on: biological samples, comorbidities, family history, etc.

10.4. Future perspectives

1. The single-center origin of the studied cases. Subsequent to the doctoral study, this aspect has been addressed, with currently: 79 cases processed from IC Fundeni, 902 cases in processing from the Emergency Clinical University Hospital Elias, 336 cases in processing from the Emergency Clinical Hospital Bucharest, and advanced agreements for data acquisition from two other hospital units (Emergency Military Hospital Dr. Carol Davila Bucharest and Emergency County Hospital Bihor Oradea);

2. The lack of laboratory data and associated comorbidities for the processed cases. Subsequent to the doctoral study, this aspect has been partially resolved, as of the writing of this thesis (April 12, 2024), with 2117 cases in Phase II of the BUC-API registry (complete data on blood tests) and 1217 cases processed in Phase III of the BUC-API registry (partial data on biochemical tests). Comorbidities will be addressed in a subsequent phase;

3. The possibility of identifying clinically silent pathologies in the cohort. At the time of writing this doctoral thesis, we plan to conduct a genetic screening for the detection of familial hyperchylomicronemia in our cohort. Genetic screening will be performed among patients in the subgroup of hypertriglyceridemic etiology based on a risk score;

4. The impossibility of generalizing the results regarding costs at the national level. We plan to address this aspect by resuming the study once we have data from a sufficient number of hospital units distributed relatively evenly nationwide;

5. The difficulty of estimating the incidence of PA at the national level. We plan to address this aspect by resuming the study once we have data from a sufficient number of hospital units distributed relatively evenly nationwide;

6. The relatively low number of PA cases associated with diabetes. We plan to resume the study as the number of cases in the registry increases;

7. Conducting prospective studies based on this registry by actively contacting included patients;

8. Dynamically monitoring the cohort to identify long-term sequelae associated with PA.

11. Selective bibliography

1. Peery AF, Crockett SD, Murphy CC, Jensen ET, Kim HP, Egberg MD, et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2021. Gastroenterology. februarie 2022;162(2):621–44.

2. Li C li, Jiang M, Pan C qiu, Li J, Xu L gang. The global, regional, and national burden of acute pancreatitis in 204 countries and territories, 1990–2019. BMC Gastroenterol. 25 august 2021;21:332.

3. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. ianuarie 2013;62(1):102–11.

4. Ehrhardt JD, Gomez F. Embryology, Pancreas. În: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [citat 20 februarie 2024]. Disponibil la: http://www.ncbi.nlm.nih.gov/books/NBK545243/

5. Draghia F, Negoi I, Drăghia A, Negoi R. Aparatul digestiv, lucrări practice. Editura Universitară Carol Davila;

6. Bazira PJ, Mahadevan V. Anatomy of the pancreas and spleen. Surgery (Oxford). 1 aprilie 2022;40(4):213–8.

7. P L. Beitrage zur mikroskopischen Anatomie der Bauchspeicheldruse, Inaugural Disseration. Gustav Lange [Internet]. 1869 [citat 20 februarie 2024]; Disponibil la: https://cir.nii.ac.jp/crid/1570854175582054784

8. Wang GJ, Gao CF, Wei D, Wang C, Ding SQ. Acute pancreatitis: Etiology and common pathogenesis. World J Gastroenterol. 28 martie 2009;15(12):1427–30.

9. Cappell MS. Acute Pancreatitis: Etiology, Clinical Presentation, Diagnosis, and Therapy. Medical Clinics of North America. 1 iulie 2008;92(4):889–923.

10. Ganguly D, Chandra A. Cullen Sign and Grey Turner Sign in Acute Pancreatitis. The American Journal of Medicine. 1 decembrie 2022;135(12):e437–8.

11. Frank B, Gottlieb K. Amylase normal, lipase elevated: is it pancreatitis?: A case series and review of the literature. The American Journal of Gastroenterology. 1 februarie 1999;94(2):463–9.

12. Scaglione M, Casciani E, Pinto A, Andreoli C, De Vargas M, Gualdi GF. Imaging Assessment of Acute Pancreatitis: A Review. Seminars in Ultrasound, CT and MRI. 1 octombrie 2008;29(5):322–40.

13. American College of Gastroenterology Guideline: Management o... : Official journal of the American College of Gastroenterology | ACG [Internet]. [citat 25 februarie 2024]. Disponibil la: https://journals.lww.com/ajg/fulltext/2013/09000/american_college_of_gastroenterology_guideline_.6.aspx

14. Sotoudehmanesh R, Hooshyar A, Kolahdoozan S, Zeinali F, Shahraeeni S, Keshtkar AA. Prognostic Value of Endoscopic Ultrasound in Acute Pancreatitis. Pancreatology. 1 martie 2011;10(6):702–6.

15. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 1 decembrie 2008;57(12):1698–703.

