Gastrointestinal victims of alcohol: the liver and the pancreas

PhD Thesis

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Scientific metrics

Number of publications **related to the subject** of the thesis: Cumulative impact factor of publications related to the thesis: D1: 2, Q1: 1, Q2: -, Q3: -, Q4: -	3 (3 first author) 13.997
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Number of total citations by **MTM2:** https://m2.mtmt.hu/api/author/10074191 Hirsch Index: 5	67 independent
Number of total citations by Google Scholar https://scholar.google.com/citations?hl=hu&user=1OhNviUAAAAJ&view_op=list_works&sortby=pubdate Hirsch Index: 6	139

Publications related to the subject of the thesis

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Introduction

Alcohol consumption is among the leading causes of death worldwide and is the third among the causes of diseases, the first being smoking, the second hypertension. Harmful use of alcohol is a pattern of psychoactive substance use that is causing damage to health, incorporating the pattern and volume of drinking over time, the drinking context and the quality or contamination of the consumed beverages. Of note, a protective effect was observed in ischemic stroke and diabetes mellitus, which does not compensate the various detrimental effects alcohol poses on physical and mental health. According to the World Health Organisation's (WHO) report on alcohol consumption from 2018, 43% of the population reports current drinking, which translates as more than 2.3 billion consumers. In general, men are more affected by harmful alcohol consumption than women. In 2016, 53.6% of men consumed alcohol in the last 12 months, whereas only 32.2% of women drank. Interestingly, the prevalence of alcohol use disorders (AUD) is 5 times higher in men (8.6% compared to 1.7% in women), which may be explained by more excessive consumption and the preference for hard drinks. Most alcohol-related deaths are due to digestive system diseases (21.3%) and they are the second biggest contributors to the alcohol-attributable burden of disease, highlighting the role of gastroenterologists in the fields of prevention and treatment.

The most frequent and severe gastroenterological diseases caused by harmful alcohol consumption are cirrhosis, acute-on-chronic liver failure (ACLF), alcohol-induced acute pancreatitis (AP) and tumours. Alcohol consumption also facilitates the development of gastro-oesophageal reflux, alcoholic gastritis and gastropathy, peptic ulcer disease, diarrhoea and plays a role in the development of oropharyngeal, oesophageal, gastric, colorectal, pancreatic and liver cancer.

Objectives

In the work conducted for this thesis we used a triad of clinical research methodologies – a cohort analysis, a randomized controlled trial, and a meta-analysis – to assess prognostic factors, preventive and therapeutic interventions in the two gastrointestinal diseases most frequently seen in patients with harmful alcohol consumption: acute pancreatitis and acute-on-chronic liver failure.

In each project, the following objectives were set:

1) We aimed to assess the risk for severity and mortality associated with hypoalbuminemia and its predictive value in acute pancreatitis.

2) We aimed to create a cessation program utilizing brief intervention methods for the prevention of recurrent alcohol-induced acute pancreatitis.

3) We aimed to assess the efficacy and safety of different liver support devices in acute-on-chronic liver failure.

The studies

5.1 Hypoalbuminemia in acute pancreatitis: a prospective cohort analysis

5.1.1 Introduction

AP is the third most frequent cause of hospitalization and fourth most frequent reason for 30-day readmission in the United States. It is associated with immense costs, significant morbidity and mortality. Its incidence varies between 2.8 and 60.3 per 100,000, with an increasing tendency of 3% per year.

Small retrospective cohort studies have shown that hypoalbuminemia is an independent risk factor for severe AP and in-hospital mortality in adults and children. Low serum albumin has been reported to be associated with persistent organ failure and prolonged hospital stay. However, whether albumin is only a marker or there is a cause-effect relationship between hypoalbuminemia and disease severity and mortality should be further evaluated.

While comprehensive analyses are missing on AP patients with hypoalbuminemia and albumin loss in AP, we aimed to evaluate (1) on-admission and in-hospital hypoalbuminemia as a risk factor in AP, (2) the prognostic potential of human serum albumin, (3) whether there is a dose-dependent relationship between albumin level and disease outcomes and (4) the relation of albumin loss to severity and mortality.

5.1.2 Methods

5.1.2.1 Study design

This analysis of an international, prospective, multicentre cohort was conducted using data from the Acute Pancreatitis Registry operated by the Hungarian Pancreatic Study Group (HPSG). Patient data were collected from establishment of the registry to 31st December 2019 on electronic case report forms and validated using a four-tiered data validation protocol. Contributing centres are shown in the online supplementary material. The registry was approved by the Scientific and Research Ethics Committee of the Medical Research Council of Hungary (222254-1/2012/EKU) in 2012. It conforms to the Declaration of Helsinki, as revised in 2013. All participants provided written informed consent.

5.1.2.2 Participants

Analyses were performed on patients' data with albumin measurement anytime during hospitalization (lowest measured albumin cohort, n=1272) and in the first 48 hours of hospitalization (on-admission albumin cohort, n=1149) to answer a post-hoc clinical research question. The cut-off value between the low and normal albumin group was 35 g/L in both cases, based on the commonly used lower normal value. Subjects were further divided into seven subgroups (Groups 1 to 7) using the lowest (n=1272) or first measured (n=1149) albumin values. The analyses of albumin change involved selected patients (n=335) with at least two albumin measurements. Delta albumin was calculated as the difference between the first and lowest measured albumin levels.

5.1.2.3 Statistical analysis

Descriptive statistics are presented as the median with 25% and 75% percentiles (IQR) or mean with standard deviation (SD) for continuous variables and as numbers and proportions for categorical variables. The Chi-squared test or Fisher's exact test was used to assess the relationship between categorical variables. The Mann–Whitney U test or Kruskal–Wallis test followed by Dunnett's post hoc test was used to evaluate differences between groups in the case of continuous variables. Multivariate binary logistic regression analysis was performed to identify the risk factors independently associated with severe disease and mortality. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. The Receiver Operator Characteristic (ROC) curve and Area Under the Curve (AUC) with 95% CI were used to identify the ability of albumin levels to predict the mortality or severity of AP. Best cut-offs were calculated using the Youden index. $P<0.05$ was considered statistically significant, except for the Kruskal–Wallis test followed by Dunnett's post hoc test, where $p<0.025$ was considered statistically significant. All analyses were carried out in R statistical software, version 4.0.2 (R Core Team, 2020, Vienna, Austria), packages: pROC (v. 1.17.0.1) and PMCMRplus (v. 1.9.0.).

5.1.3 Results

5.1.3.1 Incidence of hypoalbuminemia on admission

Nineteen per cent of patients (n=218/1149) presented with hypoalbuminemia (<35g/L). 12.4% of patients were admitted with 30–34.99 g/L albumin levels (Group 5), whereas 4.4% and 2.2% of patients had 25–29.99 g/L (Group 6) and <25 g/L (Group 7) on-admission albumin levels.

5.1.3.2 Dose-dependent association of hypoalbuminemia with complications, severity and mortality

Significantly more patients developed local complications and organ failure in the low albumin group ($p=0.016$ and $p<0.001$, respectively) (***Figures 1-2***). Lower albumin levels correlated with a higher rate of peripancreatic fluid collection and respiratory failure ($p<0.001$ and $p=0.051$). The rate of pancreatic necrosis, pseudocyst or heart failure did not differ significantly between the groups.

