EARLY MANAGEMENT OF ACUTE PANCREATITIS

Ph.D. Thesis

Doctoral School of Pharmacological and Pharmaceutical Sciences

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University of Pécs Medical School

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I. Scientific metrics

Number of publications **related to the subject** of the thesis:	5	(4 first author)
Cumulative impact factor of publications related to the thesis:	15.714	(12.32 first author)
Q1: 5, Q2: 0, Q3: 0, Q4: 0		
Number of **total accepted/published** articles:	22	(4 first author)
Cumulative impact factor of the published articles:	64.066	(12.32 first author)
Q1: 20, Q2: 2, Q3: 0, Q4: 0		
Number of total citation by **Google Scholar**	76	
https://scholar.google.hu/citations?hl=en&user=ajPL8rgAAAAJ		
Hirsch Index	5	
Number of total citation by **MTM2**	56	
https://m2.mtmt.hu/frontend/#view/Publication/SmartQuery/1127/		
Hirsch Index	4	

II. Preface

Acute pancreatitis (AP) is one of the most challenging gastrointestinal disorders:

(1) its development is not fully understood[6];

(2) it has no specific therapy[7];

(3) its incidence rate is continuously increasing[8]; and

(4) it has an unacceptably high mortality[9].

Unfortunately, gastrointestinal scientists are devoting ever less attention to AP[10]. In the last decades it's turned out that most of the deteriorating events happen in the first 24h, which largely determine the outcome of the disease [11,12]. Therefore, we must accept the fact that AP is a "*door to the needle*" disease such as stroke or myocardial infarction. It is almost needless to say that based on the literature data we must

(1) predict the severity of the disease on admission; and importantly

(2) start the treatment of the patients as early as we can.

Therefore, when I joined to Professor Hegyi's workgroup in January 2016 and we decided to focus on the above mentioned clinical challenges. During my PhD period we not only could make important discoveries, but I had unique chance to learn the basics of Translational Medicine including the modern clinical methodology. In Chapter I, we concentrated on severity prediction, whereas in Chapter II we focused on early management.

III. Chapter I

III.1 Introduction

The annual incidence of acute pancreatitis (AP) ranges from 10 to 100 cases per 100,000 persons 11, showing an increasing tendency throughout the past decades [12]. Multiple theories have been proposed to explain the increment: better diagnostics (e.g., general access to the measurement of pancreatic enzymes) [13], lifestyle factors (e.g., obesity, alcohol consumption, and tobacco use) [14,15] as well as aging of the population [16] have been implicated.

Life expectancy has dramatically risen by 16 years (from 55.4 yrs to 71.4 yrs) in the last half century, causing a number of changes and challenges to economies and healthcare systems. Needless to say, healthcare professionals should focus more intensively on the effects of aging on the course and outcome of diseases.

Age has been used as a predictive marker in different scoring systems for AP. It has been shown that advanced age is associated with more severe AP and higher mortality. However, since the risk of morbidities increases with age, it is not clear whether aging and/or comorbidities are the key deteriorating factor [23]. In addition, it is also well reported that some of the diseases which develop based on the same etiological background (for example alcohol) are more frequent in AP. National cohort analysis showed variable rates of liver cirrhosis (LC) in alcoholic pancreatitis. The Spanish cohort showed 2% [31], the Czech one 16.7% [32], the Indian one 8.4% [33] and the Italian one 12.5% [34].

III.2 Aims

We aimed to investigate (1) the effects of aging and (2) comorbidities on the outcome of AP. Moreover, we wished to understand which factors predict mortality or severity better.

III.3 Methods

III.3.1 Methods to answer Aim III.2.1

We choose the most appropriate clinical methodologies to answer each questions. To answer Aim III.2.1 we needed a preliminary sample size calculation. The event rate of mortality in AP is very low: 3/100. Therefore, it is not surprising that 10-50 thousand of patients would be necessary to answer Aim III.2.1 precisely. The only possible methodology which is feasible to collect such a high amount of patients is meta-analyses. In this part of the study we systematically reviewed the literature and performed a detailed meta-analysis performed using

the preferred reporting items for systematic review and meta-analysis statement (PRISMA) [37]. In order to provide the highest level of quality, the meta-analysis was registered with the PROSPERO registry (CRD42017079253). All details are described in the main thesis document.

III.3.2 Methods to answer Aim III.2.2

In order to understand the effects of comorbidities on the outcome of AP detailed clinical data are necessary. We have performed a preliminary literature search which revealed that unfortunately such clinical data are not provided in the articles. Therefore, performing a meta-analysis is not feasible. To answer Aim II.1.2 we needed to get access to a high quality AP cohort. Since one of the biggest international AP registries run by the Hungarian Pancreatic Study Group, we had no difficulties to access the necessary clinical data. AP Registry has been approved by Scientific and Research Ethics Committee of the Medical Research Council (22254-1/2012/EKU). All details are described in the main thesis document.

III.4 Results

Our systematic search yielded 1100 articles (704, 379 and 17 in Embase, PubMed and Cochrane, respectively). Eleven additional articles were found with potential data eligibility for the meta-analysis in the references of the primarily selected articles. After excluding duplicates and irrelevant articles, a total of 33 articles involving 194 702 patients met the inclusion criteria (*Table 1*).

III.4.1 The effects of aging on the severity of AP

A total of 23 studies with 22451 patients were suitable for analyzing severity [45-67]. Two thousand four hundred eighty-nine severe cases were found divided into seven age groups with a low severity rate under 30 years. There was a low incidence severe AP rate in patients under 30 and rose continuously between ages 30 and 70.

Firstly, a meta-regression was performed to investigate the relationship between age and severity (*Figure 1*). The number of patients in each age group category was extremely diverse (between 24 and 11 933); however, a significant relationship was detected (coefficient: 0.035 CI: 0.019–0.052, $p<0.001$; adjusted r^2: 31.6%). A conventional regression analysis was also performed showing a **linear increase** (0.193%/year) from ages U20 to A70 (*Figure 2*).

Study	Sample Size	Severe Case	Mortality	Study type	modified Newcastle-Ottawa Quality Assessment Scale									
					Selection				Comparability	Outcome				Sum
					S1	S2	S3	S4	C1	O1.1	O1.2	O2	O3	
Abou-Assi et al 2002	156	5	14	Prospective	1	1	0	1	1	0	1	1	1	7
Albulushi et al 2014	174	14	0	Retrospective	1	1	0	0	1	0	1	1	1	6
Beltrán et al 2013	24	1	0	Retrospective	1	1	1	1	1	0	1	1	1	8
de-Madaria et al 2014	403	28	17	Prospective	1	1	1	1	0	1	0	1	1	7
Dombernowsky et al 2016	359	nd	13	Retrospective	1	1	1	1	1	0	1	1	1	8
Gompertz 2012	128	nd	2	Retrospective	1	1	1	1	0	0	0	1	1	6
Gompertz 2013	1367	nd	115	Retrospective	1	1	1	1	0	1	0	1	1	7
González-González 2012	605	nd	30	Prospective	1	1	1	1	1	1	1	1	1	9
Gornik et al 2013	1058	210	41	Prospective	1	1	0	1	0	0	1	1	1	6
Gürleyiek et al 2005	55	13	1	Prospective	1	1	1	1	1	1	1	1	1	9
Karpavicius et al 2016	102	20	5	Prospective	1	1	1	1	0	1	0	1	1	7
Knoeplifi et al 2006	310	63	8	Prospective	1	1	1	1	1	1	0	1	1	8
Lautz et al 2011	211	nd	0	Retrospective	1	1	1	1	0	1	1	1	1	8
Milherio et al 1994	91	nd	10	Retrospective	1	1	0	1	0	0	0	1	1	5
Mole at el 2016	2053	390	102	Retrospective	1	1	0	1	0	0	1	1	1	6
Muller et al 2006	109	66	8	Prospective	1	1	1	1	1	1	1	1	1	9
Nijmeijer et al 2013	622	119	20	Prospective	1	1	0	1	0	0	0	1	1	5
Ocampo et al 2015	854	140	nd	Prospective	1	1	0	1	1	0	1	1	1	7
Pant et al 2014	55012	nd	509	Retrospective	1	1	0	0	0	0	0	1	1	4
Parniczky et al 2016	600	53	17	Prospective	1	1	1	1	1	1	1	1	1	9
Radenkovic et al 2009	91	24	8	Prospective	1	1	1	1	0	1	0	1	1	7
Rashidi et al 2016	670	43	37	Prosp and Retrosp	1	1	1	1	1	1	0	1	1	8
Spanier et al 2013	78257	nd	9515	Retrospective	1	1	0	1	1	0	1	1	1	7
Uomo et al 2007	1173	167	36	Prospective	1	1	1	1	0	1	1	1	1	8
Waele et al 2007	40	14	6	Retrospective	1	1	1	1	0	1	0	1	1	7
Wang et al 2015	120	31	13	Retrospective	1	1	0	1	0	0	0	1	1	5
Wei Ho et al 2015	12284	765	nd	Retrospective	0	1	0	1	0	0	0	1	1	4
Weitz et al 2016	346	21	12	Retrospective	1	1	1	1	0	1	1	1	1	8
Wu et al 2008	36178	nd	569	Retrospective	1	1	0	0	0	0	0	1	1	4
Yeung et al 1995	43	nd	1	Retrospective	1	1	0	0	1	0	1	1	1	6
Yue et al 2015	169	68	nd	Prospective	1	1	0	1	0	0	0	1	1	5
Zhang et al 2016	974	223	58	Retrospective	1	1	1	1	0	1	1	1	1	8
Zuidema et al 2014	64	11	3	Prospective	1	1	0	1	0	0	0	1	1	5

