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

Ph.D. Thesis

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Table of content

Content

1. List of abbreviations

AP - acute pancreatitis

ALAT - alanine aminotransferase

ALP – alkaline phosphatase

Amox/clav. - amoxicillin/clavulanic acid

ANAL - analgesics

ASAT - aspartate aminotransferase

AUC - area under the curve

AUD - alcohol use disorder

BI - brief intervention

BMI - body mass index

CF - cystic fibrosis

CFRD - CF-related diabetes

CFTR – cystic fibrosis transmembrane conductance regulator

CP - chronic pancreatitis

CROSS - Consensus - Based Checklist for Reporting of Survey Studies

CRP - C-reactive protein

DSM-5 - The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

EBM - evidence-based medicine

EPC – European Pancreatic Club

EPI - exocrine pancreatic insufficiency

ERCP - endoscopic retrograde cholangiopancreatography

EST - endoscopic sphincterotomy

EUS - endoscopic ultrasound

FEV1% - expressed by forced expiratory volume in the first second of expiration

FFM – fat-free mass

Fl - femtoliter

FM - fat mass

FRAMES - Feedback, Responsibility, Advice, Menu Options, Empathy and Self-Efficacy

GGT - gamma-glutamyl transferase

GOT - glutamic-oxaloacetic transaminase

GPT - glutamic-pyruvic transaminase

Group E - Group with elevated GGT level

Group N - Group with non-elevated GGT level

HPSG - Hungarian Pancreatic Study Group

IAP/APA - International Association of Pancreatology/ American Pancreatic Association

IBD - inflammatory bowel disease

LOH - length of hospitalization

MCV – mean corpuscular volume

MD - mean difference

Metronid. - metronidazole

NJF - nasojejunal feeding

non-GI – non-gastrointestinal

NPO - nil per os diet

OF - oral feeding

OR – odds ratio

PP - paediatric pancreatitis

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROSPERO – International Prospective Register of Systematic Reviews

QUIPS - Quality in Prognosis Studies

SD - standard deviation

RAP - recurrent acute pancreatitis

RCT - randomized control trials

VAS - visual analog scale

PI – pancreatic insufficiency

PPI - proton pump inhibitors

REE - resting energy expenditure

WMD – weighted mean difference

2. Ph.D. profile

a. Vision

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

b. Mission

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

c. Specific goals

To achieve these objectives, we used a dual of clinical research methodologies; two cohort analyses, a case report, and a meta-analysis. We analyzed data from patients with acute pancreatitis (AP) and also with cystic fibrosis (CF) 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 favourable outcomes in the CF population.

d. Scientometric parameters

Number of papers:	**14 (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

e. List of publications

Already published papers related to the thesis

1. **Nagy R,** Ocskay K, Váradi A, Papp M, Vitális Z, Izbéki F, Boros E, Gajdán L, Szentesi A, Erőss B, Hegyi PJ, Vincze Á, Bajor J, Sarlos P, Mikó A, Márta K, Pécsi D, 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. **(IF: 5.7; D1)**
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-
3. nalysis. **JAMA Netw Open**.2022 Mar 1;5(3):e220740. doi:10.1001/jamanetworkopen.2022.0740. **IF: 13.3; D1**
4. **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. **IF: 3.9 ; Q1**

- **Already submitted paper related to the thesis**

5. **Nagy R**, Ocskay K, Sipos Z, Szentesi A, Párniczky A, Hegyi P. Discharge protocol in acute pancreatitis: an international survey and cohort analysis – submitted paper to **Scientific Reports** *Please NOTE: This article is NOT included in the Scientometric parameters, but included in the thesis*).