Most importantly, hypoalbuminemia was associated with increased mortality ($p=0.020$), disease severity ($p=0.015$) and hospital stay ($p=0.025$) (***Figure 3***). Groups 6 and 7 had significantly higher mortality ($p=0.005$ and $p=0.007$, respectively) and severity ($p=0.028$ and $p<0.001$, respectively) compared to the normal group. Maximum C-reactive protein (CRP) levels during the course of AP significantly and dose-dependently increased with the degree of serum albumin ($p<0.001$) (***Figure 3***).

5.1.3.3 On-admission hypoalbuminemia is an independent risk factor for severity and mortality

Age, hypertriglyceridemia-induced (with or without concomitant alcoholic aetiology) and idiopathic AP were independently associated with mortality. Severe on-admission hypoalbuminemia proved to be an independent risk factor for mortality with an OR of 3.782 (CI: 1.313–9.462) in Group 6 (<30 g/L) and an OR of 5.256 (CI: 1.389–16.112) in Group 7 (<25 g/L). Albumin levels were examined with a 35 g/L cut-off in a separate analysis, which found an independent relation between hypoalbuminemia and mortality (OR: 2.070; CI: 1.021–4.033). Age, hypertriglyceridemia-induced AP, and, among the multifactorial aetiologies, a combination of hypertriglyceridemia and alcohol were independent risk factors for disease severity. On-admission albumin levels <25 g/L were independently associated with severe AP (OR: 3.620; CI: 1.128–9.978).

5.1.3.4 Dose-dependent association of hypoalbuminemia during hospitalization with severity and mortality

The proportion of patients with hypoalbuminemia anytime during hospitalization was 35.7% (454 patients). A significant, dose-dependent increase was seen in the low albumin groups (Group 5–7) compared to the normal albumin group as regards the rate of all examined systemic and local complications (***Figures 1-2***). The lowest measured albumin levels throughout hospitalization were significantly and dose-dependently associated with severity ($p<0.001$), mortality ($p<0.001$), length of stay ($p<0.001$) and maximum CRP values ($p<0.001$) (***Figure 3***).

5.1.3.5 Lower albumin levels and greater albumin loss is associated with severity and mortality

Compared to mild cases, patients with moderate and severe AP showed a greater decrease in albumin levels (medians 5.4 vs. 9.0 and 15.25 g/L; $p<0.001$ for both comparisons). The comparison of delta albumin between the moderate and severe groups also yielded significant results ($p=0.003$). Patients who died also lost significantly more albumin during hospitalization (medians 6.7 vs. 15.75 g/L; $p=0.002$). The median time to the lowest albumin levels from admission was 4 days (IQR: 3–7 days).

5.1.3.6 Extreme hypoalbuminemia increases the risk of severe AP and death

Age is an independent risk factor for severe AP and mortality, whereas hypertriglyceridemia-induced and idiopathic AP and a combination of alcoholic and biliary causes are independently associated with mortality. Hypoalbuminemia below 25–29.99 g/L (OR: 2.912; CI: 1.176–6.893) and below 25 g/L (OR: 16.828; CI: 8.323–35.129) were associated with an increased risk of mortality. In a separate analysis, hypoalbuminemia (<35 g/L) was also an independent risk factor for mortality (OR: 4.185; CI: 2.286–8.039). Furthermore, hypoalbuminemia anytime during hospitalization was associated with a higher risk for severe AP (OR: 10.664; CI: 6.188–19.614), and a gradual increase of odds ratios can be observed in the low albumin groups (OR: 2.359; CI: 1.030–5.240 for Group 5; OR: 11.709; CI: 6.038–23.515 for Group 6; and OR: 48.761; CI: 25.276–98.908 for Group 7).

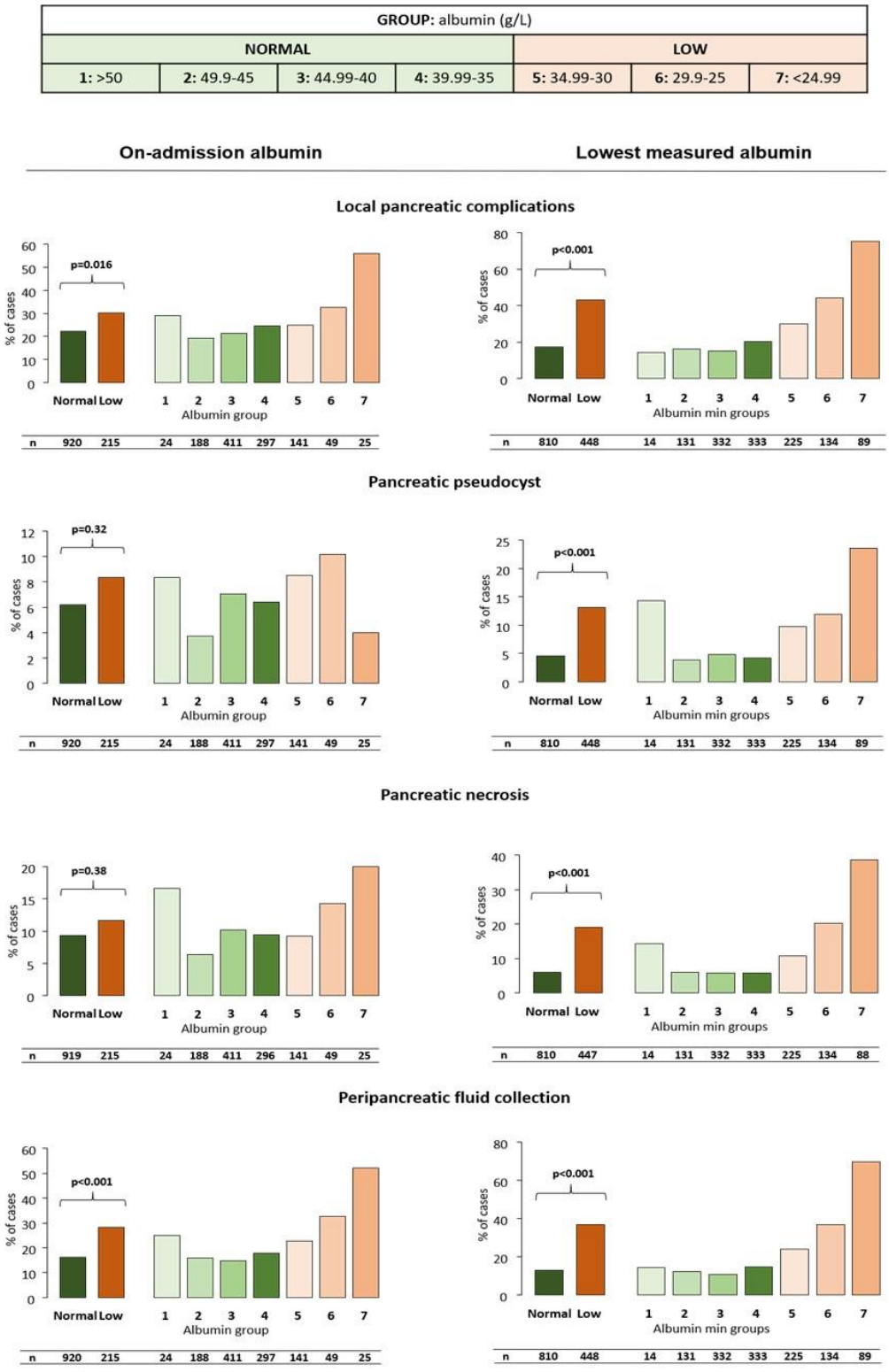


Figure 1 Relation between albumin level and local complications, as defined by the Revised Atlanta Criteria in acute pancreatitis *All types of local complications were significantly more frequent in the low albumin group. A dose-dependent increase was seen in the rate of local complications and peripancreatic fluid collection in both cohorts and in pancreatic necrosis and pseudocyst in the lowest measured albumin cohort. P<0.05 is considered significant. Patients with albumin levels <35 g/L were included in the low albumin group (Groups 5–7).*