Table 1. The modified Newcastle–Ottawa Quality Assessment Scale. Ranks in three categories (green-1: low risk; red-0: high risk; yellow-0: unclear risk) are shown. S1: non-selected etiology AP; S2: all participants have an AP diagnosis; S3: AP diagnosis is confirmed using the latest guidelines; S4: non-selected severity cases. C1: comparability defined by exact age ranges in years. O1.1: severity assigned according to the latest guidelines; O1.2: described mortality (in-hospital and pancreas-related); O2–O3: adequate follow-up for outcome occurrence mortality and severity.

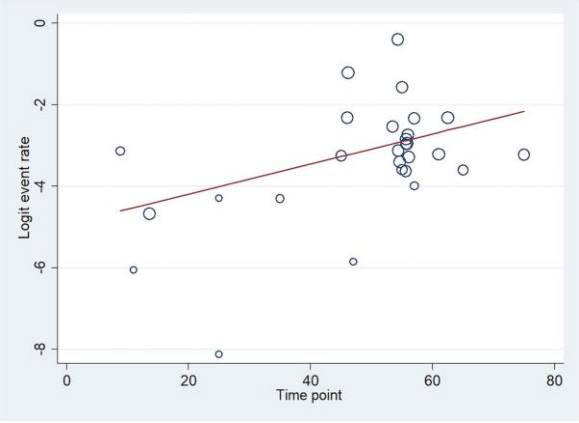

Figure 1. Meta-regression of severity. The figure shows 29 data from 23 reports where x= age (mean), y=logit event rate: ln(p/(1-p)), and circle diameters show the weight of each study based on the random effect model. The meta-regression shows a significant ($p<0.001$) relationship between age and severity ($r^2=31.6$), therefore the risk for developing severe cases is elevated by ageing.

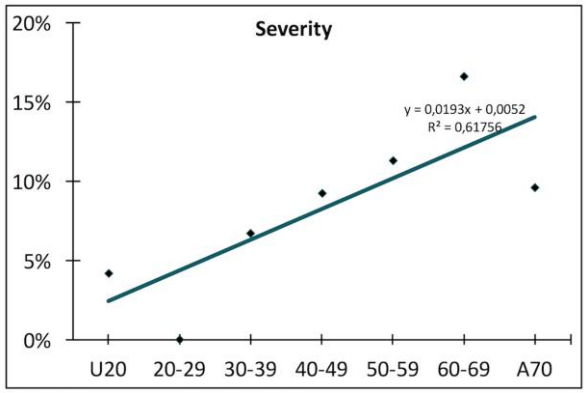

Figure 2. Conventional regression of severity. The conventional regression, which is independent of distortion from diverse numbers of patients, shows a linear rise (0.193%/year) in severity from young to old age.

III.4.2 The effects of aging on the mortality in AP

30 studies involving 181,395 subjects contained data on mortality (*Table 1*) [16,45-57,60,62-76]. 11 170 deceased cases were found in the seven age groups with the highest rates in groups

40–49 and A60. The mortality rate was 0.9% in patients under 20 and demonstrated a continuous, linear elevation until 59, however from this age the mortality rate started elevating with 9 times higher rate until the age of 70 (*Figure 3*). The mortality rate grew 0.086%/year between ages 20 and 59 and 0.765%/year between 59 and 70 (*Figure 3*). Overall, patients above 70 had a mortality rate 19 times higher than those under 20. The mortality rate rising with age was also confirmed by forest plots.

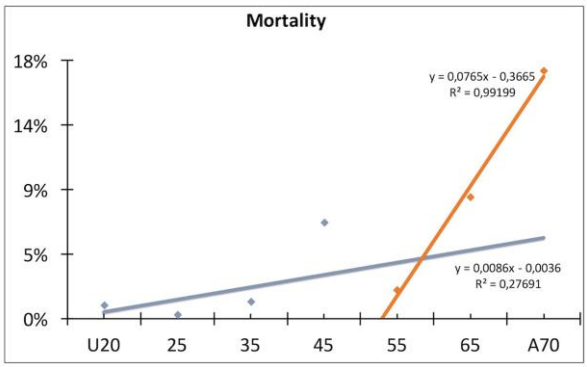

Figure 3. Conventional regression of mortality. The conventional regression shows a linear elevation until 59, however from this age the mortality rate started elevating with 9 times higher rate until the age of 70.

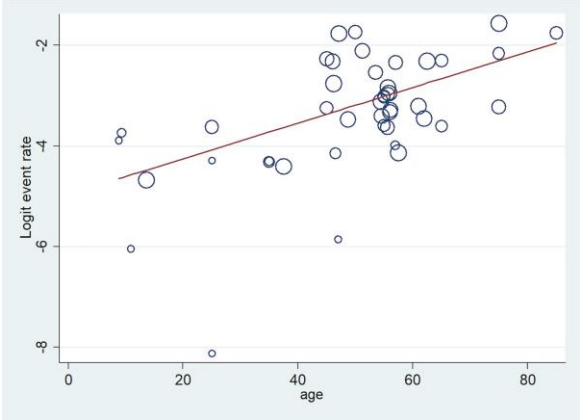

Figure 4. Meta-regression of mortality. The figure shows 43 data from 30 reports where x= age (mean), y=logit event rate: ln(p/(1-p)), and circle diameters show the random size of each study. The meta-regression shows a significant relationship (p=0.022) between age and mortality.

A meta-regression analysis on mortality showed a significant difference (coefficient: 0.037 CI: 0.006–0.068, p=0.022; adjusted r^2: 13.8%, *Figure 4*). Publication bias was tested by funnel plot and Egger's test (CI: -0.901–9.234; p=0.104) and showed mild asymmetry, but based on Egger's test publication bias was unlikely.

III.4.3 Demography of the AP cohort

In order to understand the relationship between aging, comorbidity, severity and mortality we used the high quality AP Registry built up by the HPSG. It contained 1241 cases, of them 1203 (96.9%) from 18 centers were eligible for inclusion. Demography of study population and that of AP Registry are presented in *Figure 5*. Study population proved to be representative to that of AP Registry regarding demography and disease outcomes (p>0.05 for all variables analyzed). Data quality for all variables was >99% in study population.

