Bridging the Gap: Integrating Research Findings into Clinical Practice for Pancreatitis and Cystic Fibrosis Management

Ph.D. Thesis

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1. Ph.D. profile

1.1. Vision

To provide the most safe and effective clinical patient care as much as possible based on our current knowledge.

1.2. Mission

Our aim is to draw attention to the gap in current recommendations or patient care through a number of diseases (e.g., acute pancreatitis and cystic fibrosis).

1.3. Specific goals

To achieve these objectives, we have used several approaches. First, we analyzed data from patients with acute pancreatitis to highlight:

1. methods to prevent recurrence: either in biliary or in alcoholic acute pancreatitis
2. discharge protocols are missing in AP care worldwide
3. following discharge protocols can result in shorter length of stay
4. by specific analysis of the HPSG-protocol, it is proved to be safe and results in shorter length of stay
5. higher-than-normal BMI is associated with favorable outcomes in the CF population.

1.4. Scientometric parameters

Number of papers:	**13 (3 first author)**
Cumulative IF:	127.4
Av IF/publication:	9.1
Ranking (Sci Mago)	D1: 8, Q1: 6
Number of publications related to the subject of the thesis	**3 (3 first author)**
D1: 2, Q1: 1, Q2: -, Q3: -, Q4:	
Number of citations on Google Scholar	89
Rita Nagy - Google Tudós	
Number of citations on MTMT (independent)	58
Nagy Rita (Gyermekgyógyászat) (MTMT)	
H-index:	5

1.5. List of publications

- **First author papers**

1. **Nagy R,** Ocskay K, Váradi A, Párniczky A, Hegyi P. In-Hospital Patient Education Markedly Reduces Alcohol Consumption after Alcohol-Induced Acute Pancreatitis. **Nutrients.** 2022 May 20;14(10):2131. doi: 10.3390/nu14102131.
2. **Nagy R**, Gede N, Ocskay K, Dobai BM, Abada A, Vereczkei Z, Pázmány P, Kató D, Hegyi P, Párniczky A. Association of Body Mass Index With Clinical Outcomes in Patients With Cystic Fibrosis: A Systematic Review and Meta-analysis. **JAMA Netw Open**.2022 Mar 1;5(3):e220740. doi:10.1001/jamanetworkopen.2022.0740.
3. **Nagy R**, Harangi F, Tárnok A, Vincze Á, Ocskay K, Párniczky A, Hegyi P. Revisiting the evidence-based management of paediatric pancreatitis. **Pancreatology**. 2021 Aug;21(5):1011-1013. doi: 10.1016/j.pan.2021.06.008.

- **Co-author papers**

1. Czapári, D., Váradi, A., Farkas, N., Nyári, G., Márta, K., Váncsa, S., **Nagy, R.**, Teutsch, B., Bunduc, S., Erőss, B., Czakó, L., Vincze, Á., Izbéki, F., Papp, M., Merkely, B., Szentesi, A., Hegyi, P., & Hungarian Pancreatic Study Group (2023). Detailed Characteristics of Post-discharge Mortality in Acute Pancreatitis. **Gastroenterology**, S0016-5085(23)00801-6. Advance online publication. https://doi.org/10.1053/j.gastro.2023.05.028. **(IF:33.8; D1)**
2. Váncsa, S., Sipos, Z., Váradi, A**., Nagy, R**, Varga, M., Török, I., Mickevicius, A., Erőss, B., Párniczky, A., … Hungarian Pancreatic Study Group (2023). Metabolic-associated fatty liver disease is associated with acute pancreatitis with more severe course: Post hoc analysis of a prospectively collected international registry**. United European gastroenterology journal,** 10.1002/ueg2.12389. Advance online publication. https://doi.org/10.1002/ueg2.12389áncsa, S., Sipos,
3. Pomozi E, **Nagy R**, Fehérvári P, Hegyi P, Kiss B, Dembrovszky F, Kosztin A, Nardai S, Zima E, Szeberin Z. Direct Oral Anticoagulants as the First Choice of Anticoagulation for Patients with Peripheral Artery Disease to Prevent Adverse Vascular Events: A Systematic Review and Meta-Analysis**. J Cardiovasc Dev Dis**. 2023 Feb 3;10(2):65. doi: 10.3390/jcdd10020065.
4. Horváth IL, Bunduc S, Fehérvári P, Váncsa S, **Nagy R**, Garmaa G, Kleiner D, Hegyi P, Erőss B, Csupor D. The combination of ulinastatin and somatostatin reduces complication rates in acute pancreatitis: a systematic review and meta-analysis of randomized controlled trials. **Sci Rep.** 2022 Oct 26;12(1):17979. doi: 10.1038/s41598-022-22341-7.
5. Inflammatory bowel disease does not alter the clinical features and the management of acute pancreatitis: A prospective, multicenter, exact-matched cohort analysis. Dohos D, Farkas N, Váradi A, Erőss B, Párniczky A, Szentesi A, Hegyi P, Sarlós P; Hungarian Pancreatic Study Group (including **Nagy R**). **Pancreatology**. 2022 Dec;22(8):1071-1078. doi: 10.1016/j.pan.2022.09.241.
6. Kiss S, Pintér J, Molontay R, Nagy M, Farkas N, Sipos Z, Fehérvári P, Pecze L, Földi M, Vincze Á, Takács T, Czakó L, Izbéki F, Halász A, Boros E, Hamvas J, Varga M, Mickevicius A, Faluhelyi N, Farkas O, Váncsa S, **Nagy R**, Bunduc S, Hegyi PJ, Márta K, Borka K, Doros A, Hosszúfalusi N, Zubek L, Erőss B, Molnár Z, Párniczky A, Hegyi P, Szentesi A; Hungarian Pancreatic Study Group. Early prediction of acute necrotizing pancreatitis by artificial intelligence: a prospective cohort-analysis of 2387 cases. **Sci Rep**. 2022 May 12;12(1):7827. doi: 10.1038/s41598-022-11517-w.
7. Sebők J, Édel Z, Váncsa S, Farkas N, Kiss S, Erőss B, Török Z, Balogh G, Balogi Z, **Nagy R,** Hooper PL, Geiger PC, Wittmann I, Vigh L, Dembrovszky F, Hegyi P. Heat therapy shows benefit in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. **Int J Hyperthermia**. 2021;38(1):1650-1659.
   doi: 10.1080/02656736.2021.2003445.
8. Vereczkei Z, Farkas N, Hegyi P, Imrei M, Földi M, Szakács Z, Kiss S, Solymár M, **Nagy R**, Bajor J. It Is High Time for Personalized Dietary Counseling in Celiac Disease: A Systematic Review and Meta-Analysis on Body Composition. **Nutrients**. 2021 Aug 25;13(9):2947. doi: 10.3390/nu13092947.
9. Dembrovszky F, Váncsa S, Farkas N, Erőss B, Szakó L, Teutsch B, Bunduc S, **Nagy R,** Dohos D, Kiss S, Párniczky A, Vinkó Z, Péterfi Z, Hegyi P. Immunoglobulin Response and Prognostic Factors in Repeated SARS-CoV-2 Positive Patients: A Systematic Review and Meta-Analysis. **Viruses**. 2021 Apr 30;13(5):809. doi: 10.3390/v13050809.

10. Váncsa S, Dembrovszky F, Farkas N, Szakó L, Teutsch B, Bunduc S, **Nagy R**, Párniczky A, Erőss B, Péterfi Z, Hegyi P. Repeated SARS-CoV-2 Positivity: Analysis of 123 Cases. **Viruses.** 2021 Mar 19;13(3):512. doi: 10.3390/v13030512
11. Szentesi A, Farkas N, Sipos Z, Mátrai P, Vincze Á, Izbéki F, Párniczky A, Hegyi P; Hungarian Pancreatic Study Group (including **Nagy R**). Alcohol consumption and smoking dose-dependently and synergistically worsen local pancreas damage. **Gut**. 2022 Dec;71(12):2601-2602. doi: 10.1136/gutjnl-2021-326853. Epub 2022 Jan 19.

2. Introduction

In the past decade, the concept of evidence-based medicine (EBM) has been clearly defined. The advantage of this approach is to avoid deficiencies in clinical care that rely on local expert opinion and provide a framework for assessing and using the latest available evidence for decision making. Implementation of EBM offers standards that potentially provide the best quality of medical care at a reasonable cost. The unfulfilled need for new clinically-important information has a negative impact on our clinical competency after completing formal training. This decline is evident when clinicians' knowledge is measured on even basic care for disorders such as hypertension. Research shows a significant negative correlation between up-to-date care knowledge and years elapsed since graduation from medical school. In addition, a study of clinical behavior found that the decision to prescribe antihypertensive drugs was more closely related to the number of years since medical school graduation than to the severity of target organ damage in the patient.

I would like to demonstrate the importance of clinical guidelines and protocols throughout an acut and chronic disease, namely acute pancreatitis and cystic fibrosis.

Objectives

Our aim was to highlight areas in upper mentioned disease groups where interventions are needed, to update current care, to expand guidelines. In this thesis we conclude the findings of two registry analyzes, one case report and one systematic review and meta-analysis with the following clinical questions:

- Does discharge protocol exist in AP?
- Does the existence of discharge protocols in AP result in shorter hospitalization?
- Is there any tool to reduce the number of recurrences in alcohol-induced AP?
- Are the clinical outcomes better in patients with cystic fibrosis with higher-than-normal BMI?