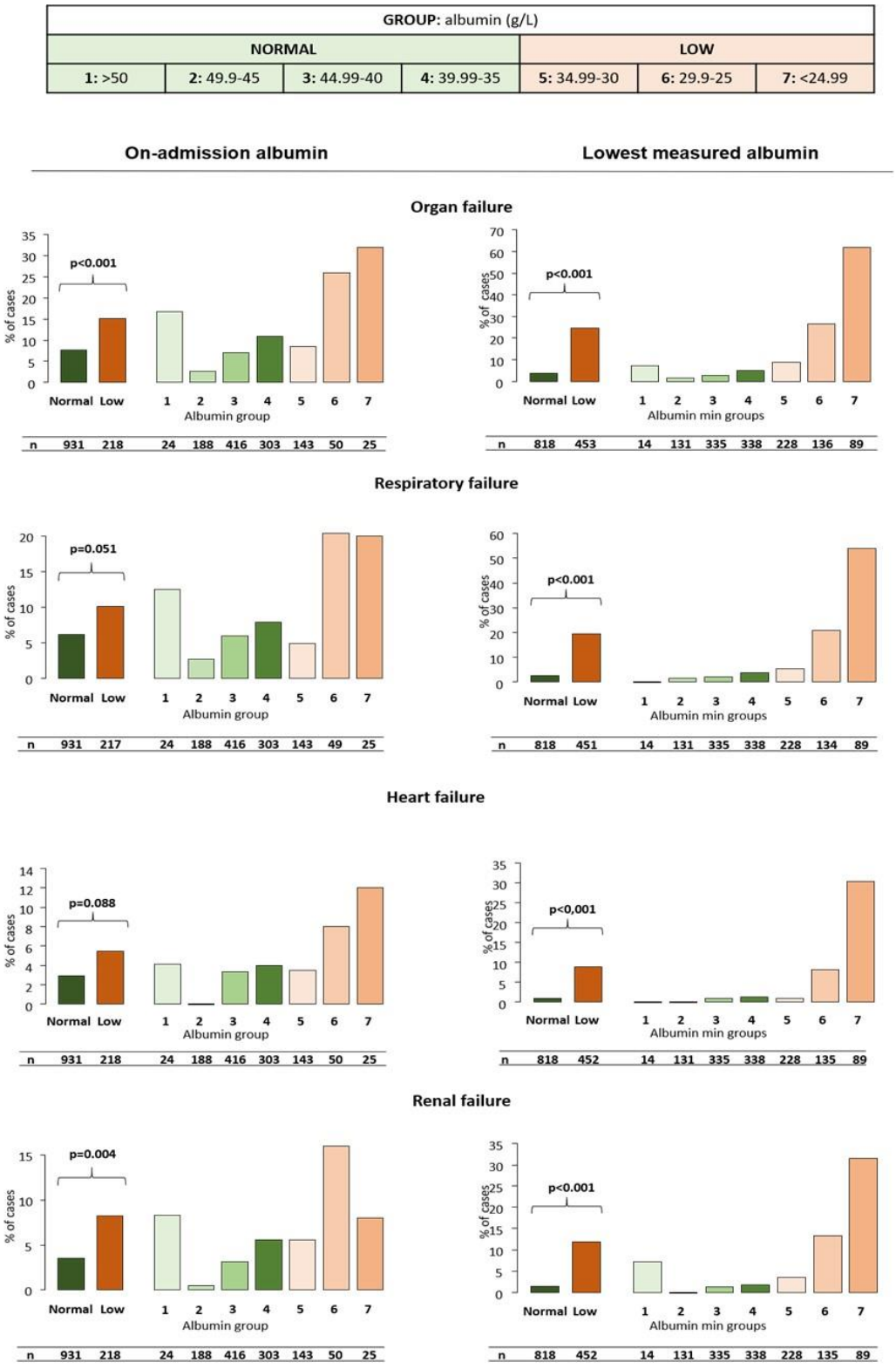
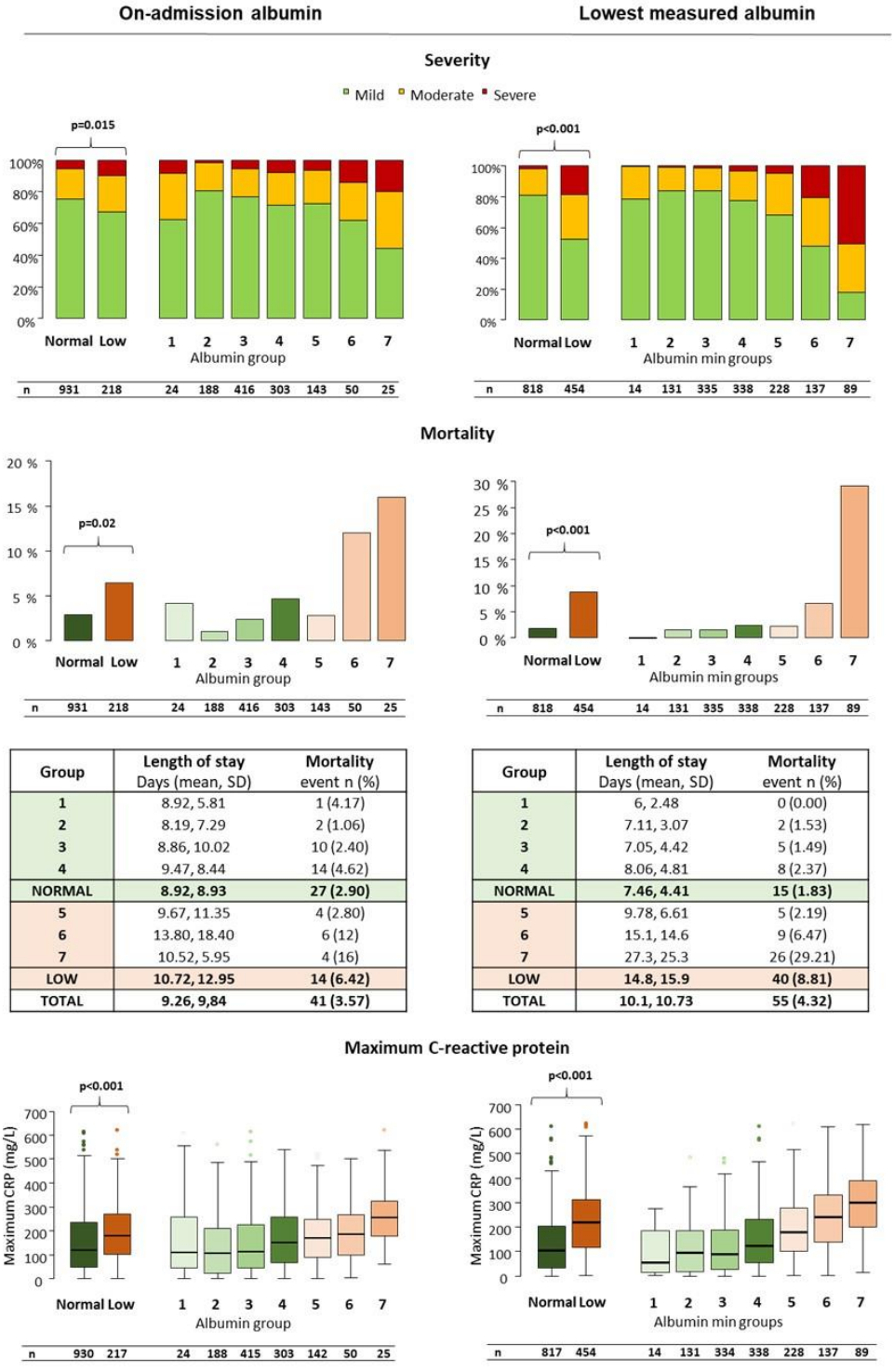