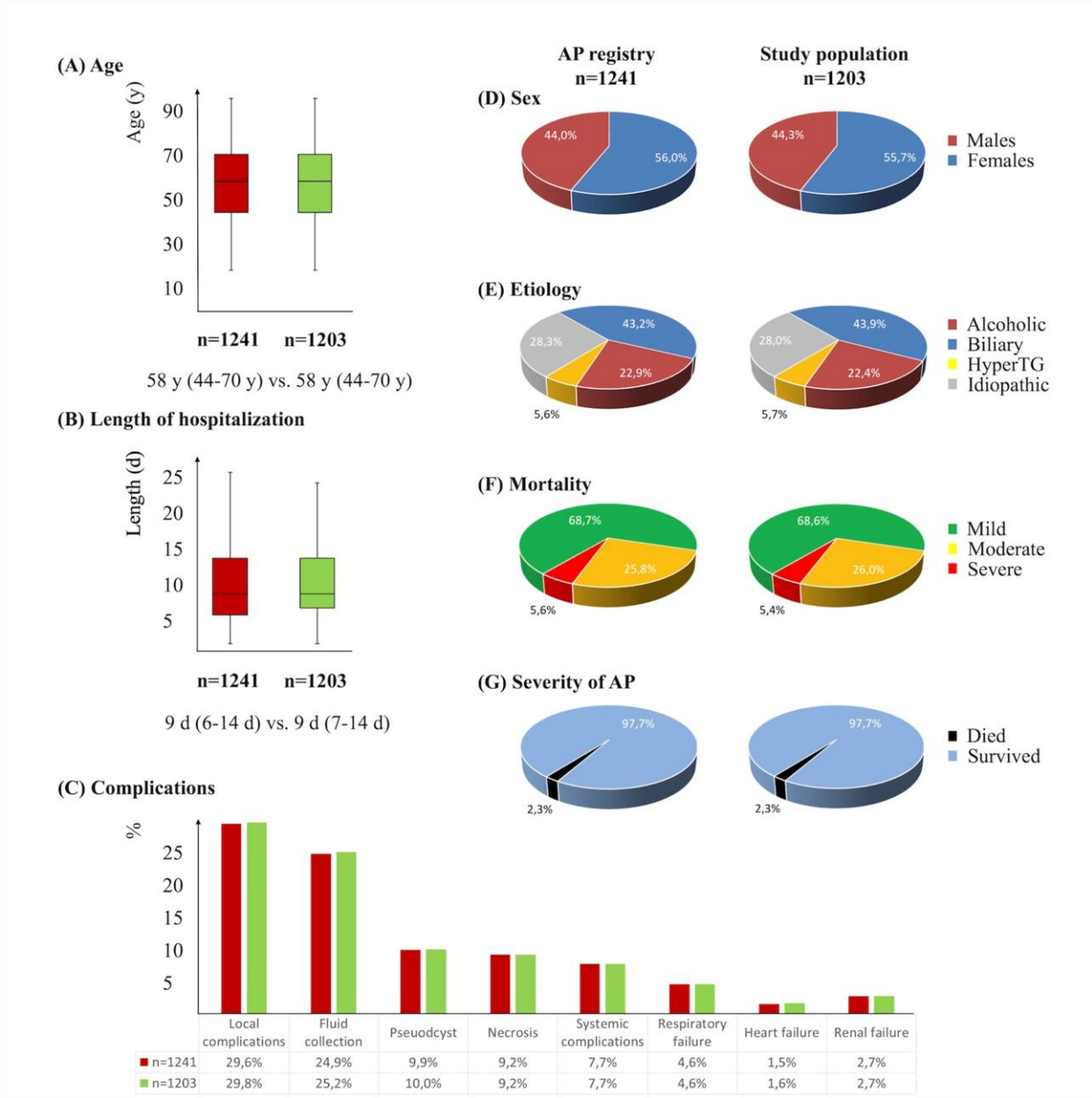

Figure 5. Demography and representativeness of the study population. Analysis of representativity showed no difference between the features of the population in AP Regsitry (n=1241) and that included in Study Population (n=1203), p≥0.05 for all comparisons. Representativeness of the included population was tested by binomial (sex, etiology, mortality, and complications), one sample median (age and length of hospitalizaton), and Goodness-of-fitχ2 tests (severity of AP).

III.4.4 Association between aging and comorbidities in AP

Median age on admission was 58 y (Q_1-Q_3: 44-70 y, range: 18-95 y). Deceased were older than survivors (65 y [Q_1-Q_3: 56-78 y] vs. 58 y [Q_1-Q_3: 44-70 y], p=0.017, respectively). The age difference between severe and non-severe cases was of borderline significance (61 y [Q_1-Q_3: 48-71 y] vs. 58 y [Q_1-Q_3: 43-70 y], p=0.076).

Specifically, respiratory (p=0.001) and heart failure (p=0.009) were age-dependent. These data suggest that aging strongly influences the outcomes of AP in univariate models.

Concerning comorbidity, Median CCI was 2 (Q_1-Q_3: 0-2, range: 0-10). Deceased had higher CCI than survivars (3 [Q_1-Q_3: 1-4] vs. 1 [Q_1-Q_3: 0-2], p=0.001, respectively), as well as those with severe AP (1 [Q_1-Q_3: 0-3] vs. 1 [Q_1-Q_3: 0-2], p=0.024) compared to those with non-severe AP, respectively. A weak, significant, positive correlation was detected between age and CCI (r=0.073, p=0.012).

Furthermore, bivariate analysis of age and CCI revealed a moderate, positive correlation between the variables (r=0.334, p<0.001). Importantly, patients with previous myocardial infarction, co-existing congestive heart failure, peripheral arterial disease, and cerebrovascular disease were significantly older than those without these conditions (p<0.001 for each).

Summaries of multivariate analysis are presented in *Table 2*. The exclusive predictor of mortality was a CCI≥3 (ß=1.50; OR=4.48; CI: 1.57-12.80); in accordance, the main predictor of severe AP was a CCI≥3 (ß=0.74; OR=2.10, CI: 1.08-4.09), though the middle- and old-aged were exposed to a severe episode with a high OR of borderline significance.

Variables	Deceased vs. survivors			Severe vs. mild AP			LOH≤9 days vs. LOH>9 days		
	β	OR (95% CI)	p-value	β	OR (95% CI)	p-value	β	OR (95% CI)	p-value
Age categories									
18-34 y (young-aged)	NA[a]	NA[a]	0.961	0	1 (reference)		0	1 (reference)	
35-64 y (middle-aged)	0.76	0.76 (0.35-1.67)	0.493	2.00	7.40 (0.99-55.31)	0.051	0.62	1.86 (1.22-2.83)	0.004
> 65 y (old-aged)	0	1 (ref)		1.93	6.92 (0.91-52.70)	0.062	0.40	1.50 (0.96-2.33)	0.073
Comorbidity categories									
CCI=0 (none)	0	1 (reference)		0	1 (reference)		0	1 (reference)	
CCI=1 (mild)	0.11	1.12 (0.32-3.90)	0.863	0.04	1.04 (0.52-2.08)	0.911	0.00	1.00 (0.75-1.34)	0.983
CCI=2 (moderate)	0.09	1.10 (0.26-4.68)	0.900	-0.02	0.98 (0.45-2.24)	0.960	0.30	1.35 (0.95-1.92)	0.092
CCI>2 (severe)	1.50	4.48 (1.57-12.80)	0.005	0.74	2.10 (1.08-4.09)	0.029	0.15	1.16 (0.83-1.62)	0.387

Table 2. Joint effect of aging and comorbidities on the **outcomes** of acute pancreatitis**.** Red highlights indicate p<0.05, orange highlights indicate p<0.10 but ≥0.05. AP: acute pancreatitis; Charlson Comorbidity Index; CI: confidence interval; LOH: length of hospitalization; NA: not applicable; OR: odds ratio. [a]analysis is impossible due to zero events.