- **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**., Ocskay, K., Juhász, F. M., Márta, K., Teutsch, B., Mikó, A., Hegyi, P. J., Vincze, Á., Izbéki, F., Czakó, L., Papp, M., Hamvas, J., 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 Gastroenterol J.,** 10.1002/ueg2.12389. Advance online publication. https://doi.org/10.1002/ueg2.12389, **(IF:6.9; D1)**
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. **(IF: 4.4;Q1)**
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. **(IF:4.4 ; D1)**
5. Inflammatory bowel disease does not alter the clinical features and the management of acute pancreatitis: A prospective, multicentre, 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. **(IF:3.9 ; Q1)**
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. **(IF:4.4 ; D1)**
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. **(IF:3.9; Q1)**
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. **(IF:5.7; D1)**
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. (IF: 5.8; Q1)
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. (IF: 5.8; Q1)
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. **(IF:23, D1)**

3. Introduction

3.1. Evidence-based medicine

In the past decade, the concept of evidence-based medicine (EBM) has been clearly defined (1). 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 (2). Implementation of EBM offers standards that potentially provide the best quality of medical care at a reasonable cost (3).

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 regarding highly prevalent and generally well-researched disorders such as hypertension. Research shows a significant negative correlation between up-to-date care knowledge and years elapsed since graduation from medical school (4). 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 (4, 5). I would like to demonstrate the importance of clinical guidelines and protocols throughout an acute and a chronic disease, namely acute pancreatitis and cystic fibrosis.

3.2. Acute pancreatitis

Acute pancreatitis (AP) is one of the most common gastrointestinal system-related reasons for hospital admission affecting 13-80/100,000 people worldwide with the primary causes of gallstone and excessive alcohol consumption (6-8). The incidence of acute pancreatitis (AP) is continuously increasing by approximately 30% in the past two decades (9, 10). The disease itself, especially the severe form may lead to a prolonged hospital stay which can be associated with adverse patient outcomes and high hospital occupancy (11). Moreover, longer hospital stay can result in higher costs (12). The estimated annual total cost for AP admissions reached $2.2 billion, with a mean cost per hospitalization of $9870 based on a nationwide analysis in the United States (13).

It is essential to note that the disease can recur in 20-30% of the cases, which can lead to further organ damage and even to end-stage diseases such as chronic pancreatitis (CP) or pancreatic cancer (11, 14). Therefore, specific therapy for pancreatitis of different aetiologies has utmost importance.

3.3. Cystic fibrosis

Cystic fibrosis (CF) is a common, often lethal inherited disorder caused by recessive mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene affecting 1 in 3300 Caucasian live born (15). The mutations result in diminished function of chloride, sodium, and bicarbonate ion transport leading to thick mucus production that causes damages of multiple organs e.g. lungs, gastrointestinal and reproductive system (16). Consequential frequent airway infections, chronic inflammation, exocrine pancreas insufficiency (EPI) and complications such as CF-related diabetes mellitus (CFRD) and CF-related liver disease result in general unease and poor quality of life (17).

Among CF patients, malnutrition is a commonly seen phenomenon which is mainly caused by the combination of the following disorders: 1) nutrient malabsorption and fecal energy loss due to EPI; 2) increased energy expenditure predominantly related to chronic inflammation and breathing efforts (18-20)**;** 3) loss of appetite caused by inflammation-related anorexia (21). Malnourishment may accelerate the progression of the disease, nevertheless underweight is known to be associated with worse pulmonary function and increased morbidity and mortality in patients with CF (22).

3.4. 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 analyses, one case report and one systematic review and meta-analysis with the following clinical questions:

- Is there any tool to reduce the number of recurrences in alcohol-induced AP?
- What can be the consequences of the non-adherence to clinical guidelines in AP?
- Are the clinical outcomes better in patients with cystic fibrosis with higher-than-normal BMI?
- Are specific discharge protocol used in AP in every-day clinical practice?
- Does the existence of discharge protocols in AP result in shorter hospitalization?