3. Studies

3.1. Discharge protocol in acute pancreatitis: an international survey and cohort analysis

3.1.1. Objective

In this study, our aim was to conduct a widespread international survey on the existing discharge protolols in AP and investigate the safety (readmission rate) and effectiveness (length of hospital stay) of the HPSG-protocol.

3.1.2. Methods

1. International cohort

To assess the worldwide trends in patient discharge in AP we conducted a multicenter web-based survey by following the Checklist for Reporting of Survey Studies (CROSS). We sent a letter of invitation and a questionnaire to all members of the International Association of Pancreatology (IAP) in January 2021. The questionnaire's main purpose was (i) to investigate the presence of any discharge protocol in AP and (ii) to understand the laboratory parameters and the clinical status of the patients upon discharge.

2. The HPSG discharge protocol

In 2016, the HPSG developed a discharge protocol with specific and combined elements on clinical status, laboratory parameters, and therapy. The protocol was developed based on the C20 point of the IAP/APA and HPSG EBM guideline which indicated that oral feeding in predicted mild pancreatitis can be restarted as early as the intensity of abdominal pain and inflammatory markers have started to decline (25). The protocol was as follows:

1) Patient's CRP level and either amylase or lipase levels were monitored every day.
    a. Once the patient's abdominal pain resolved and
    b. Pancreatic enzyme levels showed a decreasing trend and
    c. CRP level started to decrease and
    d. there was no clinical condition that contraindicated oral feeding,

    the patient's oral feeding with solid diet was immediately started.

2) If, 24 hours after oral refeeding,
    a. the patient has not developed any abdominal symptoms and
    b. the pancreatic enzyme level has decreased further and
    c. there were no other conditions or therapies (e.g., iv. antibiotics, endoscopic intervention) requiring hospitalization and
    d. CRP level has
        i. fallen below 50 mg/l, the patient was discharged
        ii. further decreased but remained above 50 mg/l, both hospitalization and oral feeding were continued for an additional day

3) If, after the additional 24 hours of oral feeding (i.e., 48h after refeeding was started)

a. the patient has not developed any abdominal symptoms and
b. the pancreatic enzyme level has decreased further and
c. there was no clinical condition that contraindicated feeding and,
d. CRP level has further decreased,

the patient was discharged independently of the absolute CRP value.

Three of the 17 investigated centers used the above-mentioned discharge protocol in Hungary. Therefore, for data analysis, two groups of the Hungarian cohort were identified: 1) centers where the HPSG-discharge protocol was used (688 patients – Hungarian protocol cohort) and 2) where no discharge protocol was used (941 patients – Hungarian non-protocol cohort). A multicenter, multinational, prospective AP registry developed in 2013 by HPSG was used for data analysis and patients were enrolled during the period 2016-2019.

3. Statistical analysis

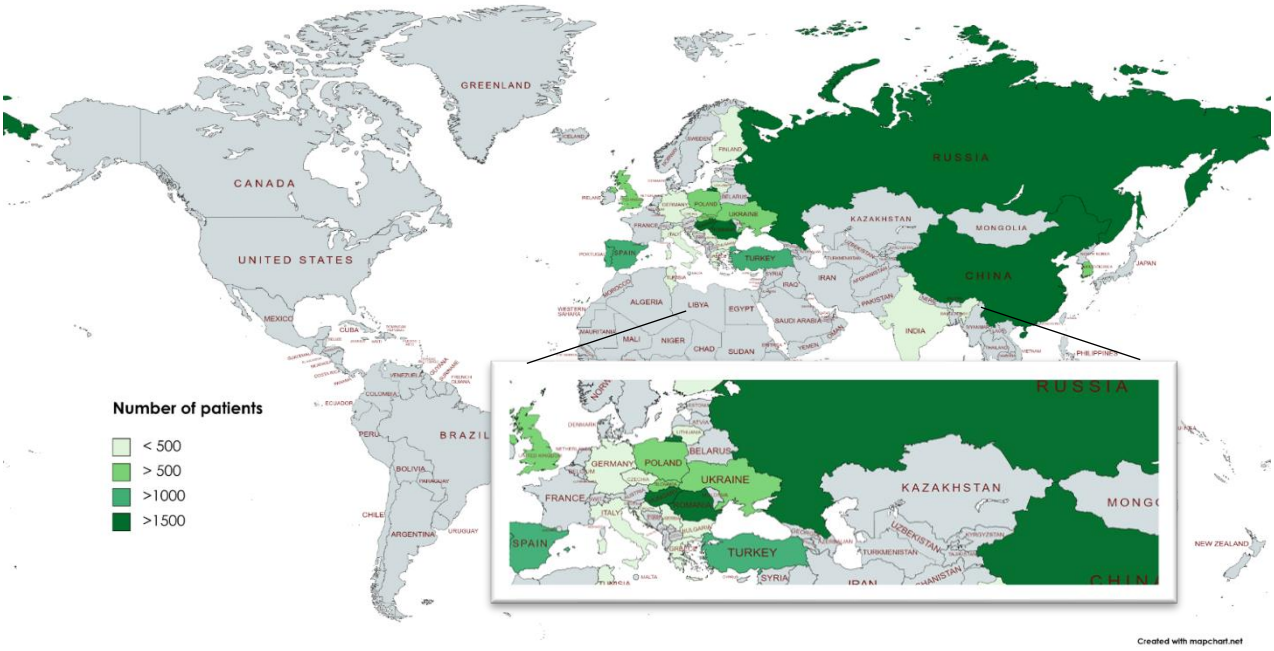
Statistical analyzes were performed by using R environment (R Core Team (2021), version 4.1.0). For descriptive statistics, the number of patients, mean, standard deviation (SD), minimum, median and maximum values were calculated for continuous variables and case number and percentage were calculated for categorical values. To determine statistical significance between two groups of independent samples, t-test was used for normally distributed data and the Mann-Whitney U and Mood's test for non-normally distributed data. The association between categorical variables was calculated by the Chi-square test and Fisher's exact test. "Pairwise Nominal Independence" post-hoc test (package: rcompanion) was conducted using Bonferroni correction for a 2-dimensional matrix of two categorical variables in which at least one dimension has more than two levels. Receiver operating characteristics (ROC) analysis was performed to assess the accuracy of the prediction of discharge CRP value in terms of 1-month readmission. The threshold of significance was $p<0.05$.

3.1.3. Results

1. Basic characteristics of the international cohorts

Overall, 13930 cases from 3 continents, 23 countries, 56 centers participated in the survey and were analyzed. Altogether 1754 (12.59%) cases belonged to the international protocol group. The participating countries and the number of uploaded cases are illustrated on a colour-scaled map (Figure 1). The median age was significantly lower in the non-protocol group (58 (Q1;Q3: 44;71) vs. 56 (Q1;Q3: 42;70) years, p=0.012). Furthermore, in the non-protocol group the number of severe cases was significantly higher (14.1% vs 5.3%) as well as the overall mortality rate (4.2% vs 2.9%, p=0.03) (Figure 2).

Figure 1. Map of the participating countries in the survey and analysis



The map shows the number of patients provided for analysis in different shades of green. A darker shade indicates more patients included. Created by MapChart (https://mapchart.net/world.html).