In univariate analysis, out of the six comorbidities associated with higher mortality, moderate/severe liver diseases and metastatic solid tumors proved to be the strongest predictors (OR=8.04, CI: 2.22-29.13 and OR=8.47, CI: 1.78-40.23, respectively). Peripheral vascular diseases, cerebrovascular diseases, and diabetes without complications predicted severe AP. Patients with mild liver diseases were two times more likely to develop local complications, including necrotizing pancreatitis (OR=1.86, CI: 1.25-2.75).

III.5. Discussion

Here we provide the first detailed meta-analysis on the effects of aging on AP. Aging has been demonstrated to play an important role in AP; however, due to the lack of detailed mathematical analysis, there is a great difference between the cut-off values used in predictive scoring systems [17-22].

One main observation was that up until 59 yrs (this cut-off value was mathematically calculated), both severity and mortality rise linearly (*Figure 2 and 3*). The rate of severity increases 0.193%/year, and mortality grows 0.086%/year. It has been documented that almost all death cases come from the severe AP group; therefore, we can assume that although the number of severe cases rises every year, the risk for mortality in severe AP remains constant at around 20% [7].

We found that above 59 yrs the mortality rate rapidly increases; meanwhile, the rate of severe pancreatitis follows a slightly elevated pattern (*Figure 2 and 3*). These data clearly suggest that additional factors which are lacking or rare below 59 yrs also affect mortality in AP. One of the best candidates responsible for the increased elevation of mortality in elderly is definitely co-morbidity. It has been shown that the burden of co-morbidities increases with age [23,25]. In addition, it has been also reported that the outcome of AP is worsen by severe co-morbidities [27,83]. Therefore, we can hypothesize that the elevation of severity and mortality with age is attributed to co-morbidity rather than ageing.

The incidence of severe AP in patients, however, showed a continuous, linear rise between the ages of 20 and 70 (0.193%/year) of up to 16.6%. The mortality rate was 0.9% in patients under 20 and demonstrated a continuous increase until the age of 70. The mortality rate between 20 and 59 grew 0.086%/year and 0.765%/year between 59 and 70. Overall, patients above 70 had a mortality rate 19 times higher than patients under 20. The rise of mortality rate with age was thus also confirmed. This result completely confirms the observation of Ranson et al. that age is associated with a significantly increased risk of death over 55 yrs. [20,84]. Imrie et al. [85] modified the scoring system; however, they still considered age above 60 as a valuable parameter. Balmey et al. [20] evaluated a prospective study with 347 patients in a seven-year period to simplify the system and to improve its accuracy. With regard to age, they also found the cut-off point at 55 yrs.

The BISAP scoring system was established as the first population-based prognostic scoring system in order to evaluate the risk of in-hospital mortality prior to the onset of organ failure [17]. The CART analysis identified age above 60 years for prediction of in-hospital

mortality based on parameters collected in 2000–2001 in the first 24 h from a patient population of 17 922 suffering from AP [17].

In summary, the predictive scoring systems correspond with our results that mortality rises quickly above 59 years of age. These data suggest that other factors such as comorbidity may be associated with older age and can elevate the mortality in AP. Importantly, our analysis showed that severe comorbidities (CCI≥3) predict mortality (OR=4.48; CI: 1.57-12.80) much better than age, suggesting that comorbidity is an important additional predictor for mortality (*Figure 6*).

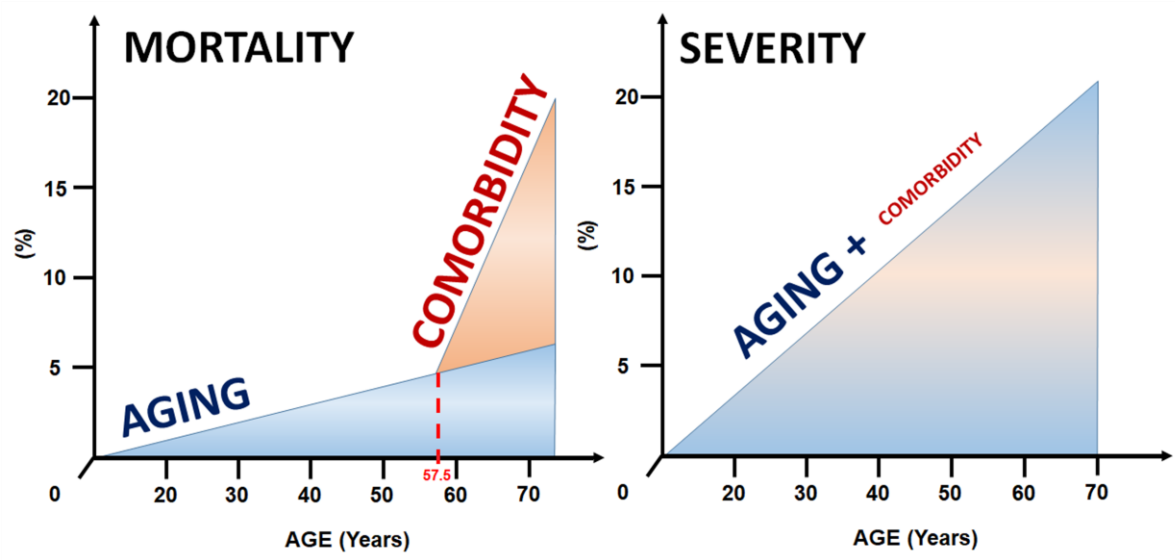

Figure 6. Model for the joint effect of **aging and comorbidities on mortality and severity.** **A** The excess in mortality in the elderly is likely to be explained by the increment in comorbidities with aging. **B** In contrast, age seems to be the strongest predictor of the severity of acute pancreatitis, whereas comorbidities have a less prominent effect.

IV. Chapter II

IV.1 Introduction

Despite the extensive research in the field, no specific therapy is available to treat AP [46].With regard to the pathomechanism of the disease, it is clear that mitochondrial injury and ATP depletion play key roles in the early phase of AP almost irrespectively of the etiology of the disease [88-90]. Bile acids, ethanol, and fatty acids were shown to be responsible for around 80% of the etiological factors initiating AP [91]. All of these factors were shown to induce a toxic calcium signal and severe mitochondrial damage in both acinar and ductal cells [12,90,92-95]. Importantly, direct administration of ATP (i.e., energy) into the cells restored their functions and prevented cell death [96,97]. Therefore, if we take a translational approach, it is more than likely that patient energy intake would be beneficial. Not surprisingly, enteral nutrition (EN) has almost been the only therapeutic change in recent decades to be highly beneficial and to be widely utilized in severe AP (SAP)[98]. However, in mild and moderate AP (MAP), the primary

therapy is still the nil per os diet (NPO) [99]. Since the results in basic science have demonstrated the crucial role of energy breakdown in the early phase of AP, in this chapter we focused on providing evidence whether early enteral feeding is beneficial in AP.

IV.2 Aim

The major aim of this chapter is to understand whether enteral feeding should be the primary therapy in the early phase of AP.

IV.3 Materials and Methods

A randomized controlled trial (RCT) is the only type of clinical scientific methods which can reduce selection bias when testing a new treatment. However, before performing a time consuming, expensive RCT a meta-analysis is crucially important.

(i) If the meta-analysis is decisive, no RCT is needed. The intervention can be used in clinical practice directly.

(ii) If the meta-analysis suggests a significant difference but has several limitations, RCT should be performed.

In this chapter firstly we performed a meta-analysis and than we developed a prestudy protocol for an RCT.

IV.3.1 Article Search for the meta-analysis

A meta-analysis was performed using the preferred reporting items for systematic review and meta-analysis (PRISMA)[37]. An article search was performed in the PubMed, EMBASE, and Cochrane databases in February 2016. The PICO process was used to frame and answer our clinical questions. We split our data into two groups: SAP and MAP. In SAP, only three primary endpoints were checked (mortality, multiorgan failure, and intervention), whereas in MAP, due to the low amount of data, 14 secondary endpoints were collected besides the primary endpoints. All details are described in the main thesis document.