4. Studies

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

4.1.1. Background

A significant proportion of aetiologies have specific treatments to avoid recurrences, like cholecystectomy in biliary etiology or fibrate or statin therapy in hyperlipidemic AP, and steroid therapy in the case of autoimmune AP (23-25). Unfortunately, alcohol-induced pancreatitis stands out in this field, and alcohol-induced AP is by far the most common form of recurrent acute pancreatitis (RAP) (26, 27). Therefore, research on specific therapies for decreasing the number of recurrent alcohol-induced AP has crucial importance (28, 29).

Alcohol misuse is a broad spectrum ranging from binge drinking to alcohol use disorder (AUD) which is determined based on the criteria of Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). Heavy drinking (14 or 7 drinks per week for men and women, respectively) and consequent recurrent inflammation can lead to permanent damage in the pancreatic tissue and facilitate the development of CP (30). Furthermore, excessive alcohol intake itself can decrease life expectancy by 24-28 years compared to the general population, as shown in Nordic countries (31). The results of Razvodovsky et al. suggested that 63% of all male pancreatitis deaths in Russia could be attributed to alcohol consumption (32). 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 (33).

Since excessive alcohol consumption is a global emerging healthcare issue, there are several therapeutic options available for the initiation of cessation of alcohol, including psychosocial and pharmacological interventions. Alcohol misuse must be highlighted since alcohol is responsible for 1 out of 7 male and 1 out of 13 female deaths in the age range of 15-64 years in the European Union (34). Generally, psychological approach is the cornerstone of cessation programs often combined with pharmacological treatment to

achieve the most favorable results (35). Following motivation assessment, brief intervention is generally the first step provided to patients. Brief interventions (BIs), a type of psychological intervention that ranges from 5 to 30 minutes, aim to highlight the fact of risky alcohol consumption and its adverse effects and emphasize the patients' responsibility to quit (36).

4.1.2. 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 (37). 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 etiology was identified, were also included.

Exclusion criteria

We excluded patients with alcoholic and biliary mixed etiology 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 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 (38). 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 analysed. 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 analyses 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 $p \leq 0.05$.

Ethical approval

The study was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (17787-8/2020/EÜIG) and conducted in accordance with Helsinki Declaration. Informed consent was obtained from all subjects involved in the study.