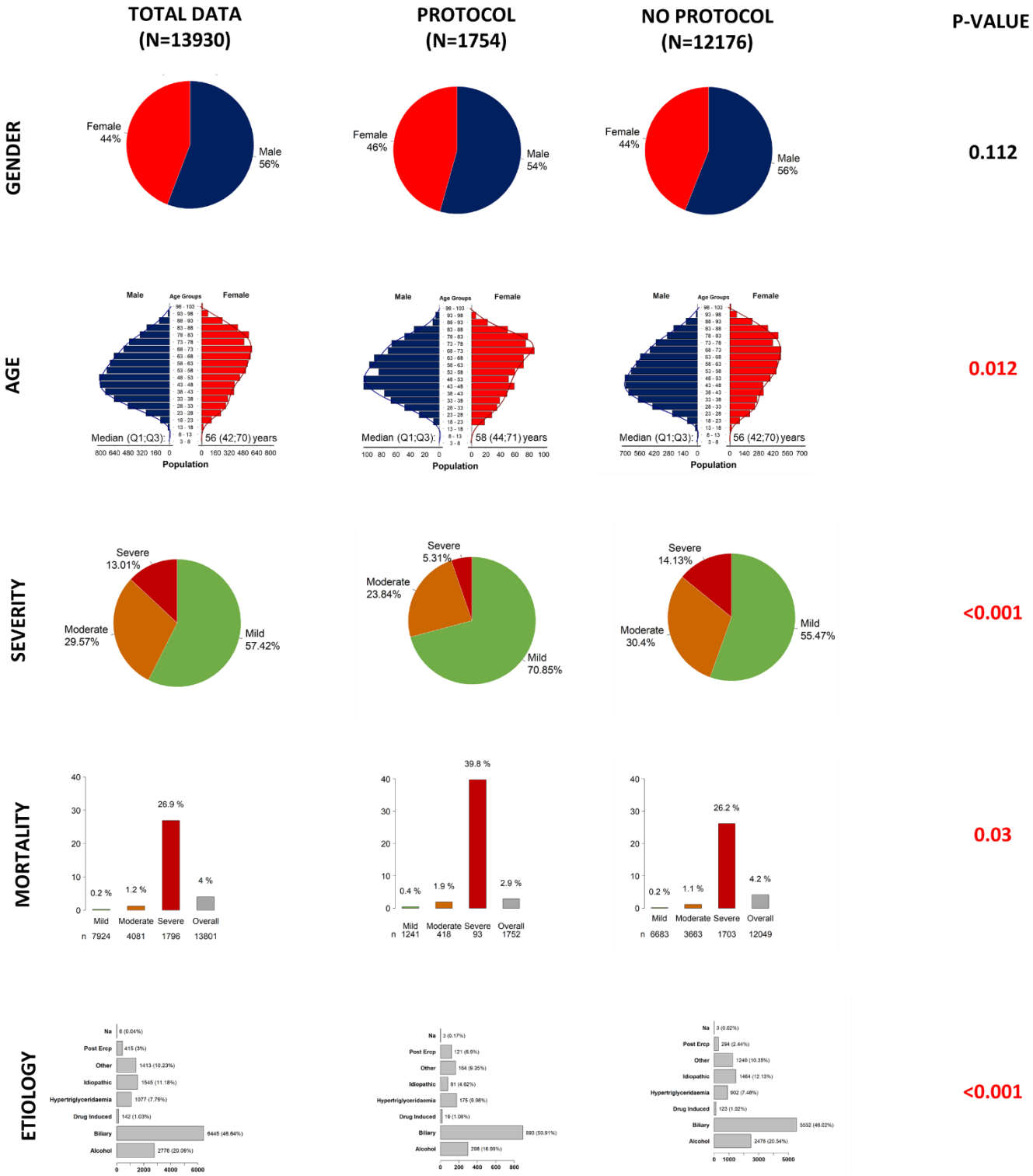
2. The majority (87.5%) of the international centers have no protocols to discharge patients in AP

According to our international survey, 87.5% (49/56) of the centers did not apply an AP discharge protocol. Notably, the protocols were moderately different from each other. Abdominal pain status was a part of every protocol, but for example, appetite was mentioned only in one case.

3. Protocolized discharge strategy results in shorter length of hospitalization

Patients discharged based on protocols have significantly shorter length of hospitalization (LOH) (7 (Q1;Q3: 5;10 days) vs 8 (Q1;Q3: 5;12 days), $p<0.001$) and lower rate of readmission due to RAP (2.8% vs 3.9%) (Table 1.). When separately analysing the cohorts based on severity, protocolized discharge decision still resulted in significantly shorter LOH both in the mild and moderate/severe cases (10 (Q1;Q3: 7;15 days) vs 12 (Q1;Q3: 8;18 days)), $p<0.001$). There was no significant difference in the discharge CRP values between the groups (29.75 (9.26; 80.00) mg/l vs. 28.50 (11.80; 58.40) mg/l, $p=0.586$) (Table 1). However, when separately analysing the patients based on severity, in the moderate/severe cases the discharge CRP was significantly higher 46.24 (16.65; 100.25) vs 34.00 (15.70; 59.75) mg/l, $p=0.002$).

Figure 2. General characteristics of the international cohorts



Comparison of the protocol and non-protocol international cohorts. In terms of age, distribution of severity and etiology, and overall mortality there is a significant difference among the subcohorts ($p<0.05$).

Table 1. Comparison of centers based on the presence of discharge protocol worldwide and in Hungary.

	International			Hungarian		
	Protocol	**No-Protocol**	**p-values**	**Protocol**	**No-Protocol**	**p-values**
Patient number	**1754**	**12176**	**NA**	**688**	**941**	**NA**
Length of hospitalization						
n (%not missing)	1754 (100)	12146 (97.8)		688 (100)	920 (97.8)	
mean (SD)	8.55 (8.12)	11.75 (14.30)		8.20 (7.71)	13.04 (15.80)	
median (Q1; Q3)	7 (5; 10.)	8 (5;12)	<0.001[1]	6 (5; 9)	10 (7;15)	<0.001[1]
Discharge CRP						
n (%not missing)	1124 (64.1)	8102 (67.2)		688 (100)	482 (51.2)	
mean (SD)	54.31 (61.99)	48.61 (61.95)		48.31 (46.38)	47.41 (59.82)	
median (Q1; Q3)	29.75 (9.26, 80.00)	28.50 (11.80, 58.40)	0.586[1]	35.40 (13.78, 68.40)	22.88 (8.80, 62.03)	0.003[1]
Readmission within 1 month						
n (%not missing)	1727 (98.4)	11829 (97.2)		688 (100)	609 (64.7)	
readmission n (%)	167 (9.7%)	1101 (9.3%)	0.629[2]	35 (5.09%)	114 (19%)	<0.001[2]
Not pancreas related	62 (3.6%)	309 (2.6%)		12 (1.7%)	67 (11%)	
Complication of index AP	39 (2.3%)	275 (2.3%)	0.005[2]	4 (0.6%)	24 (3.9%)	<0.001[2]
Recurrent episode of AP	48 (2.8%)	464 (3.9%)		19 (2.7%)	23 (3.8%)	

[1] Mood's median test

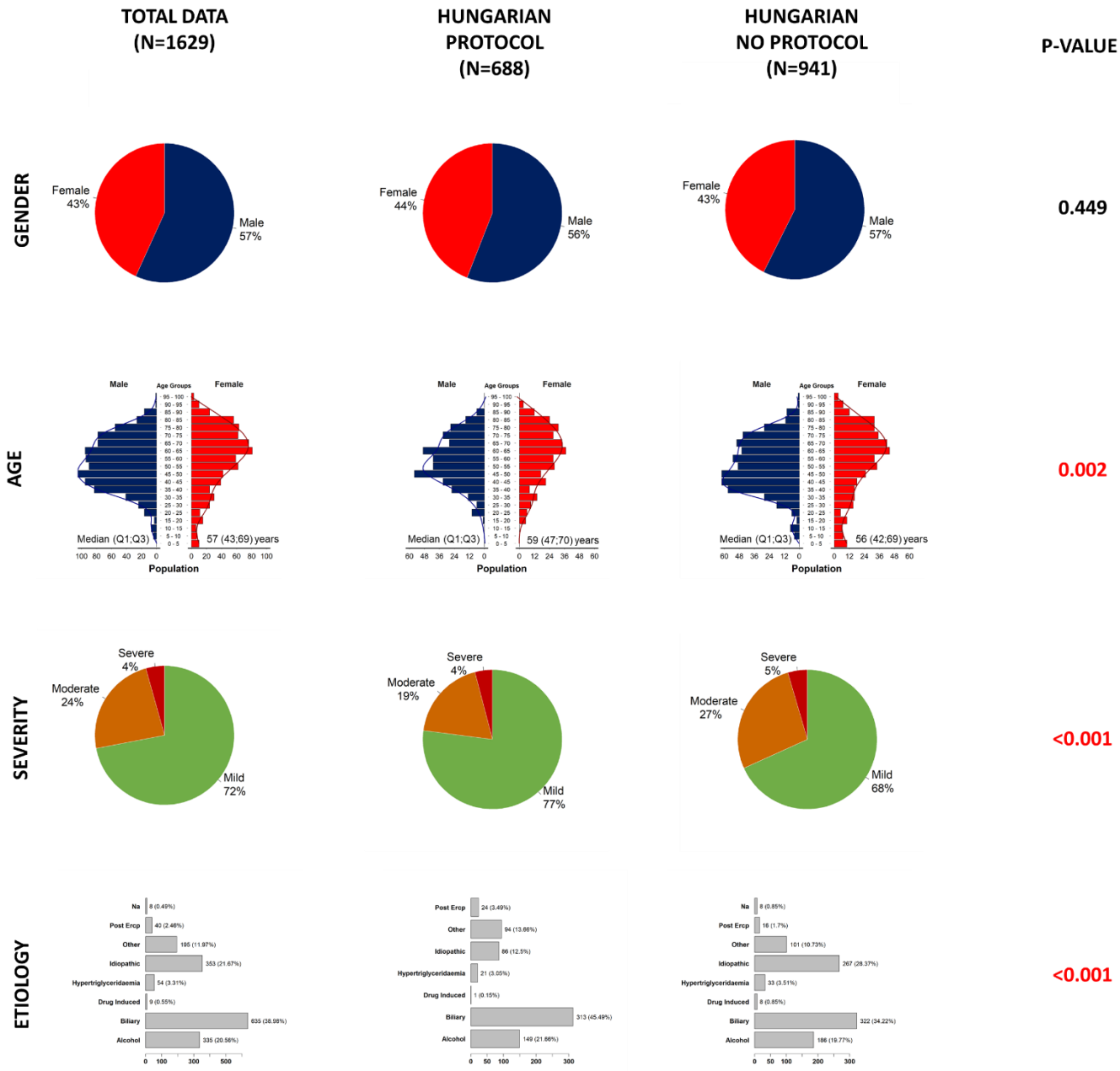
[2] Chi-squared test

The table shows the comparison of centers with and with no discharge protocol, clearly describing that protocolized discharge results in shorter LOH, higher discharge CRP values and lower rate of readmission. LOH is expressed in days, while CRP in mg/l.