IV.4 Results

IV.4.1 The effects of early enteral feeding in severe AP

Seven out of seven articles contained analyzable data on mortality [100,106,109,117,119,126, 127]. Risk differences and CI were calculated in each article to analyze the effects of EN compared to the NPO nutrition. The calculated average risk difference (RD) was −0.050 (lower limit (LI): −0.134; upper limit (UI): 0.035; p-value: 0.249) (*Figure 7*). Because of the considerable heterogeneity (Q = 16.488; DF: 6; p = 0.011; I^2 = 63.61%) random-effect model was applied. Four out of seven articles contained analyzable data on multiorgan failure (MOF). With regard to MOF, the calculated odds ratio (OR) was 0.258 (LI: 0.072; UI: 0.930; p-value: 0.038; heterogeneity: Q = 13.833; DF: 3; p = 0.003; I^2 = 78.31%) in favor of EN (*Figure 8*). With regard to interventions, a fixed-effect model was used. The calculated average odds ratio (OR) was 0.162 (LI: 0.079; UI: 0.334; p-value: <0.001; Q = 7.221; DF: 3; p = 0.065; I^2 = 58.45%) also in favor of EN (*Figure 9*). Because of the moderate heterogeneity, the random-

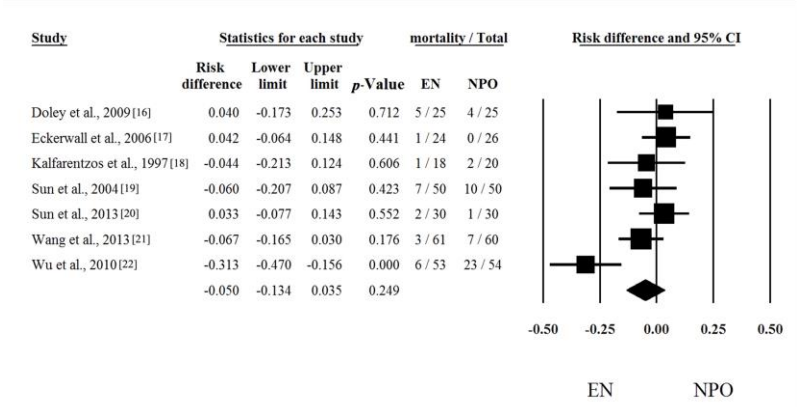

Figure 7. Forest plot of studies evaluating **mortality** data in severe acute pancreatitis (SAP). Risk differences and confidence interval (CI) were calculated to compare the enteral nutrition (EN) with the nil per os diet (NPO). Black squares and lines represent the results for individual studies, the diamond shows the pooled result of the meta-analysis.

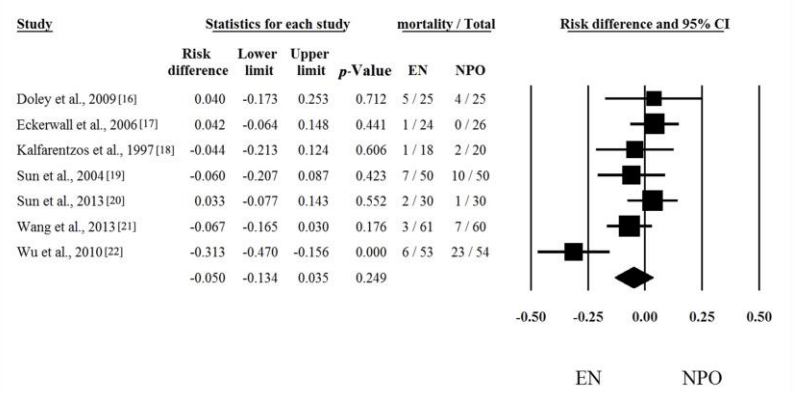

Figure 8. Forest plot of studies evaluating **multiorgan failure (MOF)** in severe acute pancreatitis (SAP). Odds ratio (OR) and confidence interval (CI) were calculated to compare the enteral nutrition (EN) with the nil per os diet (NPO). Black squares and lines represent the results for individual studies, the diamond shows the pooled result of the meta-analysis.

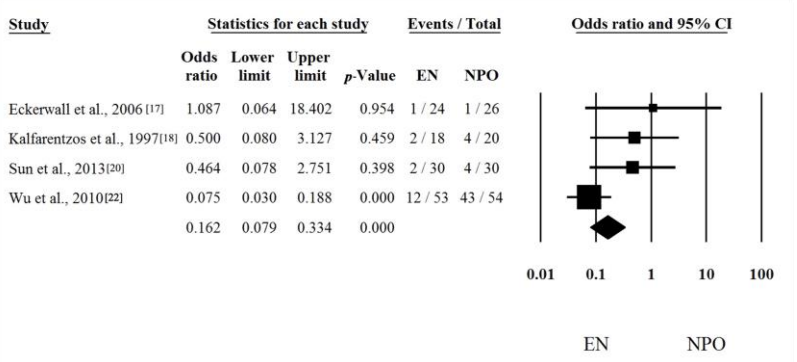

Figure 9 Forest plot of studies evaluating **intervention** in severe acute pancreatitis (SAP). Odds ratio (OR) and confidence interval (CI) were calculated to compare the enteral nutrition (EN) with the nil per os diet (NPO). Black squares and lines represent the results for individual studies, the diamond shows the pooled result of the meta-analysis.

effect model was applied as well (OR was 0.274 (LI: 0.073; UI: 1.025; p = 0.054)). These data clearly suggest that EN is beneficial and should be the primary therapy in SAP.

IV.4.2 The effects of early enteral feeding in mild and moderate AP

Unfortunately, there is much less research activity in patients suffering from MAP than from SAP. Moreover, the frequency of death and MOF are also much less common in the MAP group vs the SAP group. Not surprisingly, analyses of low amounts of data in which the mortality and MOF are close to zero could not reveal any significant difference between the two groups.

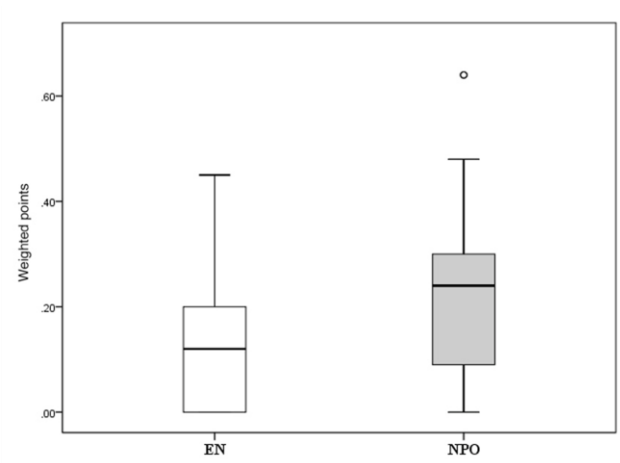

Figure 10. Summary of the uniform data point system in MAP. EN versus NPO. The Mann–Whitney U test was used to detect significant differences between the pooled weighted scores (see Figure 6). o = p < 0.05 vs EN

However, the five articles contained several other secondary parameters (see Methods). Unfortunately, each study group concentrated on different parameters, resulting in the fact that almost none of the parameters had a complete data set. Due to the low n number, statistical analyses could not be calculated separately. Importantly, pooling the data from the 17 parameters (3 primary and 14 secondary endpoints) showed a significant difference in favor of EN (*Figure 10*).

These data strongly suggest that early enteral feeding is beneficial in AP. However, due to the several limitations of our meta-analysis we had to develop an RCT (*see V.5*) to answer our question decisively. Until the submission of this thesis 278 patients were already recruited by four centres (Pécs, Székesfehérvár, Gyula, Debrecen). We plan to finish the study in 2022.