4.1.3. Results

1. Basic characteristics and data quality

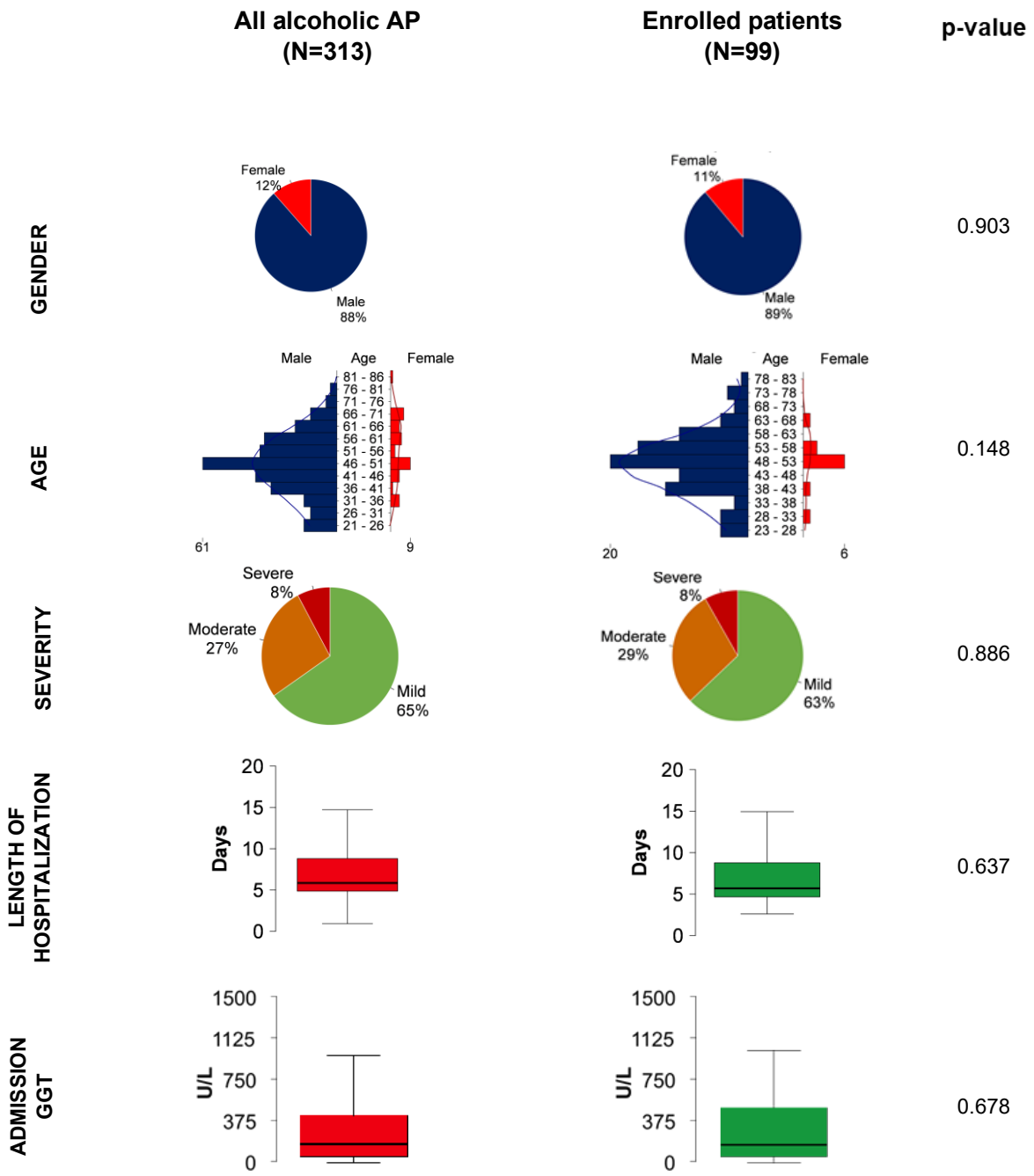
Altogether 99 alcohol-induced AP cases were included in our analysis. Out of the 99 patients, 79 belonged to the elevated GGT group, while 20 cases were included in the non-elevated GGT group. Overall, 89% of the patients were male and the mean age at admission was 50.05±11.37 years. Regarding severity, 62% of the AP episodes were mild and the median length of hospital stay was 6 (5-9) days. Details are shown in Table 1. The investigated cohort represented the total cohort of patients with alcohol-induced AP. Representativity analysis can be seen in Figure 1.