Figure 2 Relation between albumin level and organ failure, as defined by the Revised Atlanta Criteria in acute pancreatitis *Significantly more patients developed organ failure in the low albumin group in both cohorts. A dose-dependent increase was seen in the case of all analyses in the lowest measured albumin cohort. Heart failure was dose-dependently increased in the on-admission cohort as well. P<0.005 is considered significant.*

GROUP: albumin (g/L)						
NORMAL				LOW		
1: >50	2: 49.9-45	3: 44.99-40	4: 39.99-35	5: 34.99-30	6: 29.9-25	7: <24.99



Group	Length of stay Days (mean, SD)	Mortality event n (%)
1	8.92, 5.81	1 (4.17)
2	8.19, 7.29	2 (1.06)
3	8.86, 10.02	10 (2.40)
4	9.47, 8.44	14 (4.62)
NORMAL	**8.92, 8.93**	**27 (2.90)**
5	9.67, 11.35	4 (2.80)
6	13.80, 18.40	6 (12)
7	10.52, 5.95	4 (16)
LOW	**10.72, 12.95**	**14 (6.42)**
TOTAL	**9.26, 9,84**	**41 (3.57)**

Group	Length of stay Days (mean, SD)	Mortality event n (%)
1	6, 2.48	0 (0.00)
2	7.11, 3.07	2 (1.53)
3	7.05, 4.42	5 (1.49)
4	8.06, 4.81	8 (2.37)
NORMAL	**7.46, 4.41**	**15 (1.83)**
5	9.78, 6.61	5 (2.19)
6	15.1, 14.6	9 (6.47)
7	27.3, 25.3	26 (29.21)
LOW	**14.8, 15.9**	**40 (8.81)**
TOTAL	**10.1, 10.73**	**55 (4.32)**

Figure 3 Relation between albumin level and disease severity, mortality, length of stay and maximum C-reactive protein level in acute pancreatitis *Severity, mortality, length of stay and maximum C-reactive protein levels were significantly and dose-dependently associated with hypoalbuminemia in both cohorts. P<0.05 is considered significant.*

5.1.4 Discussion

To date, this is the most comprehensive evaluation of AP patients with hypoalbuminemia, using the largest, prospectively collected, high-quality dataset. We found that almost one-fifth of patients had hypoalbuminemia on admission (19%), and a further 25% developed hypoalbuminemia during hospitalization, meaning that every third patient was affected.

In our analysis, hypoalbuminemia under 25 g/L anytime during hospitalization was independently associated with a more than 47-fold higher chance for severe AP and a more than 16-fold higher chance for mortality. Our findings are consistent with results for hypoalbuminemia in other diseases. Hypoalbuminemia was a prominent risk factor in community-acquired bloodstream infection with severe sepsis and septic shock. A retrospective analysis of data from more than 20,000 emergency medical patients in Ireland found that hypoalbuminemia is independently associated with 30-day in-hospital mortality, with a non-linear relationship between mortality and on-admission albumin levels. Moreover, in a secondary analysis of a prospective cohort, AP patients with multiple organ failure (MOF) (n=18) demonstrated a sharper decline in serum albumin ($P<0.001$) compared to non-MOF patients (n=39).

5.1.5 Conclusion

Hypoalbuminemia is remarkably common in AP and represents an independent risk factor for severity and mortality. Importantly, albumin loss during hospitalization was also associated with severity and mortality, suggesting that routine monitoring of serum albumin is recommended, and that albumin administration should be examined as a therapeutic intervention in AP.

5.1.6 Implications for research

Clinical trials are needed to assess the potential benefit of albumin replacement in AP.

5.1.7 Implications for practice

(1) Albumin levels should be measured for all AP patients, (2) albumin levels should be controlled at least in those patients whose condition is worsening during AP, and (3) albumin administration should at least be considered in patients with severe hypoalbuminemia (<25 g/L).

5.2 Recurrence prevention in alcohol-induced acute pancreatitis: protocol of a randomized controlled trial

5.2.1 Introduction

AP is an often-unheeded issue by clinicians and healthcare professionals, with significant medical charges. Although alcohol is reportedly the first or second most frequent cause of AP worldwide, only a very small proportion (2-5%) of high-risk drinkers develop the disease. Alcoholic AP is often seen together with smoking and hypertriglyceridemia, further worsening prognosis. Yadav et al. found a linear increase in the prevalence and amount of smoking with alcohol consumption in AP patients. Smoking is a long-established independent risk factor of AP and chronic pancreatitis (CP). Findings are controversial regarding the effects of smoking cessation.

Cohort studies have found that 10 to 30% of patients have recurrent attacks based on medical history, and a recent meta-analysis has shown that 10% of the patients after a single episode of AP and 26% of those with recurrent acute pancreatitis (RAP) later progress to CP. Despite the importance and potentially preventable nature of alcoholic RAP, preventive efforts are still scarce. With 6-month alcohol cessation counselling in a randomized controlled trial (RCT), Nordback et al. achieved a significant reduction in the recurrence rate of alcoholic AP in Finland.

It is known that more than half of patients suffering from AUD are also dependent on tobacco, and that continued tobacco use represents a more than two-fold risk for relapse. To this day there are no adjusted protocols for the treatment and follow-up of heavy-drinking smokers.

5.2.2 Objectives

The study encompasses a randomized controlled trial (REAPPEAR-T) and a concomitant cohort study (REAPPEAR-C). The REAPPEAR-T's objective is to investigate the effect of an alcohol and smoking cessation program combined with patient education on the recurrence rate of alcohol-induced AP, CP and quality of life (QoL). Additionally, the REAPPEAR-C's objective is to investigate the effect of alcohol and smoking cessation (irrespective of intervention) on the recurrence rate of alcohol-induced AP, CP and QoL.

5.2.3 Methods

5.2.3.1 Design

The REAPPEAR study, designed in accordance with the SPIRIT statement , utilizes a combined design to answer two questions in one particular patient population. The REAPPEAR-T will be an international, single-blind, 2-arm, parallel group, superiority randomized controlled trial, testing the efficacy of a cessation program for alcohol and smoking, using brief interventions. The REAPPEAR-C is a prospective 4-arm cohort study, which includes all patients participating in REAPPEAR-T with further enrolment after the termination of enrolment to the trial. In the cohort, patients will be grouped by smoking status and alcohol consumption at the end of the study, irrespective of intervention. The same eligibility criteria and outcomes will be used in both sub-studies and differences will be described in the appropriate sections in detail.