5. Safety and effectiveness of the HPSG-guided discharge protocol

Overall, 688 patients were discharged with HPSG-protocol whereas 941 patients without it. The median age of the 2 subcohorts differed in terms of age (median (Q1;Q3): 59 (47;70) vs (56 (42;69), severity (moderately severe cases: 19% in protocol vs 27% in non-protocol group) and the distribution of the aetiologies (Figure 3.). The median CRP value at discharge was shown to be significantly higher in the HPSG protocol group compared to the non-protocol Hungarian centers (35.40 (13.78; 68.40) vs 22.88 (8.80; 62.03) mg/l, p=0.003) (Table 1). This remarkable difference was also shown in the mild and moderate/severe cases separately (29.35 (12.22; 59.80 vs 21.60 (8.33; 60.45) mg/l, p=0.021 and 56.95 (23.17; 95.65) vs 33.90 (10.55; 71.71), p<0.001, respectively).

Figure 3. General characteristics of the Hungarian cohorts



Comparison of the protocol and non-protocol Hungarian cohorts. In terms of age, distribution of severity and etiology there is a significant difference among the subcohorts ($p<0.05$).

a. The HPSG-developed discharge protocol was associated with a lower readmission rate vs non-protocolized discharge (5% vs. 19%)

In order to check the safety of the HPSG-protocol, patients were examined 1 month after discharge. Concerning the protocol-guided discharge, 45 out of 688 patients had elevated CRP value on the 1-month control visit compared to the discharge level. Nine (20%) had biliary tract inflammation

(cholangitis, cholecystitis), 14 (31%) had recurrent episode, 6 (13%) had tumour-related complaints, whereas the remaining cases were mostly related non-GI diseases (rheumatoid arthritis, respiratory tract infection; 58%). Out of the 688 patients 35 (5%) were readmitted within 1 month. Among the readmitted patients 19 (54%) had recurrent episode of AP (alcohol induced: 47%, biliary: 26% CP/idiopathic: 26%), 4 (11%) had pseudocyst infection, 4 (11%) had cholecystitis/cholangitis. Five (14%) readmissions occurred due to tumour-related complaints, 2 (6%) other patients had IBD and gastroenteritis, and 1 (3%) was admitted because of trauma. In comparison, in the non-protocolized cohort, 179 of 941 (19%) patient were readmitted, mainly due to non-pancreas-related causes and index episode complication (59% vs 21%).

b. Implementation of the new discharge protocol results in shorter hospital stay

One of the most relevant indices concerning the effectiveness is the LOH. Our cohort was shown to have significantly shorter LOH (6 (Q1;Q3: 5; 9) days) compared to centers with no protocol either internationally (8 (Q1;Q3: 5; 12) days) or nationally (10 (Q1;Q3:7; 15) days) (Table 1). The difference in LOH in the Hungarian cohort was shown both in mild and moderate/severe cases when analyzed separately (6 (5; 7) vs 9 (7; 12.) days).

6. CRP value proved to be a poor prediction tool

We investigated whether the inflammatory biomarker CRP can predict readmission in AP. Discharge CRP has been identified as a poor prediction tool both in total and only in mild cases for readmission (AUC: 0.56 and 0.56 p=ns, respectively). In addition, readmission could not be predicted by the rate of decrease after the maximum CRP level (either investigated a 24 or a 48-hour period). (p=0.116, 0.208, respectively).

3.1.4.Discussion

In this study we tested the safety and effectiveness of discharge protocols in AP. We found that protocols significantly decrease the LOH and do not elevate the risk of readmissions. Protocolized discharge also resulted in higher discharge CRP values that may suggest, physicians are more confident in making discharge decisions in the presence of a protocol-based care.

According to our results the protocol follower centers were identified to have lower 1-month readmission rate. This finding can be explained by the fact that these institutions most probably follow additional AP-related guidelines, such as on-admission cholecystectomy or implement efficient patient education. The proportion of severe cases in the non-protocol group is markedly higher, especially in the international cohort, despite the fact that it can be assumed that protocolized institutions operate as tertiary centers where a relatively large number of severe cases are transferred. However, we need to mention that since there is a higher proportion of moderate or severe cases in the non-protocol groups

requiring antibiotic treatment, and having local or systemic complications, it could also contribute to the longer LOH and lower CRP level at discharge.

Implication for practice and research

Implementing scientific data in the daily practice have high importance. The HPSG-discharge protocol can be immediately used in practice. Following an evidence-based discharge protocol will result in shorter LOH and thus, lower costs and also lower risk of hospital-acquired infections. Is this the best possible protocol to implement? Probably not, therefore new protocols are warranted.

Conclusion

Using discharge protocols in AP shorten the hospital stay. The HPSG-protocol resulted in the shortest LOH and still did not increase the risk of readmittance. There is a particular need for evidence-based recommendations on discharge in guidelines.

3.2. In-hospital patient education markedly reduces alcohol consumption after alcohol-induced acute pancreatitis

3.2.1. Objective

Alcohol-induced AP is by far the most common form of recurrent acute pancreatitis (RAP). Therefore, research on specific therapies for decreasing the number of recurrent alcohol-induced AP has crucial importance. Even though heavy drinking and AUD is continuously spreading worldwide leading to increased health, economic and social burden, there is a lack of intention to encourage patients either to participate in cessation programs or to keep long-term abstinence. With this study, we investigated if in-hospital BI reduces alcohol consumption after an alcohol-induced AP episode.

3.2.2. Methods

Setting and study design

We conducted a post-hoc analysis of a prospective electronic data registry. In 2016, three major centers of the Hungarian Pancreas Study Group (HPSG) started to integrate BIs into hospital care for patients with alcohol-induced AP (University of Pécs, University of Debrecen, Szent György University Teaching Hospital of Fejér County). Patients were enrolled between 2016-2021.

Patients

Altogether 313 consecutively enrolled patients with alcohol-induced AP were checked for eligibility. Based on inclusion and exclusion criteria, 99 patients were eligible for analysis.

Inclusion criteria

AP was defined based on the modified Atlanta classification's "two out of three" criteria: abdominal pain, pancreatic enzyme elevation at least three times above the upper limit and characteristic morphological changes on imaging. Alcohol-induced pancreatitis was defined as AP caused by either regular alcohol intake or consumption of an excessive amount of alcohol on one occasion. Patients who denied alcohol intake but there was clear evidence of heavy drinking in medical history and no other aetiology was identified, were also included.

Exclusion criteria

We excluded patients with alcoholic and biliary mixed aetiology from the study since biliary stones often influence GGT levels and also might cause recurrent AP independently of alcohol intake. Patients who did not present at the 1-month visit or whose admission and discharge values were not available were excluded from the analysis.

Intervention

Patients with alcohol-induced AP received a BI including patient education from their attending physician at least once during the patient care. The structure of the oral education includes components of BI based on the FRAMES model and a focused and goal-directed approach as in a motivational interview model, emphasising the patients' responsibility for their health. Besides, leaflets were available to provide information about excessive alcohol consumption, its impact on health, and options for professional help.

Investigated parameters

Data on age, gender, aetiology, severity, alcohol consumption (amount and frequency), previous RAP, presence of CP and in-hospital mortality were collected. GGT and MCV values were measured on admission (first 24h), at discharge, and 1-month (23-37 days) follow-up visit. The number of recurrent acute pancreatitis (RAP) episodes were recorded between discharge and the 1-month visit. For those who were readmitted within one month, the readmission GGT and MCV values were analyzed. Patient questionnaires were applied on admission and at the 1-month control visit to measure alcohol consumption.

Outcome parameters

The main outcome parameter was alcohol abstinence confirmed by a) laboratory parameters (GGT and MCV levels) b) self-reported alcohol consumption:

Analysis

For data analysis the cohort (n=99) was divided into 2 subgroups: Elevated GGT group (E): Patients admitted with elevated GGT levels (>50 U/L). Non-elevated GGT group (N): Patients admitted with non-elevated GGT levels.

Statistical analysis

Statistical analyzes were performed using R 4.1 software (R Core Team; 2020.) For descriptive statistics, mean, standard deviation (SD), median, first and third quartile values were calculated for continuous variables. Wilcoxon-Mann–Whitney U test or Kruskal-Wallis rank sum test was conducted, as applicable. For categorical variables Chi-square test and Fisher exact test were performed. For further analysis Dunn's post hoc test was conducted with Benjamini – Hochberg correction and Spearman correlation was made to measure the link between two variables. The level of significance was considered $p \leq 0.05$.

3.2.3. Results

1. Basic characteristics and data quality

Altogether 99 alcohol-induced AP cases were included in our analysis. Out of the 99 patients, 79 belonged to the elevated GGT group, while 20 cases were included in the non-elevated GGT group. Overall, 89% of the patients were male and the mean age at admission was 50.05±11.37 years. Regarding severity, 62% of the AP episodes were mild and the median length of hospital stay was 6 (5-9) days.