IV.5 The GOULASH trial - Prestudy protocol of a randomized controlled double blind clinical trial

IV.5.1 Design

This is a randomized controlled two-arms double-blind multicentre trial. Patients suffering from acute pancreatitis will be randomly assigned to groups A (high energy administration starting within 24h of hospital admission) and B (no energy administration after 24h of hospital admission). The study was designed using the SPIRIT guideline (Figure 13). All details are described in the main thesis document.

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	*<24h*	0	*day1*	*day2*	*day3*	*dayx*	*discharge*	*1m after discharge*
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Laboratory test	X							
CT examination	X							
Allocation		X						
INTERVENTIONS:								
High energy administration			♦	—	—	♦		
Low energy administration			♦	—	—	♦		
ASSESSMENTS:								
Questionnaire A		X						
Questionnaire B			X	X	X	X	X	
Questionnaire C								X

Figure 13 shows the flow chart of participants according to SPIRIT 2013 statement

IV.5.2 Study population

All patients diagnosed with AP will be informed of the possibility of taking part in the GOULASH study. After the consent form is signed, a computer using a block randomization protocol will randomize the patients.

Inclusion criteria: (1) Patients over 18y of age, (2) diagnosed AP on the base of the "2 out of 3" criteria of the IAP/APA guideline: (a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging; however those patients without abdominal pain will be excluded because the onset of AP cannot be determined, (3) written informed consent form is signed.

Sample size: In order to detect a treatment effect of at least 50% of the early treatment a sample size of 957 subjects will be necessary to be recruited using a 10% drop-out rate, 80% power and 95% significance level. The calculation was performed by the Independent data management and biostatistics provider company (IDMB, Adware Research LTD, Balatonfüred, Hungary).

Randomization: In each centre participants will be divided into 2 groups receiving one of the two study treatments. The allocation of participants to the different groups will be carried out based on predefined randomization lists created separately for each recruiting centre. The randomization lists will be prepared with a block size of 4 and with an allocation ratio of 1:1.

IV.5.3 Intervention

Groups: In **group A,** high energy will be delivered after admission. Patients will receive a 10 Ch nasogastric (NG) or nasojejunal (NJ) feeding tube on admission. EN will be immediately started as follows: On Day 0 (from admission until the start of EN (can vary from 2-24 h)): calorie intake will be 0 kcal/kg/day. From Day 1 high energy enteral tube feed 30 kcal/kg/day will be provided until the oral feeding starts. In **group B,** low energy administration after hospital admission. Patients will receive a NG or NJ feeding tube at admission as described above. On Day 0 (from admission until the start of EN): calorie intake will be 0 kcal/kg/day. On day 1 0 kcal/kg/day, on day 2 10 kcal/kg/day, on day 3 20 kcal/kg/day and from day 4 30 kcal/kg/day calorie will be delivered until the oral feeding starts. However, between groups A and B only the amount of calories administered will be different. Patients will receive the same amount of fluid and ions during EN.

Type of enteral tube: Patients neither vomiting nor having gastric fluid retention >250 ml will receive primarily NG tube. Patients either vomiting or having gastric fluid retention >250 ml will receive NJ tube (placement will be done either endoscopically or radiologically). In case of GCS 14 or lower in a patient who is not intubated, NG tube will be replaced by NJ tube (risk of aspiration). Abdominal X-ray will be used to check the tube's position.

IV.5.4 Discharge of patients

Uniformization of the length of hospital stay is necessary to avoid bias concerning LOH. Re-admission within one week after discharge has to be considered as the same hospital admission. Patients has to be counted as discharged from hospital/from the study when (1) oral feeding was tolerated for 24h, (2) no amylase/lipase level are elevated after total enteral feeding, (3) CRP level is less than 50 mg/L, (4) abdominal pain has completely resolved (5) no other pancreatitis-related complication requiring hospitalization is detected.

IV.5.5 Endpoints

The following primary endpoints will be calculated: A combination of MOF more than 48h and Mortality. The following secondary endpoints will be analyzed: (1) pancreatic necrosis, (2) nutrition related complications: diarrhea, aspiration pneumonia, pneumothorax due to central TPN catheter placement, (3) need for conversion from NG to NJ feeding tube (4) need for conversion from EN to TPN, (5) days until the start of total feeding, (6) use of antibiotics,

(7) pain relapse, (8) CRP, (9) WBC, (10) PCT, (11) infection, (12) length of hospital stay, (13) need for ICU admission, (14) length of ICU therapy, (15) organ failure, (16) complications, (17) costs calculation. Notably, only direct costs will be calculated that include all medications, services, salaries of healthcare professionals, equipment and day care costs.

IV.5.6 Ethics and dissemination.

The trial is registered at the ISRCTN registry (ISRCTN63827758) and got the relevant ethical approval with the reference number of 55961-2/2016/EKU issued by The Scientific and Research Ethics Committee of the Medical Research Council. It is almost needless to say that at the end of the project we will disseminate our results in the medical community. We will publish our results in an open access way.

IV.6 Discussion

There are different therapeutic approaches available with regard to nutrition in acute pancreatitis. The recently published IAP/APA (International Association of Pancreatology/American Pancreatic Association) guidelines recommend that enteral tube feeding be the primary therapy in patients with predicted severe and severe acute pancreatitis who require nutritional support (recommendation G. Nutritional support 21-GRADE 1B, strong agreement)[46], whereas point K22 in the Japanese guidelines states that enteral nutrition can reduce the incidence of complications in the early phase of SAP and can contribute to an increased rate of survival [134]. However, neither of the guidelines provides recommendations on MAP. The reason is understandable. (1) Strong endpoints are missing. The mortality rate is less than 1% in mild AP and 10% in moderate AP, whereas almost no MOF can be detected; (2) since there is a better outcome of the milder disease, researchers have had much less interest in MAP than SAP.

First, we wanted to systematically review the current literature to understand the beneficial effects of early enteral nutrition versus the nil per os diet both in SAP and MAP. Interestingly, there were not many articles in which analyzable data could be found on the two treatments of AP. However, in SAP, the amount of data was sufficient to prove the beneficial effects of enteral feeding. Early enteral feeding was clearly beneficial for MOF and intervention and showed beneficial tendency for mortality. Nevertheless, as predicted, MAP data analyses revealed no significant difference between enteral nutrition and a nil per os diet. However, analyses of the secondary endpoints in the articles demonstrated that enteral feeding could be beneficial compared to a nil per os diet in mild and moderate AP as well.

Therefore, finally we vent further and developed the GOULASH trial, which is a randomized controlled two-arm double-blind multicentre trial. It will provide the first evidence concerning the necessity of early energy supply for patients suffering from acute pancreatitis.

In summary, this study provides the first and type A evidence concerning the necessity of energy intake for patients suffering from AP. Please note that this protocol is the first version of the trial completed on 24th May 2017. The latest protocol can be red at https://tm-centre.org/en/trials/goulash/.

V. Limitations

All kind of scientific methodology has its own limitations. The quality of the included articles and the published data in a meta-analysis is questionable. However, in a prospectively collected cohort population the quality of data is much better but on the other hand the number of recruited patients is significantly less. Concerning the clinical usability of the results of investigations the well designed randomized controlled trials are the most reliable, however the arrangement of the study requires financial, human resources and valuable time support. All the limitations are summarized in the main thesis.

VI. Conclusions - new observations – clinical benefits

1) Pancreatitis-associated mortality is more common with advanced age.
2) The rapid elevation of mortality above the age of 59 suggests the involvement of additional deteriorating factors such as co-morbidity in elderly. Changing age to comorbidity might be reasonable in the predicting scoring systems.
3) Comorbidities determine mortality whereas both comorbidities and aging predict severity of AP.
4) Enteral feeding is beneficial compared to a nil per os diet not only in severe, but also in mild and moderate AP.
5) Development of the GOULASH trial.