5.2.3.2 Population

Inclusion criteria:

- patient hospitalized with alcohol-induced AP (defined by the revised Atlanta criteria)
- regular consumption of at least 40g (women)/ 50g (men) alcohol daily or 280g (women)/ 350g (men) alcohol during the preceding week of onset of abdominal pain
- everyday smoker with at least 1-year history of smoking
- aged 18-65 years
- completed the standard intervention (see below)
- provided written informed consent

Exclusion criteria:

- possible aetiologies for AP other than alcohol (eg. gallstone-related, hypertriglyceridemia above 11.5 mM , hypercalcemia, viral infection) and cases with combined etiological factors will be excluded
- major psychiatric illnesses (e.g., schizophrenia, bipolar disorder, dementia)
- currently receiving therapy for AUD or taking part in a smoking cessation program
- three or more documented lifetime episodes of AP or CP criteria are met
- undergoing active or palliative treatment for malignancy
- pregnancy
- life expectancy is less than two years

5.2.3.3 Standard intervention

The standard intervention will be incorporated into standard medical therapy in all centres, and will be provided to all patients hospitalized for alcohol-induced AP by a specially trained nurse. The intervention will be based on the WHO initiative 'Assist-linked brief intervention', using psychoeducational and motivational interviewing techniques. It will also provide educational information about the nature of alcoholic AP and the risk of recurrence to the patients.

5.2.3.4 Intervention in REAPPEAR-T

The repeated intervention will be provided by the same specially trained personnel and structured similarly to the standard intervention. Each session will have the same structure but can be tailored to the patient's needs to strengthen motivation. Sessions will consist of 3 parts. First, the negative effects of alcohol and smoking on the pancreas will be highlighted. Second, the patient's motivation for abstinence and smoking cessation will be discussed. Third, the individual's responsibility in achieving the goals set after motivation assessment, with personalized advice. We wish to enhance the efficacy of the repeated intervention by providing feedback for the patient based on the mean corpuscular volume (MCV) and gamma glutamyl-transferase (GGT) values measured at the day of the interview. The trained personnel providing the interventions will not take part in patient care in any form.

5.2.3.5 Outcomes

The primary endpoint of the REAPPEAR Study will be the composite of 2-year recurrence rate of AP irrespective of aetiology and 2-year all-cause mortality.

Secondary endpoints:

1) RAP irrespective of aetiology (given as cumulative incidence and as rate of event) within 6, 12, 18 and 24 months.
2) Recurrence of alcohol-induced AP (rate of event) within 2 years.
3) The condition of 'likely pancreatitis' (fulfilling the diagnostic criteria of epigastric pain, a serum amylase or lipase level at least two times the upper normal level, and elevated leukocyte count or CRP levels, defined by Pelli et al)
4) Length of hospital stay given in days (specifically due to recurrent pancreatitis and cumulative during follow-up)
5) Presentation to the emergency unit with and without hospital re-admission (cumulative incidence)
6) Change of alcohol consumption and tobacco use (compared to baseline), estimated separately form biomarker levels and patient-reported consumption
7) Chronic pancreatitis (incidence within 2 years)
8) Changes in body mass index and blood pressure (compared to baseline)
9) Healthcare cost from the perspective of the health insurance fund within 2 years and quality adjusted life years

5.2.3.6 Flow and timing

Patients who met the inclusion criteria and none of the exclusion criteria will be offered to participate in the REAPPEAR-T trial. The enrolment period lasts from 48 hours before, until one week after hospital discharge. After informed consent and randomization, participants will be assigned to the cessation program or the control group (***Figure 4***). All patients will appear at the clinic according to the study schedule (***Figure 5***), within ±14 days from the pre-scheduled date.

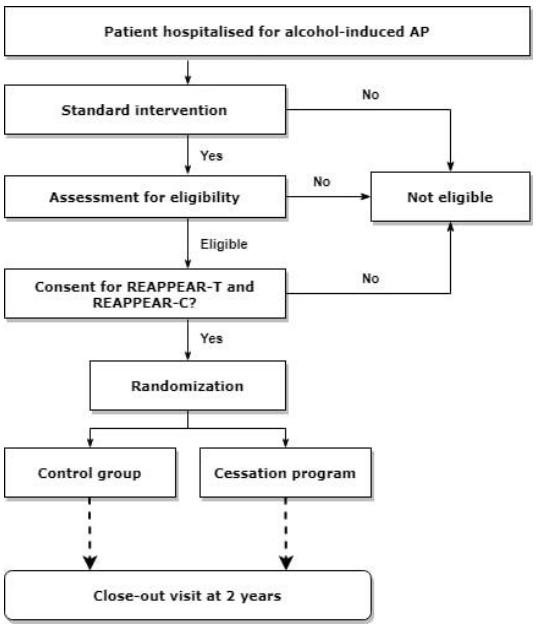


Figure 4 SPIRIT flowchart *Standard intervention will be provided for every patient as part of standard therapy. All randomized participants will be included in the REAPPEAR-T (trial) and REAPPEAR-C (cohort) as well. After reaching the required patient numbers for the REAPPEAR-T, further patients will be enrolled to the REAPPEAR-C in accordance with the estimated sample size.*

We chose 3-monthly visits in the cessation program based on a Swedish cohort study, in which 3-monthly brief interventions for selected patients with increased GGT levels were introduced and GGT levels were used for feedback. These interventions were found to reduce mortality, hospitalization and sick leave significantly. Hopefully, frequent visits will help in upholding motivation and improve adherence. Patients in the control group will have 2 pre-scheduled appointments, at 12 and 24 months.

	STUDY PERIOD	Screening enrollment period	Allocation	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Close-out
			day 0	3 months		6 months		9 months		12 months		15 months		18 months		21 months		24 months
	GROUP	Both	Both	CG	CP	CG	CP	CG	CP	CG	CP	CG	CP	CG	CP	CG	CP	Both
ENROLLMENT	Eligibility screen	X																
	Standard intervention	X																
	Informed consent	X																
	Allocation		X															
INTERVENTION					X		X		X		X		X		X		X	
ASSESSMENT	BP, HR, BMI		X		X		X		X	X	X		X		X		X	X
	Laboratory testing		X		X		X		X	X	X		X		X		X	X
	Questionnaires		X		X		X		X	X	X		X		X		X	X
	Sample collection		X		X		X		X	X	X		X		X		X	X

Figure 5 SPIRIT timetable *Abbreviations: control group (CG), cessation program (CP), blood pressure (BP), heart rate (HR), body mass index (BMI)*

5.2.4 Ethics

The trial has been registered at the clinicaltrials.gov (NCT04647097). Amendments will be published under this registration number. The Scientific and Research Ethics Committee of the Hungarian Medical Research Council approved the study (40394-10/2020/EÜIG). All local ethical approvals are in place. The study will be performed in accordance with the declaration of Helsinki, the principles of ICH-GCP guidelines and local legal and regulatory requirements.