2. Acute pancreatitis was often followed by another episode

Overall, 40% of the patients have already had a previous AP episode. From the analyzed cohort, 14% of the patients had the diagnosis of CP at admission and in 17% of the cases, hypertriglyceridemia was noted in the medical history.

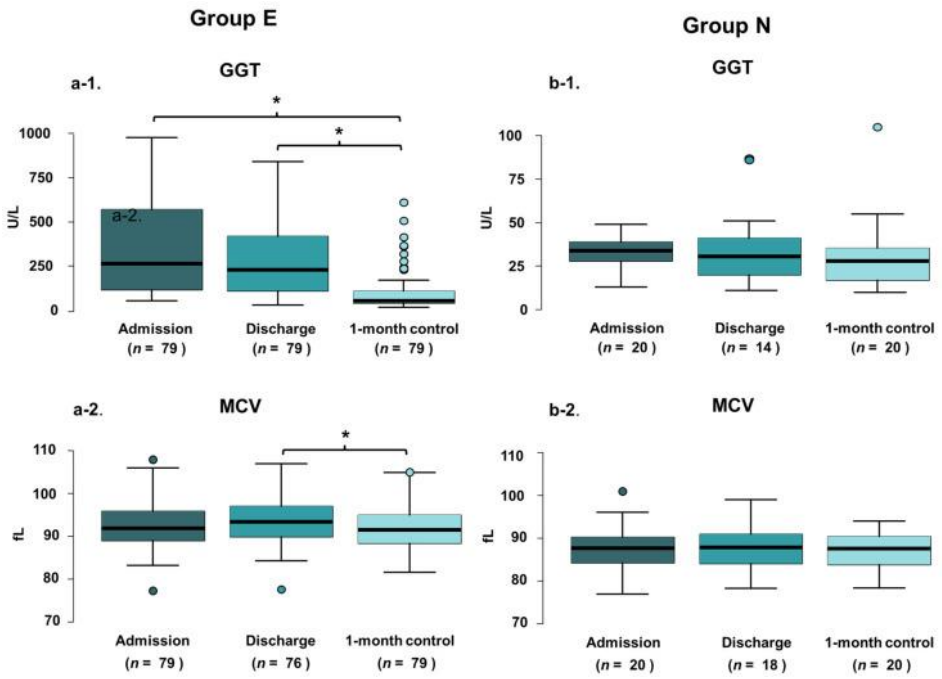
3. Frequent alcohol drinkers had a higher GGT level

More than half of the admitted patients (54%) reported daily alcohol consumption and the average amount of consumed alcohol was 81.06±65.26 grams. There was a significant difference in the on admission GGT values between the occasionally and daily drinker group (210±268 U/L vs. 267±470 U/L, respectively, p=0.01). More than half of the patients (66%) in E subgroup reported daily intake, while only 5 patients (25%) reported daily consumption in N subgroup (p=0.004). There was no significant difference between admission MCV levels based on the alcohol consumption frequency. No correlation was found between alcohol consumption amount and on admission GGT (p=0.14) and MCV (p=0.23).

4. Significant decrease was detected in GGT value 1-month following in-hospital patient education

The mean value of discharge GGT in group E was 294.00±250.75 U/L, while at the 1-month control visit 103.20±113.50 U/L was measured meaning an average decrease of 49.25±74.50 % ($p<0.001$) (Fig4-5). In group N out of 20, only 2 patients' GGT level increased above the normal level at the 1-month control visit. The effectiveness of BI on serum GGT levels in patients with elevated or non-elevated admission GGT levels is visualised in Figure 4.

Figure 4. GGT and MCV values of patients in Groups E and N in different time points visualized by boxplots.

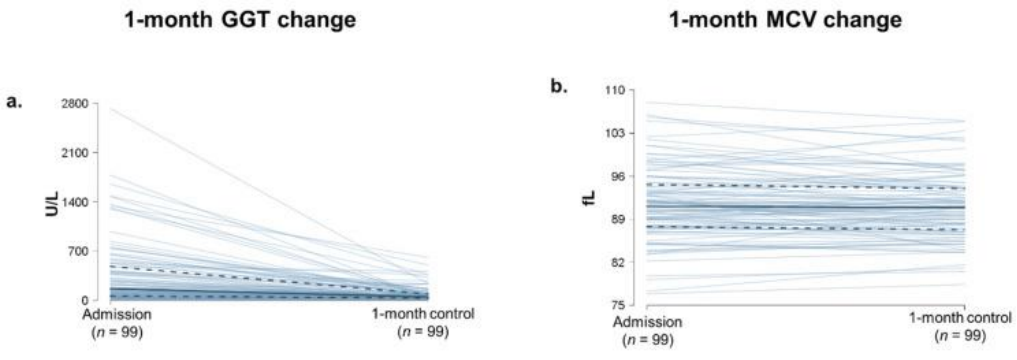


E - patients with elevated on-admission GGT level (**a**); N-patients with non-elevated on-admission GGT level (**b**); GGT—gamma-glutamyltransferase; MCV—mean corpuscular volume. * $p < 0.01$

5. MCV value showed significant reduction 1-month following in-hospital patient education

In group E the mean value of MCV was 93.73±5.30 fl at discharge and 92.07±5.10 fl at the follow-up visit, which means an average 1.85±3.12% decrease ($p<0.001$) (Fig.4-5). No one had macrocytosis (MCV>95 fl) at the 1-month visit.

Figure 5. Analysis of the change in GGT and MCV levels. Figures show the change in laboratory values between discharge and the 1-month control visit.



e.

1-month change (%)	Mean	SD	Median	Q1	Q3
Elevated GGT	49.25	74.50	66.39	50.10	80.76
Normal GGT	8.04	43.42	19.90	2.42	27.04

f.

1-month change (%)	Mean	SD	Median	Q1	Q3
Elevated GGT	1.85	3.12	2.11	0.36	4.07
Normal GGT	0.31	3.06	0.56	−1.96	1.75

(**a**,**b**) Line chart; median — Q1; 3 -----; (**c**,**d**) change in absolute value; (**e**,**f**) change in percent value. Note: in the group of patients with elevated (E) admission GGT level, discharge and 1-month values, and admission and 1-month values in the group of patients with non-elevated (N) admission GGT level, were included in the analysis. fL—femtoliter; U/L—unit/liter; E: patients with elevated admission GGT; N: patients with non-elevated admission GGT.

6. 75-80% of the patients kept abstinence 1-month following in-hospital patient education

Collecting self-reported alcohol intake at the control visit, most of the patients, 63/79, (80%) in the group E, while 15/20 (75%) in the subgroup N kept abstinence from alcohol. Out of the 99 analyzed patients 3 (all belonged to group E) were readmitted due to alcohol-induced RAP.

4.2.4. Discussion

It is generally known that alcohol abuse can lead to liver cirrhosis, but it is less known worldwide that alcoholic pancreatitis is one of the most painful and severe consequences of alcohol abuse and can subsequently lead to CP. Probably abstinence from alcohol is the best prevention against recurrent episodes since the biggest risk factor of having RAP is the continuous alcohol intake in a dose-dependent manner. Although several studies have shown the beneficial effects of BIs on alcoholic patients, their structure and frequency are still debated.

Implication for patients

Incorporating psychological interventions, such as BI in the regular in- and outpatient care could promote abstinence and prevent recurrent episodes. Besides, these communication methods need to be extended among practitioners especially in the field of gastroenterology and general practice.

Implications for research

Longitudinal studies and RCTs are needed to identify the adequate structure and frequency of BIs to achieve alcohol abstinence and minimalize the risk of alcohol-induced RAP.

Conclusion

BI is an effective tool to reduce alcohol consumption and to prevent RAP. In accordance with previous observations, decreasing serum GGT values correlated with the self-reported alcohol avoidance thus, serum GGT can be a reliable, easy-to-use clinical marker to follow patients' drinking habits after an alcohol-induced AP.

3.3. Revisiting the evidence-based management of paediatric pancreatitis

3.3.1. Background

Although paediatric acute pancreatitis (PP) is a relatively rare disease, its incidence has been rising continuously. Therefore, experts in the field felt important to develop and publish evidence-based guidelines for PP. Here we provide a case study which clearly demonstrate the importance of the recently published EPC/HPSG evidence-based paediatric pancreatitis guidelines.