Table 1. Summary of patient characteristics and laboratory values

	Unit	Overall	Elevated admission GGT	Non-elevated admission GGT
Patients	n	99	79	20
Epidemiology				
Gender				
Male	n (%)	88 (89)	68 (86)	20 (100)
Female	n (%)	11 (11)	11 (14)	0
Age (year)	mean±SD	50.05±11.37	48.84±11.21	54.85±10.96
	median (IQR)	50 (44-57)	50 (41-56)	54 (49-59)
Outcomes				
Length of hospitalization (days)	mean±SD	9.94±10.53	9.56±9.65	11.45±13.66
	median (IQR)	6 (5-9)	6 (5-9)	7 (4-10)
Severity				
Mild	n (%)	61 (62)	50 (63)	11 (55)
Moderate	n (%)	28 (28)	21 (27)	7 (35)
Severe	n (%)	8 (8)	6 (8)	2 (10)
Medical history				
Previous acute pancreatitis	n (%)	40 (40)	31 (39)	9 (45)
Chronic pancreatitis	n (%)	14 (14)	9 (11)	5 (25)
Hypertriglyceridaemia	n (%)	17 (17)	15 (20)	2 (10)
Alcohol consumption (frequency)				
none	n (%)	6 (6)	5 (6)	1 (5)
occasionally	n (%)	24 (24)	14 (18)	10 (50)
monthly	n (%)	2 (2)	2 (3)	0 (0)
weekly	n (%)	13 (13)	9 (11)	4 (20)
daily	n (%)	54 (54)	49 (62)	5 (25)
Alcohol consumption (gram/occasion)	mean±SD	81.06±65.26	84.43±69.25	67.55±44.88
Laboratory parameters				
Admission GGT (U/L)	mean±SD	364.57±471.14	448.58±493.43	32.7±10.34
	median (IQR)	166 (64-493)	263 (115.5-571)	34 (28.5-39)
Discharge GGT (U/L)	mean±SD	255.28±248.88	294±250.75	36.79±23.78
	median (IQR)	194 (70-399)	229 (108-419)	30.50 (21.25-40.25)
1-month GGT (U/L)	mean±SD	88.55±105.80	103.2±113.5	30.65±20.90
	median (IQR)	91 (87.3-94)	53 (41-108)	28 (18-35.25)
Admission MCV (fL)	mean±SD	91.45±6.04	92.51±5.69	97.29±5.70
	median (IQR)	166 (87.8-94.65)	92 (89-95.90)	35 (28.5-39)
Discharge MCV (fL)	mean±SD	92.58±5.79	93.73±5.3	97.74±5.34
	median (IQR)	92.5 (88.93-96.25)	93.4 (89.95-97.03)	87.85 (84.25-90.95)
1-month MCV (fL)	mean±SD	91.02±5.34	92.07±5.10	86.9±4.22
	median (IQR)	90.9 (87.3-94)	91.5 (88.35-95)	87.6 (83.92-90.33)
1-month GGT change (U/L)	mean±SD	152.67±195.94	190±202.16	2.05±17.69
1-month GGT change (U/L; %)	mean±SD	40.92±71.13	49.25±74.50	8.04±43.42
1-month MCV change (fL)	mean±SD	1.50±2.95	1.79±2.93	0.38±2.83
1-month MCV change (fL; %)	mean±SD	1.53±3.16	1.85±3.12	0.31±3.06
Self-reporting				
1-month abstinence	n (%)	74 (79)	60 (80)	14 (70)

GGT- gamma-glutamyl transferase; MCV – mean corpuscular volume

Figure 1. Representativity analysis



Comparison of basic characteristics (age, gender, severity, length of hospitalization, admission GGT level) of all patients with alcohol-induced acute pancreatitis and enrolled patients. There is no significant difference in terms of basic characteristics between the two groups.

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.