The results written in **Chapter 1 change the thinking on severity prediction**. Until now only aging is included in the scoring systems. However, based on our results it is obvious that **comorbidity** should be included as well. This may lead to the development of more sensitive and specific **risk stratification** in AP.

The results written in **Chapter 2** change our understanding concerning the nutrition in AP. Based on the meta-analysis showing that early enteral feeding is beneficial not only in severe but also in mild AP we started early enteral nutrition in our GI division. Within 1 year **we could decrease the mortality from 30 to 10% in severe AP**, in addition, we could decrease the length of hospitalization with around **400 days/year**.

VII. My own work

Article No1

I was involved in: i) the study design, ii) article search, iii) data extractation, iv) risk of bias and quality assessment, v) consultation with biostatisticians, vi) developing the data interpretation with biostatisticians and the PI and in vii) developing the publication strategy. I wrote version No1 of the article, and took part in developing the final version as well. I also prepared v1 of the ‚answers to he reviewers' and the revision.

Article No2

In this knowledge publication I was involved in literature search for relevant publications and helped to develop publication strategy. I wrote the version 1 of the article, and I took part in developing of the final version. I prepared the version 1 of the ‚answers to he reviewers' and the revision.

Article No3

During the three years I recruited patients suffering from AP to the registry (approxymately 50 to 70 patients). I was also actively involved in monitoring of data quality. I also helped data interpretation.

Article No4

I was involved in: i) the study design, ii) article search, iii) data extractation, iv) risk of bias and quality assessment, v) consultation with biostatisticians, vi) developing the data interpretation with biostatisticians and the PI, vii) publication strategy plan. I wrote the version 1 of the article, and I took part in developing of the final version. I prepared the version 1 of the ‚answers to he reviewers' and the revision.

Article No5

I was involved in: i) the study design, ii) sample size calculation, iii) randomization plan. I wrote the version 1 of the article, and I took part in developing of the final version. I prepared the version 1 of the ‚answers to he reviewers' and the revision. I was involved in: iv) the development of the local protocol, v) I coordinated the patient recruitment, vi) I recruited approximately 40 patients in Pécs, vii) I educated and later controlled Székesfehérvár, Debrecen and Gyula centers. I was involved in the safety analysis of the study.

VIII. Future carrier plan

During my PhD work I learned several clinical methodology such as study designs, retrospective and prospective data analysis, observational and interventional clinical trials, meta-analysis, network meta-analysis, case report, EBM guideline. I also had a chance to be involved in the clinical management of the patients from on admission until the discharge of the patients. However, I am also interested in the basic science part of the translational medicine therefore I spent 6 months in a high quality basic science research group focusing on the pathomechanism of the pancreatitis at the University of Szeged.

I would like to continue my personal development in basic science, therefore I moved to the USA and joined to one of the best research groups (MITOCARE) led by Professor György Hajnóczky. After my USA training I want to bring knowledge back to Hungary and wish to be an independent scientist. I wish to continue my clinical development as a trainee gastroenterology and wish to be translational gastroenterologist.

IX. Acknowledgement

I would like to express my enormous gratefulness to my supervisor **Péter Hegyi,** the head of the Center, Division and Institute for Translational Medicine for his belief in me and in my commitment to science. He managed my studies and always provided support and useful advices throughout my work. I endeavor to have a carrier he might be proud of.

I also would like to thank **Kálmán Tóth** the head of the First Department of Internal Medicine and **Áron Vincze** the head of the GI Division, who allowed me to fulfill the clinical part of my work. I am also grateful to the interdisciplinary research unit led by **Andrea Szentesi**.

I am especially thankful for the **Hungarian Pancreatic Study Group** for data collection including the highly dedicated administrators, local clinical investigators, patient

coordinator and biobank leaders. I wish to express my gratitude to the head of administrators at PTE, **Krisztina Harth**, the biostatisticians especially **Nelly Farkas**, **Péter Mátrai** and **Noémi Gede**. I thank for the great help of **Tímea Molnár** and **Krisztina Heid** for the ethical management, **Richárd Farkas** for the IT development, **Bálint Erőss, Zsolt Szakács, Dalma Dobszai** and **Dalma Erdősi** for their helpful advices. I am thankful for my mentor in teaching **Márta Balaskó**.

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I also would like to express my gratitude to **all of my colleagues** at the Institute and Department for Translational Medicine for inspiring my studies, assist my work with useful ideas and the helpfulness in need.

Last but not least, my deepest gratitude goes to **my parents, brother and other members of the family** for their love, encouragement and support during my studies and research work; this dissertation would have been impossible to accomplish without their support. I would like to dedicate this thesis to them.

X. List of abbreviations

A70 – above 70 years
ABP – acute biliary pancreatitis
AE – adverse event
AP – acute pancreatitis
APACHE – Acute Physiology and Chronic Health Evaluation
BALI – BUN, Age, LDH, IL-6
BISAP – Bedside Index for Severity in Acute Pancreatitis
BMI – body mass index
CCI – Charlson Comorbidity Index
CI – confidence interval
CRF – case report file
CRP – C-reactive Protein
DCP – data cleaning plan
DMP – data management plan
DQF – data query form
eCRF – electronic clinical report form
EN – enteral nutrition
ES – effect sizes
GOULASH – name of the study: general utilization of early energy administration in acute pancreatitis.
HPSG – Hungarian Pancreatic Study Group
ICU – intensive care unit
IDMB – Independent data management and biostatistics provider company
IQR – interquartile range
ITAB – International Translational Advisory Board
ITT – Intention to Treat
JNP– Japanese Severity Score
LOH – length of hospital stay/hospitalization
MAP – mild and moderate AP
MOF – multi organ failure
NG – nasogastric
NJ – nasojejunal
OR – odd's ratio
PCT – procalcitonin
PN – parenteral nutrition
PPS – Per Protocol Set
PRISMA – preferred reporting items for systematic review and meta-analysis statement
SAE – severe adverse event
SAP – severe AP
SAPS II – Simplified Acute Physiology Score
SAS – Safety Analysis Set
SC – Steering Committee
SD – standard deviation
TPN – total parenteral nutrition
U20 – under 20 years
WBC – white blood cell count

XI. Publications

XI.1. Publications related to subject the of the thesis

1) **Márta K**, Lazarescu AM, Farkas N, Mátrai P, Cazacu I, Erőss B, Vincze Á, Veres G, Czakó L, Sarlós P, Rakonczay Z, Hegyi P. Aging and Comorbidities in Acute Pancreatitis I: A meta-analysis ad systematic review based on 194 702 patients. **Front Physiol.** 2019 DOI: 10.3389/fphys.2019.00328 **IF: 3.394, Q1,** original publication[1]

2) **Márta K**, Hegyi P. Uncommon appearance of concurrent liver cirrhosis and chronic pancreatitis: The alcohol metabolism theory. **Dig Liver Dis**. 2019 Jan 11. pii: S1590-8658(19)30004-0. doi: 10.1016/j.dld.2018.12.023.PMID:30691775 **IF: 3.287, Q1,** knowledge publication[2]

3) Szakács Z, Gede N, Pécsi D, Izbéki F, Kovács G, Fehér E, Dobszai D, Kui B, **Márta K**, Kónya K, Szabó I, Török I, Gajdán L, Takács T, Sarlós P, Gódi S, Varga M, Hamvas J, Vincze Á, Szentesi A, Párniczky A, Hegyi P. Aging and Comorbidities in Acute Pancreatitis II.: A Cohort-analysis of 1203 Prospectively Collected Cases. **Front Physiol**. 2018 DOI:10.3389/fphys.2018.01776 **IF: 3.394, Q1,** original publication[3]