3.3.2. Case report

Our 17-year-old female patient was admitted to the paediatric ward of a local county hospital due to her first AP episode. Two out of the three criteria included in the EBM guidelines were positive (abdominal pain and at least a three-fold pancreatic enzyme elevation). On Day 9 she was discharged with a diagnosis of mild biliary pancreatitis and cholecystolithiasis with an appointment for a cholecystectomy six weeks later. However, she returned to the emergency department three days later with worsening abdominal pain and vomiting. Blood tests showed excessive elevation of amylase and lipase activity (1599 U/L and 9240 U/L, respectively). Cholestatic enzyme levels were also markedly increased (GGT: 1114 U/L; ALP: 167 U/L). Since imaging and laboratory parameters showed cholangitis, the patient was transferred to a tertiary paediatric center to perform urgent endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (EST). Bile stone or sludge could not be extracted with balloon sweep, spontaneous stone passage was suspected. After the procedure the patient's condition deteriorated rapidly, she was temporarily admitted to the intensive care unit. At the paediatric ward only temporary improvement was achieved, the abdominal computed tomography (CT) examination revealed extensive pancreatic

necrosis fluid collection, therefore the patient was transferred to the Pancreatic Center. The nasojejunal tube feeding was successful, however the oral feeding was not tolerated. Abdominal CT showed a large pseudocyst connected to the dilated duct of Wirsung causing gastric outlet obstruction. Endoscopic ultrasound-guided drainage of the pseudocyst was performed and two pigtail stents were inserted. After the procedure, her condition gradually improved, oral feeding was initiated next day. Since she was completely asymptomatic on Day 27, she was transferred to the Surgical Department for cholecystectomy. The patient had uneventful recovery and she presented at the 30-day follow-up visit with no complaints. At four-month follow-up, her abdominal CT examination showed regression of the pseudocyst, consequently, the pigtail stents were removed.

4.3.3. Discussion

Some decades ago, clinical practice generally relied on local expertise, often driven by physiological reasoning. The main aspect of AP management was to put the pancreas at rest and the routine administration of prophylactic antibiotic was also part of the therapeutic regimen. Despite the concept of EBM, it seems difficult to change these 30-year-old clinical patterns. To highlight the importance of EBM, we presented a case of a young patient whose management contained deviations from evidence-based guidelines at several phases (Table 2). The most important error is the decision on the timing of the cholecystectomy. The same-admission cholecystectomy was not performed, as it should have been according to the PONCHO trial and current EBM guideline. Unfortunately, recurrent, moderately-severe biliary AP has occurred subsequently, accompanied by excessive pancreatic necrosis, pseudocyst formation and the patient also required an intensive care treatment for more than 48 hours. Our case confirms that it is crucially important to follow the EPC/HPSG guideline in PP treatment. Paediatricians should not be afraid of doing so irrespective of whether some of the evidence in the guideline came from experience with adults. This case also raises the question of whether paediatric pancreatitis should be treated in a pancreatic center.

Table 2. Adherence to the EPC/HPSG evidence-based guidelines for the management of paediatric pancreatitis. NA∗ - not applicable.

Empty Cell	**EPC/HPSG guideline**	**First AP episode**	**Second AP episode**	
			1st phase	**2nd phase**
Aetiology screening	AP-II.1.	YES	YES	NA∗
Fluid therapy	AP-V.1.	YES	YES	YES
Antibiotic therapy	AP-V.4.1.	NO	YES	YES
Nutrition	AP-V.3.1	NO	NO	YES
Imaging	AP-IV.1-2.	YES	YES	YES

Empty Cell	**EPC/HPSG guideline**	**First AP episode**	**Second AP episode**	
			1st phase	**2nd phase**
Cholecystectomy	AP-VI.3.	NO	NA∗	YES
ERCP	AP-VI.1	YES	YES	NA∗
Pseudocyst	AP-VII.5.	NA∗	NA∗	YES

AP-II.1. Etiological factors that should be considered after the diagnosis is reached are the following: biliary and pancreatic abnormalities, medication-associated, presence of underlying systemic disease, trauma, genetic predisposition, infection, metabolic disorders and autoimmune pancreatitis. (GRADE 1/C, full agreement).
AP-V.1. Administration of dextrose containing crystalloids is recommended as the initial choice for replacement fluid therapy in AP. (GRADE 2/B, full agreement).
AP-V.4.1. Regardless of the severity of the pancreatitis or existing necrosis, routine use of prophylactic antibiotics is not recommended in AP. (Adult evidence level: GRADE 1/B, strong agreement). AP-V.4.2. In cases of systemic infectious complications, cholangitis or suspected infected pancreatic necrosis, antibiotic treatment is recommended. (GRADE 1/B, full agreement).
AP-V.3.1. Oral feeding can be started as soon as tolerated even in the presence of systemic inflammation and before the amylase or lipase values have decreased. (Adult evidence level: GRADE 2/B, full agreement). If adequate oral feeding is not tolerated or the required calories cannot be achieved by oral feeding within 72h, enteral tube feeding is recommended. (Adult evidence level: GRADE 1/A, full agreement).
AP-IV.1. Transabdominal ultrasonography is recommended as a first-choice imaging technique in paediatric AP. (GRADE 1/B, full agreement). **IV.2.** AP-IV.2. Contrast-enhanced abdominal CT is recommended in clinical deterioration in children as per adult guidelines. (Adult evidence level: GRADE 1/C, full agreement).
AP-VI.3. For uncomplicated biliary pancreatitis, cholecystectomy is recommended during the index admission if possible or, if not possible, within 30 days of the first admission for mild cholelithiasis-associated AP in children. (Adult evidence level: GRADE 1/B, full agreement; Paediatric evidence level: GRADE 1/C, full agreement).
AP-VI.1. ERCP is indicated patients with biliary pancreatitis and cholangitis. (Adult evidence level: GRADE 1/B, full agreement).
AP-VII.5. When pancreatic pseudocysts are symptomatic, endoscopic intervention should be the therapy of first choice in experienced centers. (Adult evidence level: GRADE 1/C, full agreement).

3.4. Association of Body Mass Index With Clinical Outcomes in Patients With Cystic Fibrosis

3.4.1. Objective

It is unclear whether there is an advantage of increasing weight over the normal range in CF. For instance, mortality in pneumonia has been reported to be lower in individuals without CF who are obese, known as the obesity survival paradox. To fulfill the knowledge gap, we aimed to evaluate the differences in clinically significant outcomes, such as lung function, PI, and CFRD, in patients with CF having altered BMI and/or body composition by conducting a systematic review and meta-analysis of the literature.

3.4.2. Methods

The review protocol for this systematic review and meta-analysis was prospectively registered with PROSPERO. The only deviation from our protocol was the addition of Pseudomonas aeruginosa colonization incidence. Findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyzes (PRISMA) reporting guideline.

Study Selection

The literature search was conducted November 2, 2020, in MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials. Key search terms included *cystic fibrosis*, *body fat*, *body mass*, and *body weight* without any restrictions. Two of us (R.N. and P.P.) independently conducted the selection in duplicate using reference management software (Endnote X9 software; Clarivate Analytics; 2019). Removal of duplicates was performed automatically and after that manually. The records were selected by title, abstract, and full text based on a previously determined set of rules. Any disagreements were resolved by consensus between the 2 reviewers.

Eligibility Criteria

Cohort studies, case series, and clinical trial or conference abstracts were eligible; case reports and articles with no original data were excluded from our systematic review. The research question was formulated using the Population, Exposure, Comparator, and Outcomes framework. Patients older than 2 years diagnosed with CF regardless of sex, transplant status, *CFTR* modulator therapy, or comorbidities with altered body composition (BMI, FFM, and FM values out of the reference ranges, eg, underweight, overweight, and obese) were compared with patients with the measured parameters within the reference ranges. Articles reporting coefficients regarding the association between BMI or body composition and clinical outcomes were also eligible.

The nutritional categories were accepted based on study definition; however, we intended to strictly follow the thresholds recommended by the World Health Organization[18]: underweight (BMI <18.5), normal weight (BMI = 18.5-24.9), overweight (BMI ≥25), and obese (BMI ≥30) when it was possible to analyze separately. We also compared the underweight group (BMI <20) with the nonunderweight group (≥20) and performed subgroup analyzes based on the age of the participants (adults, children, and mixed population). Primary outcomes included pulmonary function (expressed by forced expiratory volume in the first second of expiration [FEV_1%]), PI, and CFRD. Diagnosis of PI and CFRD was determined according to the definitions used in the included studies. As secondary outcomes, we investigated parameters associated with metabolic status, including fasting glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), cholesterol, and triglyceride levels, and *P aeruginosa* colonization as an additional outcome.

Data Extraction

Two of us (R.N. and D.K) independently extracted data into a standardized data collection sheet (Excel 2019; Microsoft Corp), and data extraction was validated by another one of us (B-M.D.). The following data were extracted from each eligible article: study name, first author, publication year, Digital Object Identifier (DOI), recruitment period, gender distribution, age distribution, genotype, patient number and mean or median values of outcomes of interest. Correlation coefficients were also extracted regarding the association of BMI or body composition and clinical. Most of the eligible studies were cross-sectional. For longitudinal studies, we collected baseline data only. For overlapping populations, the study working with the most patients was chosen for each outcome.

Risk of Bias Assessment

Based on the recommendations of the Cochrane Prognosis Methods Group, the Quality in Prognostic Studies (QUIPS) tool was applied by 2 of us (R.N. and P.P.) to assess the risk of bias in the included studies for each outcome separately. Any disagreement was resolved based on consensus.