5.2.5 Discussion

Although alcohol and smoking are individual risk factors for AP, RAP and CP, they can synergize each other's effects. In addition, there is a lack of evidence as to the means of preventive measures that could be used in everyday clinical practice concerning alcohol and tobacco use for AP patients. Also, the effect of smoking cessation on recurrence in drinkers and non-drinkers is not yet clear.

The REAPPEAR study aims to fill these gaps and provide specialists and primary care physicians with valuable information on the importance of alcohol and smoking cessation in AP and RAP. Furthermore, the feasibility, efficacy and cost-effectiveness of an intervention program will be tested in this population to provide basis for large-scale intervention in alcohol-induced pancreatitis.

5.3 Liver support therapy in acute-on-chronic liver failure: a network meta-analysis and systematic review

5.3.1 Introduction

ACLF is a clinical entity, observed in patients with chronic liver disease, characterized by the failure of one or more organ systems and high short-term mortality.

Studies using the European Association for the Study of the Liver – Chronic Liver Failure Consortium (EASL-CLIF) definition reported a worldwide prevalence of 24-34% in at-risk population (mostly patients hospitalized with decompensated cirrhosis). 28-day transplant-free mortality in patients with decompensated cirrhosis without ACLF was 1.9% in the CANONIC study and 2.6% in a Chinese analysis. Mortality in ACLF correlates with the number of organ failures, ranging from 23% to 23.6% in grade 1, from 31% to 40.8% in grade 2 and from 60.2 to 74% in grade 3 ACLF. 90-day mortality rates ranged from 2.1% in patients without ACLF to 84.7% in grade 3 ACLF.

The leading cause of chronic liver disease in ACLF patients in Europe and North America is alcohol. Alcoholic cirrhosis was identified in more than 60% of all cases in the CANONIC study, while active alcoholism was determined as the precipitating event in 16.8% of the cases. Hepatitis C virus infection is the second most frequent etiological factor, while mostly bacterial infections, alcohol and gastrointestinal bleeding trigger the development of organ failure.

Several therapies have been tested for the replacement of hepatic functions. So far, liver transplantation is the only curative therapy available. Survival rates are good, but availability and eligibility for transplant in ACLF differs by country. In the CANONIC study, only 4.5% of ACLF patients received transplant. Reportedly, low transplant rates are due to the high prevalence of infection and organ failure. Waiting-list mortality exceeds 50% in this population.

The Asian Pacific Association for the Study of the Liver (APASL) consensus guideline from 2019 states that “plasma exchange appears to be a promising and effective bridging therapy in patients with ACLF to liver transplant or spontaneous regeneration [1, C]”. The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines do not recommend liver support therapies for the treatment of ACLF, but underlines the importance of further studies, because in specific subgroups ACLF seems beneficial.

To facilitate international discussion and consensus, we decided to perform the first network meta-analysis (NMA) comparing all available and tested liver support systems to each other and standard medical therapy (SMT) in patients with ACLF and ranking these treatments by survival benefit.

5.3.2 Methods

The protocol for this review was registered in the PROSPERO database under registration number CRD42020155850. There were no protocol deviations. This meta-analysis was reported according to The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions (PRISMA-NMA).

5.3.2.1 Eligibility criteria

Parallel randomized controlled trials assessing the safety and efficacy of artificial and bioartificial liver support therapies in adult patients with ACLF were eligible for inclusion.

Conference abstracts were included to reduce publication bias. Crossover studies were excluded from the analyses of survival due to concerns about the carryover effect but were included in the systematic review. ACLF definitions used in the included RCTs were accepted, as there is a lack of international consensus regarding this matter.

5.3.2.2 Search strategy and selection

The systematic search was conducted up to the 15th December 2019 in the following databases: MEDLINE (via PubMed), Embase, CENTRAL, Web of Science and Scopus, with the search key designed based on the PICO format, using keywords for liver diseases and liver support systems and random*. No filters or restrictions were applied.

5.3.2.3 Risk of bias assessment and quality of evidence

The risk of bias assessment was conducted in duplicate using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) for overall (OS) and transplant-free survival (TFS) separately. For the four outcomes assessed in the NMA, quality of evidence was assessed in duplicate according to the Grading of Recommendation, Assessment, Development and Evaluation Working Group's recommendations, using a modified GRADE approach.

5.3.2.4 Statistical analysis

A Bayesian method was used to perform pairwise meta-analyses and NMAs with the random effect model for OS and TFS. We used risk ratios (RR) for dichotomous data with 95% credible intervals (95% CrI). We ranked the interventions by their posterior probability by calculating the surface under cumulative ranking (SUCRA) curve values ranging from 0 to 100%. All calculations were performed with R (V. 3.5.2) package gemtc (V. 0.8-2) along with the Markov Chain Monte Carlo engine JAGS (V. 3.4.0) and STATA 16.0 (StataCorp LLC).

5.3.3 Results

5.3.3.1 Search and selection

The systematic search yielded 2,797 records. Four additional articles were identified through manual search and from previous meta-analyses. Twenty-three articles proved to meet the eligibility criteria for the systematic review and 16 were included in the data synthesis.

5.3.3.2 Characteristics of the included studies

Of the 16 studies, enrolling 1670 patients included in the meta-analysis 15 compared a type of artificial or bioartificial liver support system to SMT and one study compared Molecular adsorbent and recirculating system (MARS) versus MARS plus plasma exchange (PE). The most common aetiologies of underlying diseases were viral infection and alcohol. From the 1526 participants with available information on gender, 1064 were males (69.8%).

5.3.3.3 Survival

Survival was reported in most of the included studies, with greatly varying follow-up lengths. Data synthesis was feasible in four cases: 1-month (28-31 days) and 3-month (84-91 days) data

were pooled for overall and transplant-free survival. The summary of the findings for these four outcomes is presented in ***Table 1.***

PE demonstrated a statistically significant survival benefit compared to SMT in the analysis for 3-month OS (RR 0.74; CrI 0.60 to 0.94), with 86% SUCRA, 46% probability of being the best and 41% probability of being the second-best option from the six listed treatments (***Figure 6)***. PE also ranked first on the cumulative curves in three out of four analyses: both 1- and 3-month OS and 1-month TFS. In the analysis for 1-month TFS PE rank second after extracorporeal liver assist device (ELAD), with 76% versus 79% SUCRA values, but had a slightly higher cumulative probability of being in the first two places than ELAD (90% versus 88%).

MARS ranked second in both OS outcomes ***(Figure 6)*** with 73% SUCRA at 1 month and 71% at 3 months. Concerning TFS, MARS ranked second last and last with SUCRA values of 27% at 1 month and 33% at 3 months.

Prometheus was included in both OS analyses and in 3-month TFS. Only MARS, PE and their combination performed better than this device in the OS outcomes and it ranked second after PE for 3-month TFS. However, the SUCRA values and the probabilities for the first ranks are much lower than for PE (SUCRA: 40% for both OS and 51% for 3-month TFS, first rank probabilities 5% for 1-month OS, 4% for 3-month OS and 13% for 3-month TFS, shown on ***(Figures 6)***. Although ELAD therapy, the only biological device ranked first for 1-month TFS, in the analysis for 3-month TFS it had a SUCRA of 38%, even lower than SMT (41%).

BioLogicDT was included in the OS analyses and ranked second last in both cases. SMT had the lowest probability of being the best or second-best option in all four analyses.