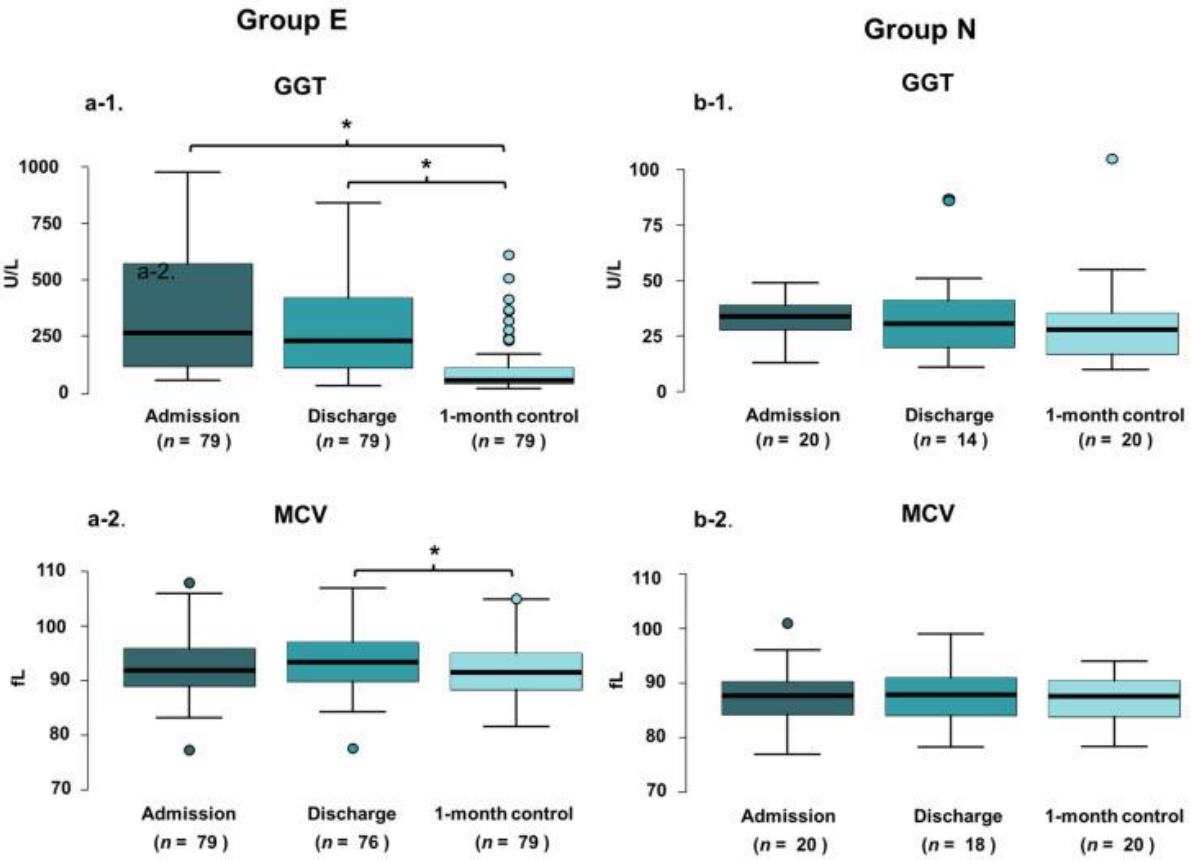
3. Frequent alcohol drinkers had a higher GGT level

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). Further details are shown in Table 1.

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) (Table 1, Figure 2-3.). 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 Fig.2.

Figure 2. GGT and MCV values of patients in Groups E and N in different time points visualized by boxplots.