Statistical analysis

A random-effects model was applied in all analyzes using the DerSimonian-Laird estimation. Pooled odds ratios (ORs) with corresponding 95% CIs were calculated for dichotomous outcomes. Pooled mean difference was calculated for continuous outcomes (weighted mean difference [WMD]). Results of the meta-analyzes are displayed in forest plots. Statistical heterogeneity was analyzed using the I^2 and χ^2 tests to gain probability values; $P < 0.10$ was defined to indicate significant heterogeneity. I^2 values representing moderate (30%-60%), substantial (50%-90%), and considerable (75%-100%) heterogeneity were based on the Cochrane Collaboration recommendations. Sensitivity analyzes were also carried out omitting 1 study and calculating the summary OR or WMD with the 95% CI to investigate whether there was an association between a single study and the final estimation. To check

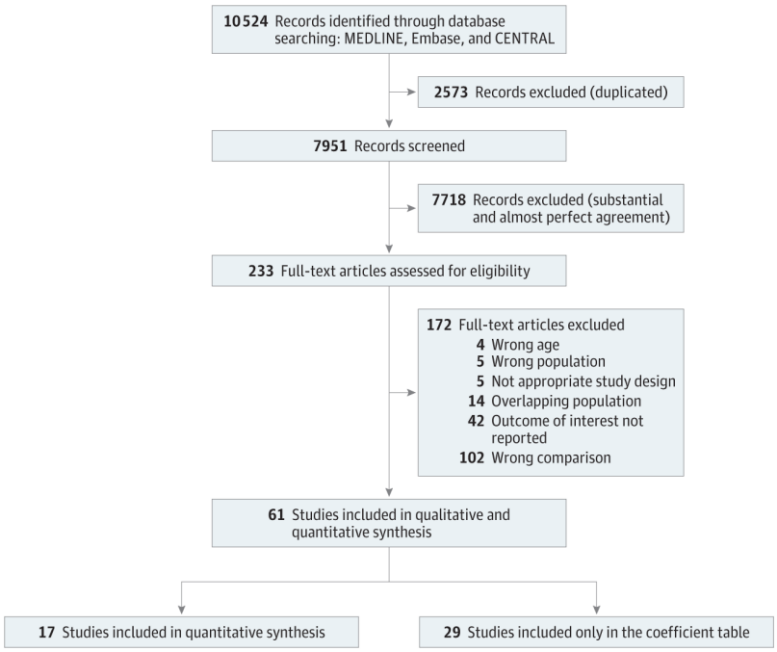
for publication bias, a visual inspection of funnel plots was performed with Egger tests. Statistical analyzes were carried out using Stata, version 16 SE (StataCorp LLC). For continuous variables, *P* values were calculated using 2-tailed unpaired analysis. Results were considered significant at $P < 0.05$

3.4.3. Results

Study Selection

The systematic literature search yielded 10 524 records. After removal of duplicates, 7951 records were screened; of these, 61 records were included in the qualitative analysis and 16 full-text articles and 1 conference abstract were included in the quantitative analysis. Of the 61 studies, 33 contained correlational coefficients from which 29 did not report outcomes of interest according to BMI categories. The selection process is shown in Figure 6.

Figure 6. Selection flowchart



Preferred Reporting Items for Systematic Reviews and Meta-analyzes (PRISMA) Flowchart. CENTRAL indicates Cochrane Central Register of Controlled Trials.

Study Characteristics

Altogether, 9114 patients were included in the systematic review and meta-analysis. Of 9114 patients, 5301 were included based on BMI categories, and studies that reported coefficients resulted in 3813 involved patients. Five studies investigated only children (<18 years), 13 studies included only adults,

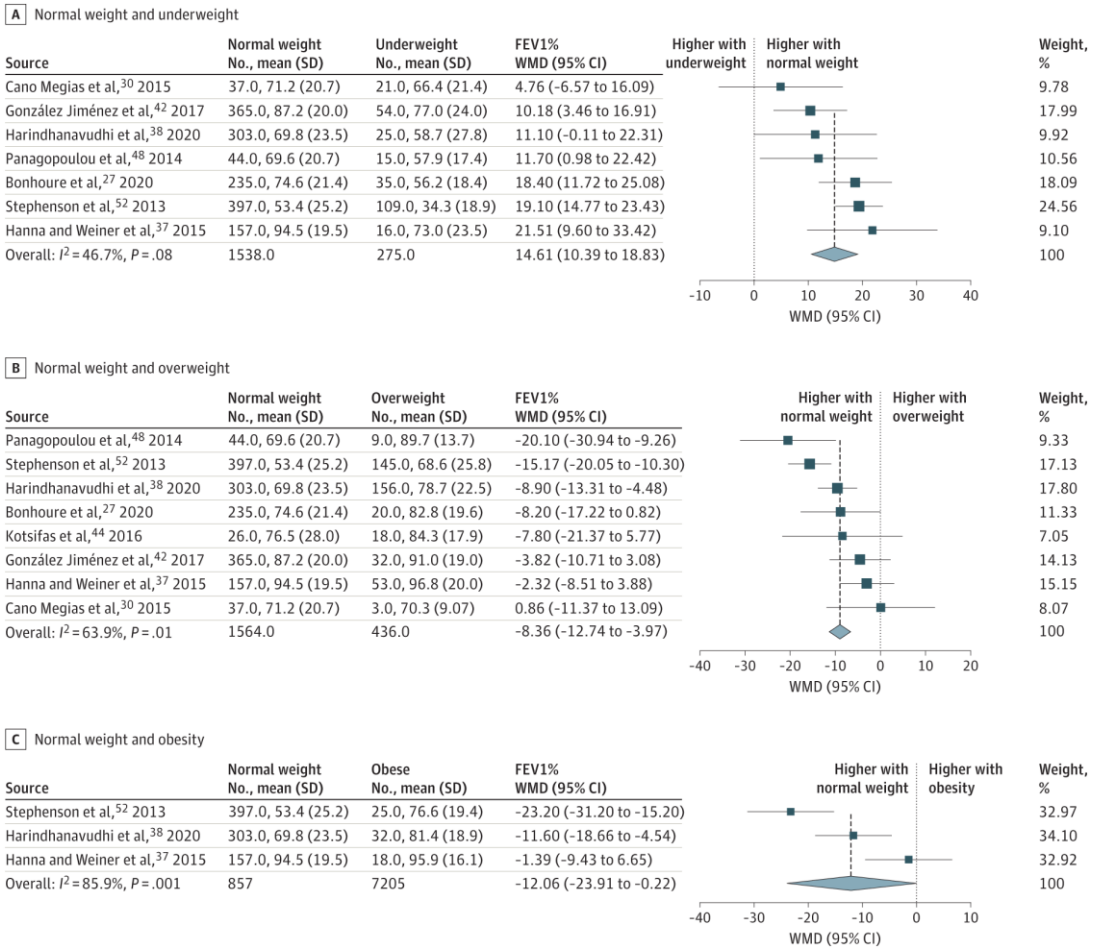
and 14 studies examined a mixed patient population. The estimated proportion of children (mixed population studies did not give the number of children) is 30%. The mean (SD) values of BMI in the analyzed groups ranged from 18.5 (1.7) to 34.8 (5.7).

Primary Outcomes

Forced Expiratory Volume in the First 1 Second of Expiration

Most studies (54 of 61) reported FEV_1% as an indicator of pulmonary function. A total of 13 studies were included in the quantitative synthesis. Based on our results, patients whose weight was considered normal had significantly higher FEV_1% values compared with those who were underweight (MD, 14.61%; 95% CI, 10.39%-18.83%). Compared with patients whose BMI was considered normal, better pulmonary function was noted in patients who were overweight (82.96% vs 74.60%; MD, –8.36%; 95% CI, –12.74% to –3.97%) or obese (84.63% vs 72.57%; MD, –12.06%; 95% CI, –23.91% to –0.22%) (Figure 7).

Figure 7. Pulmonary Function in Different Body Mass Index (BMI) Categories of Patients With Cystic Fibrosis



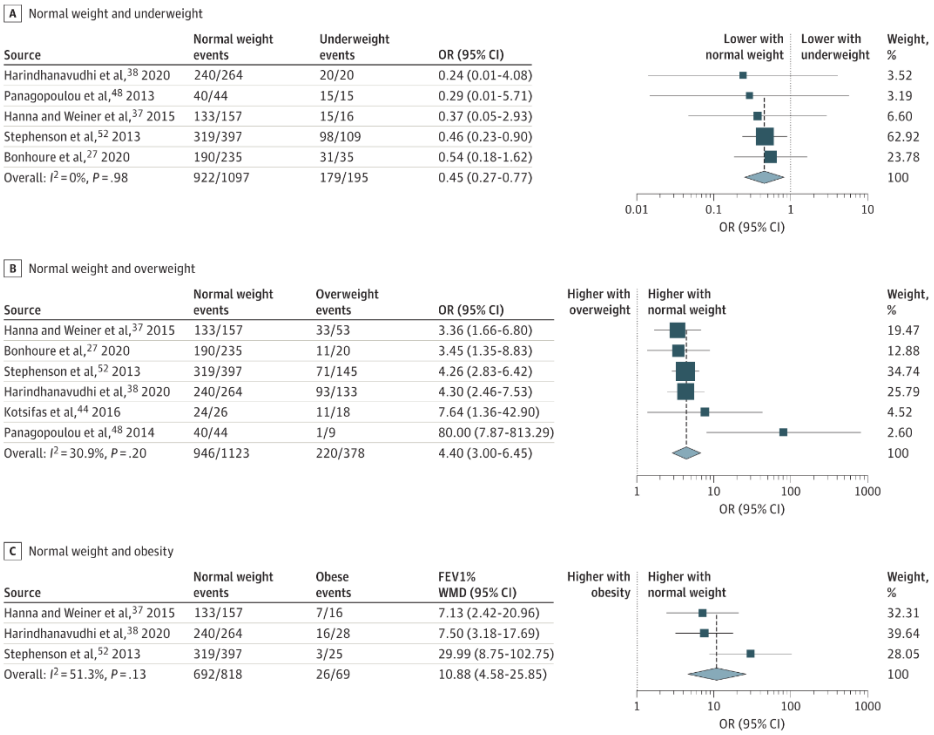
Comparison of patients with normal weight vs underweight (moderate heterogeneity detected) (A), normal weight vs overweight (substantial heterogeneity detected) (B), and normal weight vs obesity (considerable heterogeneity detected) (C). FEV_1% indicates forced expiratory volume in the first second of expiration; WMD, weighted mean difference. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI.