16. Hagjer S, Kumar N. Evaluation of the BISAP scoring system in prognostication of acute pancreatitis – A prospective observational study. International Journal of Surgery. 1 iunie 2018;54:76–81.

17. Hoilat GJ, Mathew G, Ahmad H. Pancreatic Pseudoaneurysm. În: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [citat 26 februarie 2024]. Disponibil la: http://www.ncbi.nlm.nih.gov/books/NBK430937/

18. Gapp J, Tariq A, Chandra S. Acute Pancreatitis. În: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [citat 26 februarie 2024]. Disponibil la: http://www.ncbi.nlm.nih.gov/books/NBK482468/

19. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN, Crockett S, et al. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology. 1 martie 2018;154(4):1096–101.

20. Wang Z, Shi K, Mo S, Liu Z, Yao J. A meta-analysis of Lactate Ringer's solution versus Normal Saline in the treatment of acute pancreatitis. Gastroenterología y Hepatología [Internet]. 13 decembrie 2023 [citat 26 februarie 2024]; Disponibil la: https://www.sciencedirect.com/science/article/pii/S021057052300496X

21. Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. Pathophysiology, Diagnosis, Management. 10th edition. Saunders; 2015.

22. Lee DW, Cho CM. Predicting Severity of Acute Pancreatitis. Med Lith. iunie 2022;58(6):787.

23. Matta B, Gougol A, Gao X, Reddy N, Talukdar R, Kochhar R, et al. Worldwide Variations in Demographics, Management, and Outcomes of Acute Pancreatitis. Clinical Gastroenterology and Hepatology. iunie 2020;18(7):1567-1575.e2.

24. Nawacki L, Gluszek S. Hospital mortality rate and predictors in acute pancreatitis in Poland: A single-center experience. Asian J Surg. ianuarie 2024;47(1):208–15.

25. Fagenholz PJ, Fernández-del Castillo C, Harris NS, Pelletier AJ, Camargo CA. Direct medical costs of acute pancreatitis hospitalizations in the United States. Pancreas. noiembrie 2007;35(4):302–7.

26. Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet. 15 iulie 2023;402(10397):203–34.

27. Iannuzzi JP, King JA, Leong JH, Quan J, Windsor JW, Tanyingoh D, et al. Global Incidence of Acute Pancreatitis Is Increasing Over Time: A Systematic Review and Meta-Analysis. Gastroenterology. 1 ianuarie 2022;162(1):122–34.

28. Zhi M, Zhu X, Lugea A, Waldron RT, Pandol SJ, Li L. Incidence of New Onset Diabetes Mellitus Secondary to Acute Pancreatitis: A Systematic Review and Meta-Analysis. Front Physiol. 31 mai 2019;10:637.

29. Paragomi P, Papachristou GI, Jeong K, Hinton A, Pothoulakis I, Talukdar R, et al. The relationship between pre-existing diabetes mellitus and the severity of acute pancreatitis: Report from a large international registry. Pancreatology. ianuarie 2022;22(1):85–91.

30. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. ianuarie 2011;34(Suppl 1):S62–9.

31. Andersson B, Appelgren B, Sjödin V, Ansari D, Nilsson J, Persson U, et al. Acute pancreatitis – costs for healthcare and loss of production. Scandinavian Journal of Gastroenterology. decembrie 2013;48(12):1459–65.

32. Valverde-López F, Wilcox CM, Redondo-Cerezo E. Evaluation and management of acute pancreatitis in Spain. Gastroenterol Hepatol. decembrie 2018;41(10):618–28.

33. Lilja HE, Leppäniemi A, Kemppainen E. Utilization of Intensive Care Unit Resources in Severe Acute Pancreatitis.

34. Durrani R, Murphy O, Kibeida A, Fitzpatrick G. Severe acute pancreatitis in ICU: a 5-year audit. Crit Care. 17 martie 2014;18(1):P197.

35. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017;17(2):155–65.

36. Zamfir R, Braşoveanu V, Boroş M, Herlea V, Popescu I. Hepatocellular carcinoma in Riedel's lobe. Chirurgia (Bucur). 2008;103(1):121–3.

37. Szatmary P, Grammatikopoulos T, Cai W, Huang W, Mukherjee R, Halloran C, et al. Acute Pancreatitis: Diagnosis and Treatment. Drugs. 1 august 2022;82(12):1251–76.

38. Verde F, Fishman EK, Johnson PT. Arterial Pseudoaneurysms Complicating Pancreatitis: Literature Review. Journal of Computer Assisted Tomography. februarie 2015;39(1):7.

39. Abdelgabar A, d'Archambeau O, Maes J, Van den Brande F, Cools P, Rutsaert RR. Visceral artery pseudoaneurysms: two case reports and a review of the literature. J Med Case Reports. 4 mai 2017;11(1):126.