5.3.3.4 Harms

In the numbers of adverse events (AEs) and reporting protocols an immense heterogeneity was shown; therefore, quantitative data synthesis was not carried out. All devices were evaluated to be safe, and the number of AEs was comparable to the control groups. Hassanein et al. described nine possibly treatment-related adverse events in the MARS group, however, the nature of these was not detailed. Acute haemolysis developed in one patient in the ELAD group and treatment was discontinued in several cases due to adverse events not specified. Heemann et al. compared AEs in the MARS group to patients who received dialysis and found no significant difference. Two out of the twelve patients treated with MARS had fever/sepsis possibly related to the catheter.

AEs were reported in all but four papers in general. The most frequent complications were bleeding at the site of the catheter, clotting in the apparatus, and thrombocytopenia. Hypotension was reported in patients treated with PE and Prometheus.

5.3.4 Discussion

Extracorporeal liver support therapies have been and will remain of fundamental interest in the management of ACLF. However, their benefits have been debated for long. Therefore, we conducted the first NMA focusing on patients with ACLF, assessing OS and TFS at one and three months. The analyses for OS yielded similar results, with PE ranking first and MARS

second on the cumulative ranking curves in both cases. From all comparisons, only PE was associated with a statistically significant improvement, when compared to SMT in the analysis of 3-month OS, but with very low certainty of evidence. Other comparisons did not reach statistical significance, but SMT had very low probabilities of being the best option in all analyses.

5.3.5 Implication for research

International consensus is needed to standardize the definition of ACLF, enhancing research efficiency. Further RCTs targeting carefully selected subgroups of the ACLF population, using already existing and new therapeutic methods are needed to produce high quality evidence for guideline development.

5.3.6 Implication for practice

PE seems to have the most beneficial effect at present, but liver support devices in general had higher probabilities for the first two ranks than SMT. Choosing the best option remains in the hands of the attending physician.

Intervention (Studies)	Rank	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects		Overall certainty of evidence
		SMT	Liver support		Risk with SMT	Risk difference with liver support	
1-month overall survival							
PE (1 RCT)	1	122/359 (34.0%)	19/104 (18.3%)	**RR 0.51** (0.12 to 2.40)	34 per 100	**17 fewer per 100** (from 30 fewer to 48 more)	⊕⊕⊕◯ MODERATE
MARS (3 RCTs)	2		109/113 (96.5%)	**RR 0.60** (0.15 to 1.30)		**14 fewer per 100** (from 29 fewer to 10 more)	⊕◯◯◯ VERY LOW
MARS+PE (indirect)	3		7/60 (11.7%)	**RR 0.60** (0.07 to 3.20)		**14 fewer per 100** (from 32 fewer to 75 more)	⊕◯◯◯ VERY LOW
Prometheus (1 RCT)	4		29/77 (37.7%)	**RR 1.00** (0.25 to 4.30)		**0 fewer per 100** (from 25 fewer to 100 more)	⊕◯◯◯ VERY LOW
BioLogicDT (1 RCT)	6		6/10 (60.0%)	**RR 1.10** (0.24 to 5.40)		**3 more per 100** (from 26 fewer to 100 more)	⊕◯◯◯ VERY LOW
ELAD (3 RCTs)	7		26/117 (22.2%)	**RR 1.40** (0.56 to 3.60)		**14 more per 100** (from 15 fewer to 88 more)	⊕◯◯◯ VERY LOW
1-month transplant-free survival							
ELAD (2 RCTs)	1	109/264 (41.3%)	14/43 (32.6%)	**RR 0.47** (0.13 to 1.20)	41 per 100	**22 fewer per 100** (from 36 fewer to 8 more)	⊕◯◯◯ VERY LOW
PE (1 RCT)	2		47/104 (45.2%)	**RR 0.52** (0.21 to 1.20)		**20 fewer per 100** (from 33 fewer to 8 more)	⊕⊕⊕◯ MODERATE
MARS (3 RCTs)	3		60/122 (49.2%)	**RR 0.96** (0.50 to 1.50)		**2 fewer per 100** (from 21 fewer to 21 more)	⊕◯◯◯ VERY LOW
3-month overall survival							
PE (2 RCTs)	1	334/569 (58.7%)	136/244 (55.7%)	**RR 0.74** (0.60 to 0.94)	59 per 100	**15 fewer per 100** (from 23 fewer to 4 fewer)	⊕◯◯◯ VERY LOW
MARS (2 RCTs)	2		12/17 (70.6%)	**RR 0.78** (0.38 to 1.40)		**13 fewer per 100** (from 36 fewer to 23 more)	⊕◯◯◯ VERY LOW
Prometheus (1 RCT)	3		46/77 (59.7%)	**RR 0.97** (0.68 to 1.40)		**2 fewer per 100** (from 19 fewer to 23 more)	⊕◯◯◯ VERY LOW
ELAD (4 RCTs)	4		78/213 (36.6%)	**RR 0.99** (0.76 to 1.30)		**1 fewer per 100** (from 14 fewer to 18 more)	⊕◯◯◯ VERY LOW
BioLogicDT (1 RCT)	5		5/5 (100.0%)	**RR 1.00** (0.55 to 2.10)		**0 fewer per 100** (from 26 fewer to 65 more)	⊕◯◯◯ VERY LOW
3-month transplant-free survival							
PE (1 RCT)	1	189/396 (47.7%)	42/104 (40.4%)	**RR 0.77** (0.51 to 1.10)	41 per 100	**11 fewer per 100** (from 23 fewer to 5 more)	⊕⊕⊕◯ MODERATE
Prometheus (1 RCT)	2		52/77 (67.5%)	**RR 0.96** (0.67 to 1.40)		**2 fewer per 100** (from 16 fewer to 19 more)	⊕◯◯◯ VERY LOW
ELAD (4 RCTs)	4		76/217 (35.0%)	**RR 1.00** (0.78 to 1.40)		**0 fewer per 100** (from 11 fewer to 19 more)	⊕◯◯◯ VERY LOW
MARS (1 RCT)	5		7/8 (87.5%)	**RR 1.10** (0.61 to 2.10)		**5 more per 100** (from 19 fewer to 53 more)	⊕◯◯◯ VERY LOW

Table 1 Summary of findings *Significant results are highlighted in bold. Interventions are compared to SMT as reference comparator SMT: standard medical therapy; CrI: Credible interval; PE: Plasma exchange; RCT: Randomized controlled trial; RR: Risk ratio: MARS: Molecular adsorbent and recirculating system; ELAD: Extracorporeal liver assist device*

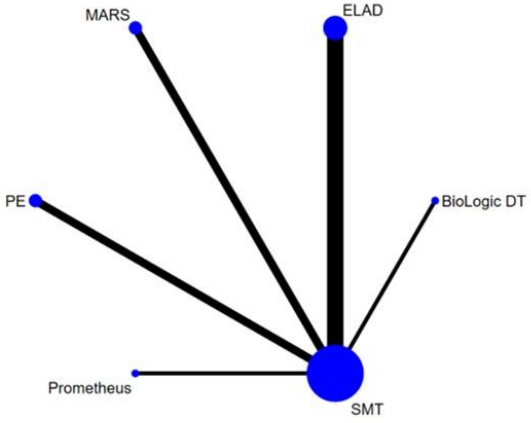
A.