Five studies investigated the connection between pulmonary function and FFM, and all of the studies reported an association between FFM and pulmonary function. Most (39 of 42 [92.9%]) of the extracted correlation coefficients indicated significant correlation between BMI or body composition parameters and FEV_1%. Considered one of the main possible confounders, use of modulator therapy was rarely reported (2 of 54 [3.7%]); therefore, we were not able to perform further analysis of these participants.

Exocrine Pancreatic Insufficiency

Our results showed that normal BMI is associated with a lower odds for PI compared with underweight (OR, 0.45; 95% CI, 0.27-0.77) and a higher likelihood of PI compared with overweight (OR, 4.40; 95% CI, 3.00-6.45) and obesity (OR, 10.88; 95% Cl, 4.58-25.85) (Figure 8). Adults who were underweight had significantly higher odds for PI (OR, 3.16; 95% CI, 1.97-5.06) compared with those of normal weight (overall OR, 2.54; 95% CI, 1.53-4.23).

Figure 8. Odds of Exocrine Pancreatic Insufficiency in Different Body Mass Index Categories

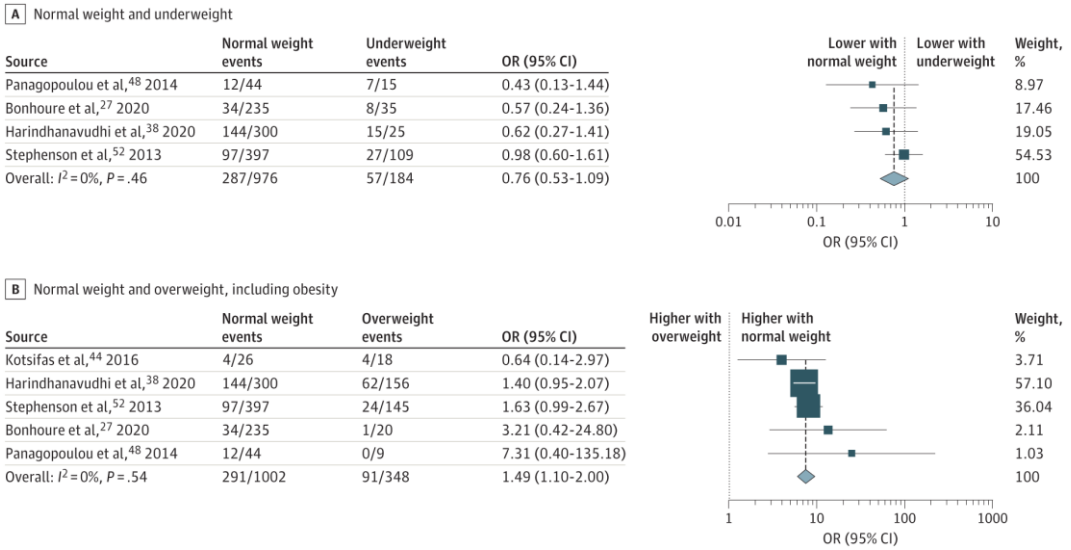


Comparison of patients with normal weight vs underweight (A), normal weight vs overweight (B), and normal weight vs obesity (C). OR indicates odds ratio. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI.

CF-Related Diabetes

Our results suggest that CFRD is more common in patients who are underweight compared with those who are of normal weight (31% vs 29.4%; OR, 0.76; 95% CI, 0.53-1.09). In addition, normal BMI is associated with higher odds for CFRD compared with overweight (OR, 1.49; 95% CI, 1.10-2.00) (Figure 9). Based on the subgroup analysis, the overall comparison showed significantly higher odds of CFRD in patients with lower BMI vs those with normal BMI (OR, 1.43; 95% CI, 1.04-1.9).

Figure 9. Odds for Cystic Fibrosis–Related Diabetes in Different Body Mass Index Categories



Comparison of patients with normal weight vs underweight (A) and normal weight vs overweight and obesity. OR indicates odds ratio. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI.

Secondary Outcomes

Glucose metabolic status indicators, such as fasting glucose, fasting insulin, and HbA_{1c} levels did not significantly differ between BMI categories. However, in accordance with our hypothesis, compared with patients having normal weight, those who were overweight or obese had significantly higher total cholesterol levels (0.11 vs 0.09 mg/dL; MD, –0.02 0.41 mg/dL; 95% CI, –0.03 to 0.01) and triglyceride levels (0.03 vs 0.02 mg/dL MD, –0.005; 95% CI, –0.009 to 0.0005 [to convert to millimoles per liter, multiply by 0.0113]). In the comparison of patients with normal weight vs underweight, both cholesterol

levels (MD, 0.008 mg/dL; 95% CI, 0.004 to 0.013) and triglyceride levels (MD, 0.003 mg/dL; 95% CI, 0.001 to 0.006) were significantly higher in the normal weight group.

Quality Assessment of Studies

Regarding FEV_1%, 23% of the eligible studies (3 of 13) were assessed to be high risk and 46% (6 of 13) as moderate risk. High risk was shown for PI (56% [5 of 9]) and CFRD (57% [4 of 7]).

3.4.4. Discussion

Our results suggest that higher BMI is associated with favorable clinical outcomes in patients with CF. Both overweight and obesity are associated with clinically significantly better pulmonary function compared with normal weight. A possible explanation could be the higher proportion of FFM in individuals who are overweight, which is associated with higher FEV_1% and physical well-being. It has also been reported that patients with CF who are overweight have markedly fewer exacerbations that could contribute to loss of appetite. The worse the condition of the lungs, the higher the level of REE. Moreover, patients with PI were reported to have a higher REE compared with those with sufficient pancreatic function. Based on these data, we hypothesized that excess weight could cover the increased energy requirement during chronic inflammation.

Conclusions

Our findings suggest that nutritional status plays an important role in maintaining organ function in patients with CF. Because we noted that a higher BMI is associated with better clinical parameters, we advise clinicians to reconsider increasing the currently recommended target BMI (22 for women and 23 for men). The use of a nutritional strategy that increases BMI, at least until the upper limit of normal BMI is reached, should be included in the daily protocol. Our results suggest that careful evaluation of body composition (FFM and FM) should be incorporated into everyday clinical practice. Studies with long-term follow-up are required to investigate the possible harmful effects of higher BMI, higher FM, and high-fat diet. Further observational studies are necessary focusing on major components of body composition (FFM and FM) with BMI.

4. Discussion

In this thesis we highlighted the importance and necessity of protocolized care and application of guidelines to achieve the most effective and still safe patient care. Protocolized care will also result the reduction of the differences in clinical approached worldwide.

We emphasized the importance of adherence to guideline through a presentation of a young female patient with recurrent biliary AP, where the patient management did not happen according to the most up-to-date recommendations leading to health complications, hospital occupancy and high costs.

Based on our findings the use of discharge protocols in AP can significantly reduce hospital stay without increasing the risk of readmissions. The study found that patients discharged based on protocolized care had higher CRP values, suggesting physicians were more confident in making discharge decisions. CRP value could not predict readmission, thus patient discharge should not depend on the absolute CRP value or the volume of the decrease but rather on the direction of the tendency.

In another study of ours we focused on a clinically very relevant patient group, namely on patients with alcohol-induced AP where the prevalence of the recurrent cases can reach 80% within four years. Continuous alcohol intake is the biggest risk factor of RAP. Abstinence from alcohol is the most effective prevention method, but it can be difficult to achieve. Several studies have shown the benefits of brief interventions in reducing alcohol consumption and preventing RAP. The structure and frequency of BIs are still being debated, but psychological approaches have shown promise in reducing alcohol and smoking habits. Our article suggests that incorporating BIs into regular in- and outpatient care could promote abstinence and prevent recurrent episodes. Longitudinal studies and randomized controlled trials are needed to identify the most effective BIs and to minimize the risk of alcohol-induced RAP.

Finally, we suggested the reconsideration of the current nutritional recommendation in patients with CF. We found that higher-than-normal BMI is associated with better clinical outcomes, like better pulmonary function, lower chance of exocrine and endocrine pancreatic insufficiency. In this regards the target BMI could be modified in the future, also with a special focus on the body composition elements, such as FFM or FM. We need to note that the long-term consequences of the higher cholesterol, LDL level could not be investigated due to the relatively low mean age of the analyzed population.