4) **Márta K**, Farkas N, Szabó I, Illés A, Vincze Á, Pár G, Sarlós P, Bajor J, Szűcs Á, Czimmer J, Mosztbacher D, Párniczky A, Szemes K, Pécsi D, Hegyi P. Meta-Analysis of Early Nutrition: The Benefits of Enteral Feeding Compared to a Nil Per Os Diet Not Only in Severe, but Also in Mild and Moderate Acute Pancreatitis. **Int J Mol Sci**. 2016 Oct 20;17(10). pii: E1691.PMID:27775609 **IF: 3.226, Q1,** original publication[4]

5) **Márta K**, Szabó AN, Pécsi D, Varjú P, Bajor J, Gódi S, Sarlós P, Mikó A, Szemes K, Papp M, Tornai T, Vincze Á, Márton Z, Vincze PA, Lankó E, Szentesi A, Molnár T, Hágendorn R, Faluhelyi N, Battyáni I, Kelemen D, Papp R, Miseta A, Verzár Z, Lerch MM, Neoptolemos JP, Sahin-Tóth M, Petersen OH, Hegyi P; Hungarian Pancreatic Study Group. High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. **BMJ Open**. 2017 Sep 14;7(9):e015874. doi: 10.1136/bmjopen-2017-015874. PubMed PMID: 28912191 **IF: 2.413, Q1,** pre-study protocol publication[5]

XI.2 Publications not related to the subject of the thesis

6) Szakács Zs, Csiszár B, Kenyeres P, Sarlós P, Erőss B, Hussain A, Nagy Á, Kőszegi B, Veczák I, Farkas N, Bódis E, **Márta K**, Szentesi A, Tőkés-Füzesi M, Berki T, Vincze Á, Tóth K, Hegyi P, Bajor J. Hemorheological and hemostatic alterations in celiac disease and inflammatory bowel disease in comparison with non-celiac, non-IBD subjects (HERMES): A case-control study protocol. **BMJ Open.** 2019 Mar 23;9(3):e026315. doi: 10.1136/bmjopen-2018-026315. **IF: 2.413, Q1,** pre-study protocol publication

7) Zsolt Szakács, Beáta Csiszár, Péter Kenyeres, Patrícia Sarlós, Bálint Erőss, Alizadeh Hussain, Ágnes Nagy, Balázs Kőszegi, Ibolya Veczák, Nelli Farkas, Emőke Bódis, **Katalin Márta**, Andrea Szentesi, Margit Tőkés-Füzesi, Tímea Berki, Áron Vincze, Kálmán Tóth, Péter Hegyi, Judit Bajor. Hemorheological and hemostatic alterations in celiac disease and inflammatory bowel disease in comparison with non-celiac, non-IBD subjects (HERMES): A case-control study protocol. **BMJ Open.** 2019 Mar 23;9(3):e026315. doi: 10.1136/bmjopen-2018-026315. **IF: 2.413, Q1,** pre-study protocol publication

8) Halász A, Pécsi D, Farkas N, Izbéki F, Gajdán L, Fejes R, Hamvas J, Takács T, Szepes Z, Czakó L, Vincze Á, Gódi S, Szentesi A, Párniczky A, Illés D, Kui B, Varjú P, **Márta K**, Varga M, Novák J, Szepes A, Bod B, Ihász M, Hegyi P, Hritz I and Erőss B. Outcomes and timing of endoscopic retrograde cholangiopancreatography for acute biliary pancreatitis. **Digestive and Liver Disease** 2019, DLD-18-1331R1, accepted on 25.03.2019 **IF: 3.287, Q1,** original publication

9) Nagy A, Mátrai P, Hegyi P, Alizadeh H, Bajor J, Czopf L, Gyöngyi Z, Kiss Z, **Márta K,** Simon M, Szilágyi ÁL, Veres G, Mosdósi B. The effects of TNF-alpha inhibitor therapy on the incidence of infection in JIA children: a meta-analysis. **Pediatr Rheumatol** Online J. 2019 Jan 18;17(1):4. doi: 10.1186/s12969-019-0305-x. Review. PMID: 30658717 **IF: 2.543, Q1,** original publication

10) Dobszai D, Mátrai P, Gyöngyi Z, Csupor D, Bajor J, Erőss B, Mikó A, Szakó L, Meczker Á, Hágendorn R, **Márta K**, Szentesi A, Hegyi P, Hungarian Pancreatic Study Group. Body-mass index correlates with severity and mortality in acute pancreatitis: A meta-analysis. **World J Gastroenterol**. 2019 Feb 14;25(6):729-743. doi: 10.3748/wjg.v25.i6.729. PMID: 30783376 **IF: 3.3, Q1,** original publication

11) Rumbus Z, Toth E, Poto L, Vincze A, Veres G, Czako L, Olah E, **Marta K**, Miko A, Rakonczay Z Jr, Balla Z, Kaszaki J, Foldesi I, Maleth J, Hegyi P, Garami A. Bidirectional Relationship Between Reduced Blood pH and Acute Pancreatitis: A Translational Study of Their Noxious Combination. **Front Physiol**. 2018 Oct 1;9:1360. doi: 10.3389/fphys.2018.01360. eCollection 2018. PMID: 30327613 **IF: 3.394, Q1,** original publication

12) Demcsák A, Lantos T, Bálint ER, Hartmann P, Vincze Á, Bajor J, Czopf L, Alizadeh H, Gyöngyi Z, **Márta K**, Mikó A, Szakács Z, Pécsi D, Hegyi P, Szabó IL. PPIs Are Not Responsible for Elevating Cardiovascular Risk in Patients on Clopidogrel—A Systematic Review and Meta-Analysis. **Front Physiol**. 2018 Nov 19;9:1550. doi: 10.3389/fphys.2018.01550. eCollection 2018. PMID: 30510515 **IF: 3.394, Q1,** original publication

13) Gódi S, Erőss B, Gyömbér Z, Szentesi A, Farkas N, Párniczky A, Sarlós P, Bajor J, Czimmer J, Mikó A, **Márta K**, Hágendorn R, Márton Z, Verzár Z, Czakó L, Szepes Z, Vincze Á, Hegyi P. Centralized care for acute pancreatitis significantly improves outcomes. **J Gastrointestin Liver Dis**. 2018 Jun;27(2):151-157. doi: 10.15403/jgld.2014.1121.272.pan. PubMed PMID: 29922760. **IF: 1.964, Q2,** original publication

14) Mikó A, Farkas N, Garami A, Szabó I, Vincze Á, Veres G, Bajor J, Alizadeh H, Rakonczay Z Jr, Vigh É, **Márta K**, Kiss Z, Hegyi P, Czakó L. Preexisting Diabetes Elevates Risk of Local and Systemic Complications in Acute Pancreatitis: Systematic Review and Meta-analysis. **Pancreas**. 2018 Sep;47(8):917-923. doi: 10.1097/MPA.0000000000001122. PubMed PMID: 30113426. **IF: 2.958, Q1,** original publication

15) Szapáry L, Tinusz B, Farkas N, **Márta K**, Szakó L, Meczker Á, Hágendorn R, Bajor J, Vincze Á, Gyöngyi Z, Mikó A, Csupor D, Hegyi P, Erőss B. Intralesional steroid is beneficial in benign refractory esophageal strictures: A meta-analysis. **World J Gastroenterol**. 2018 Jun 7;24(21):2311-2319. doi:10.3748/wjg.v24.i21.2311. PubMed PMID: 29881240; PubMed Central PMCID: PMC5989245. **IF: 3.3, Q1,** original publication

16) Kiss Z, Tél B, Farkas N, Garami A, Vincze Á, Bajor J, Sarlós P, **Márta K**, Erős A, Mikó A, Szakács Z, Pécsi D, Mátrai P, Hegyi P, Veres G. Eosinophil Counts in the Small Intestine and Colon of Children Without Apparent Gastrointestinal Disease: A Meta-analysis. **J Pediatr Gastroenterol Nutr**. 2018 Jul;67(1):6-12. doi:10.1097/MPG.0000000000001904. PubMed PMID:29394213 **IF: 2.752, Q1,** original publication

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