Treatment 1 / RR (95% CrI)					Treatment 2
PE					
0.95 (0.53, 2.0)	MARS				
0.76 (0.50, 1.2)	0.81 (0.36, 1.5)	Prometheus			
0.75 (0.53, 1.1)	0.79 (0.37, 1.5)	0.98 (0.63, 1.6)	ELAD		
0.72 (0.35, 1.4)	0.75 (0.28, 1.7)	0.93 (0.43, 1.9)	0.95 (0.46, 1.9)	BioLogicDT	
0.74 (0.60, 0.94)	0.78 (0.38, 1.4)	0.97 (0.68, 1.4)	0.99 (0.76, 1.3)	1.0 (0.55, 2.1)	SMT

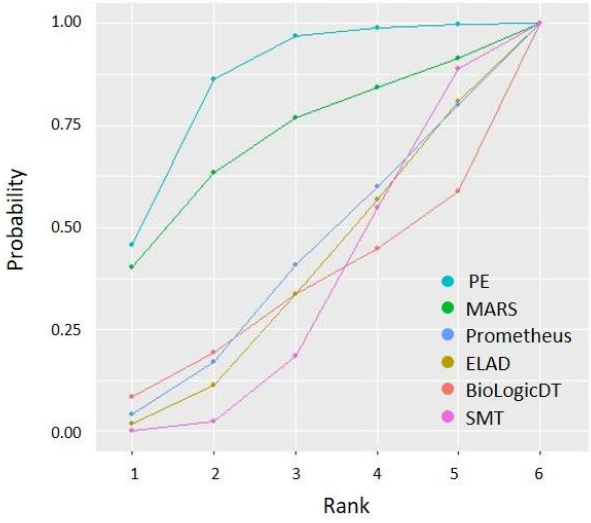
B.

Study ID	Intervention(s)	Patients/group
Thompson (2018)	ELAD/SMT	96/107
Hillebrand (2010)	ELAD/SMT	14/4
Teperman (2012)	ELAD/SMT	25/28
Pyrsopoulos (2019)	ELAD/SMT	78/73
Qin (2014)	PE/SMT	104/130
Yu (2008)	PE/SMT	140/140
Ellis (1999)	BioLogicDT/SMT	5/5
Sen (2004)	MARS/SMT	9/9
Mitzner (2000)	MARS/SMT	8/5
Kribben (2012)	Prometheus/SMT	77/68

C.



D.



E.

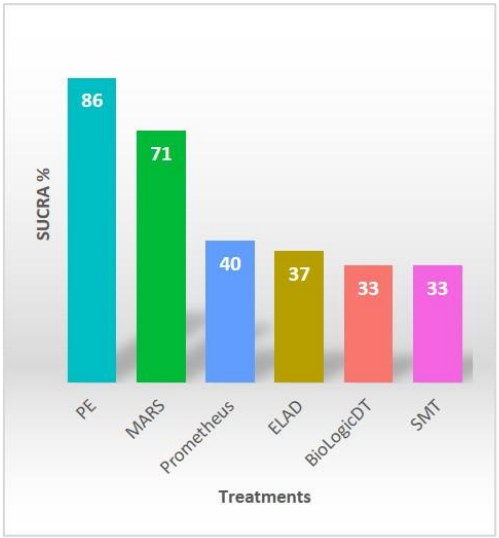


Figure 6 3-month overall survival *League table containing risk ratios and credible intervals for all comparisons (**A**), studies included in the analysis for (**B**), geometry of the network (**C**), cumulative ranking curves (**D**) and surface under the cumulative ranking curves (SUCRA) (**E**) RR: risk ratio; CrI: credible interval; PE: plasma exchange; MARS: Molecular adsorbent and recirculating system; ELAD: Extracorporeal liver assist device; SMT: standard medical therapy*

Clinical significance and implementation of the findings presented in the thesis

The immense burden of harmful alcohol consumption in the form of digestive system diseases – including AP and ACLF – necessitates the close collaboration of pancreatologists and hepatologists, to reduce alcohol-related gastrointestinal morbidity and mortality. The various similarities in the pathophysiology and therapeutic goals in AP and ACLF offer a starting block for scientific and clinical collaboration between these two fields. Due to the social and cultural context of alcohol use, effective treatment and the prevention of progression are of utmost importance and must be in the focus of gastroenterologists. Index hospitalisations with alcohol-induced AP or alcoholic liver disease provide an opportunity for the assessment of both organs and the initiation of preventive measures and cessation programs. As a result of early intervention, the damage caused by harmful alcohol consumption can be reversed, and several organs – including the liver and the pancreas – spared.

Summary of novel findings and perspectives

Hypoalbuminemia in acute pancreatitis: a prospective cohort analysis

- We found that hypoalbuminemia is remarkably common in AP (seen in 19% of patients on admission and 35.7% during hospitalization).
- We saw not only that hypoalbuminemia represents an independent risk factor for severe disease course but there is a dose-dependent association with severity and mortality in AP (<25 g/L serum albumin anytime during hospitalization have a 16.8-fold higher risk of death and 48.8-fold higher risk of severe AP than patients with normal albumin levels).
- We also observed that albumin loss during AP is associated with severity and mortality.
- Based on these findings, we formulated the following implications for practice which immediately change the treatment of AP patients:
    - Albumin levels recommended to be measured for all AP patients
    - Albumin levels suggested to be followed up at least in those patients whose condition is worsening during AP
    - Albumin administration should at least be considered in patients with severe hypoalbuminemia (<25 g/L)
- Our results point towards RCTs focusing on albumin replacement in AP.

Recurrence prevention in alcohol-induced acute pancreatitis: protocol of a randomized controlled trial

- We provide a gap-filling international, multicentre, randomized controlled trial to examine the effects of a combined intervention for the reduction of nicotine and alcohol consumption in alcohol-induced AP.
- We created a tailored alcohol and smoking cessation program for patients with alcoholic AP in order to reduce the recurrence rate and to prevent the development of CP.
- Incorporating the REAPPEAR cessation program to the everyday practice will revolutionize the care of patients with AUD, furthermore, it could result in the decrease of medical expenses in the future.

Liver support therapy in acute-on-chronic liver failure: a network meta-analysis and systematic review

- We performed the first NMA comparing all available and tested liver support systems to each other and standard medical therapy in patients with ACLF, assessing safety and efficacy, ranking these treatments by survival benefit.
- We found that all liver support systems are safe with low occurrence of complications.
- Plasma exchange therapy showed significant survival benefit at 3 months and seems to be the most effective treatment option currently available.
- Our results facilitate international discussion and a consensus expected in the near future on the clinical utility of liver support systems.

Author's contribution

In all three articles used in the thesis, the author played a key role in conceptualization, planning, performing the analyses and writing the manuscript.

Additional contributions:

Ocskay et al. Scientific Reports, 2021

The author took part in patient management at centres participating in the Acute Pancreatitis Registry of the HPSG, participated in patient enrolment, curated the data, designed the analyses, edited the figures and tables, interpreted the results, and wrote the original draft.

Ocskay et al. BMJ Open, 2021

The author was responsible for the design of the intervention program and coordination of the contributors as well as conducting the test patient interviews. The author wrote the original draft of the manuscript.

Ocskay et al. Annals of Intensive Care, 2021

The author conducted data extraction, risk of bias and certainty of evidence assessment, designed the analyses and wrote the original draft of the manuscript.