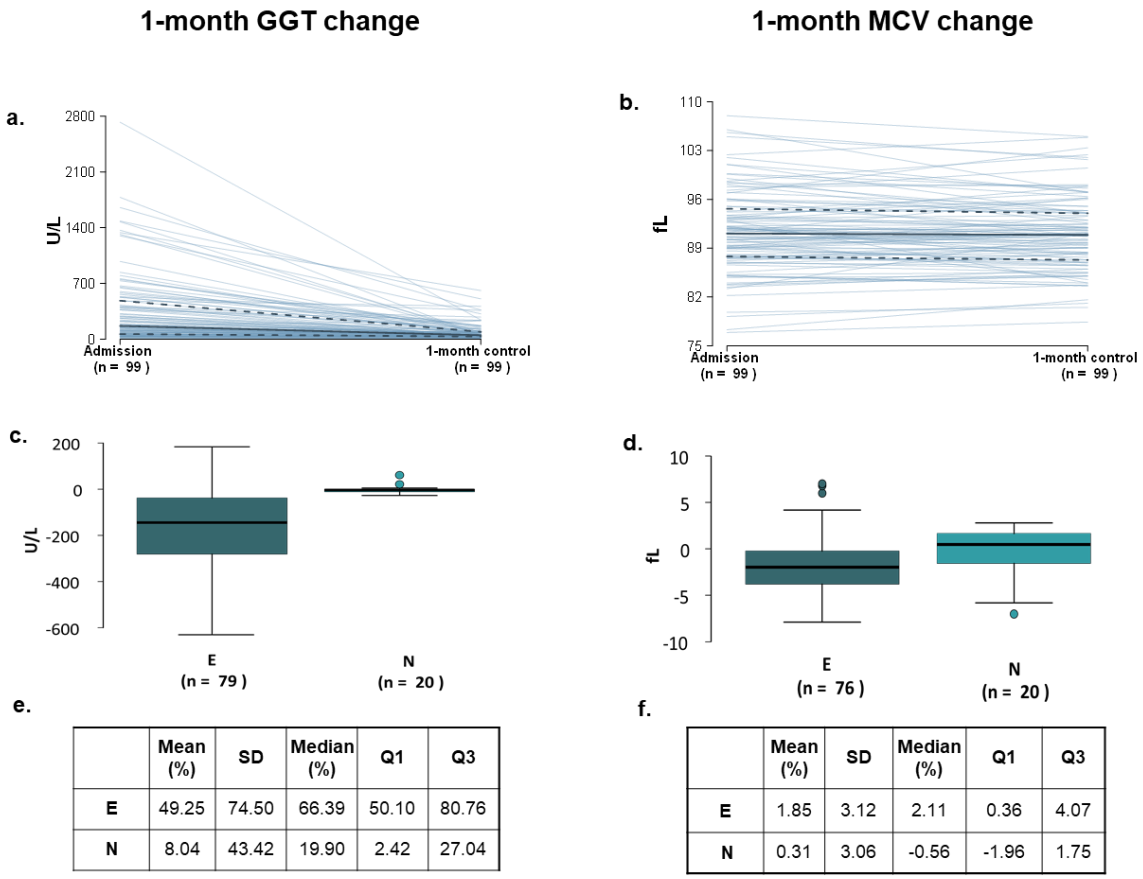


E - patients with elevated on-admission GGT level (**a**); N-patients with non-elevated on-admission GGT level (**b**); GGT - gamma-glutamyltransferase; MCV -mean corpuscular volume.
* $p < 0.01$

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 ($p<0.001$) (Table 1, Figure 1-2). No one had macrocytosis (MCV>95 fl) at the 1-month visit.

Figure 3. 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.

	Mean (%)	SD	Median (%)	Q1	Q3
E	49.25	74.50	66.39	50.10	80.76
N	8.04	43.42	19.90	2.42	27.04

f.

	Mean (%)	SD	Median (%)	Q1	Q3
E	1.85	3.12	2.11	0.36	4.07
N	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 analysed patients 3 (all belonged to group E) were readmitted due to alcohol-induced RAP.

4.1.4. Discussion

Excessive alcohol consumption has a negative effect almost on every organ causing a variety of disorders. 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 (14).

Studies investigating recurrences showed that the prevalence of RAP ranges from 25-45% (the follow-up periods were highly different) and 80% of the recurrences happen within 4 years (39, 40). In our cohort 40% of the admitted patients had a previous AP episode and 14% had the diagnosis of CP on admission which is consistent with a Dutch cross-sectional analysis (41). Three patients were readmitted due to recurrence. All of them were diagnosed with 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 (42). Pelli et al. found that none of the patients had a RAP during the 24-month period who stayed totally abstinent (43). Our results showed that among patients who reported abstinence (75%) there were no readmission due to RAP within 1-month and the majority of these patients (95%) had decreased GGT level on the control visit compared to discharge value. However, abstinence cannot be achieved as simple as it may seem first. Therefore, particular efforts are needed to be brought to the patient care in order to diminish regular alcohol consumption.

Strengths and limitations

The strengths of our study are, the multicentric uniform data collection and high data quality. The limitations are, the retrospective nature of the analysis, the short follow-up time, the absence of a control group, and we also have to consider the possible differences between BI methods since psychological interventions were performed by physicians in different centers.

Conclusion

BI is an effective tool to reduce alcohol consumption and to prevent RAP. Therefore, BI should be extended among practitioners and apply it in regular in- and outpatient care. 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.

4.2. Revisiting the evidence-based management of paediatric pancreatitis

4.2.1. Background

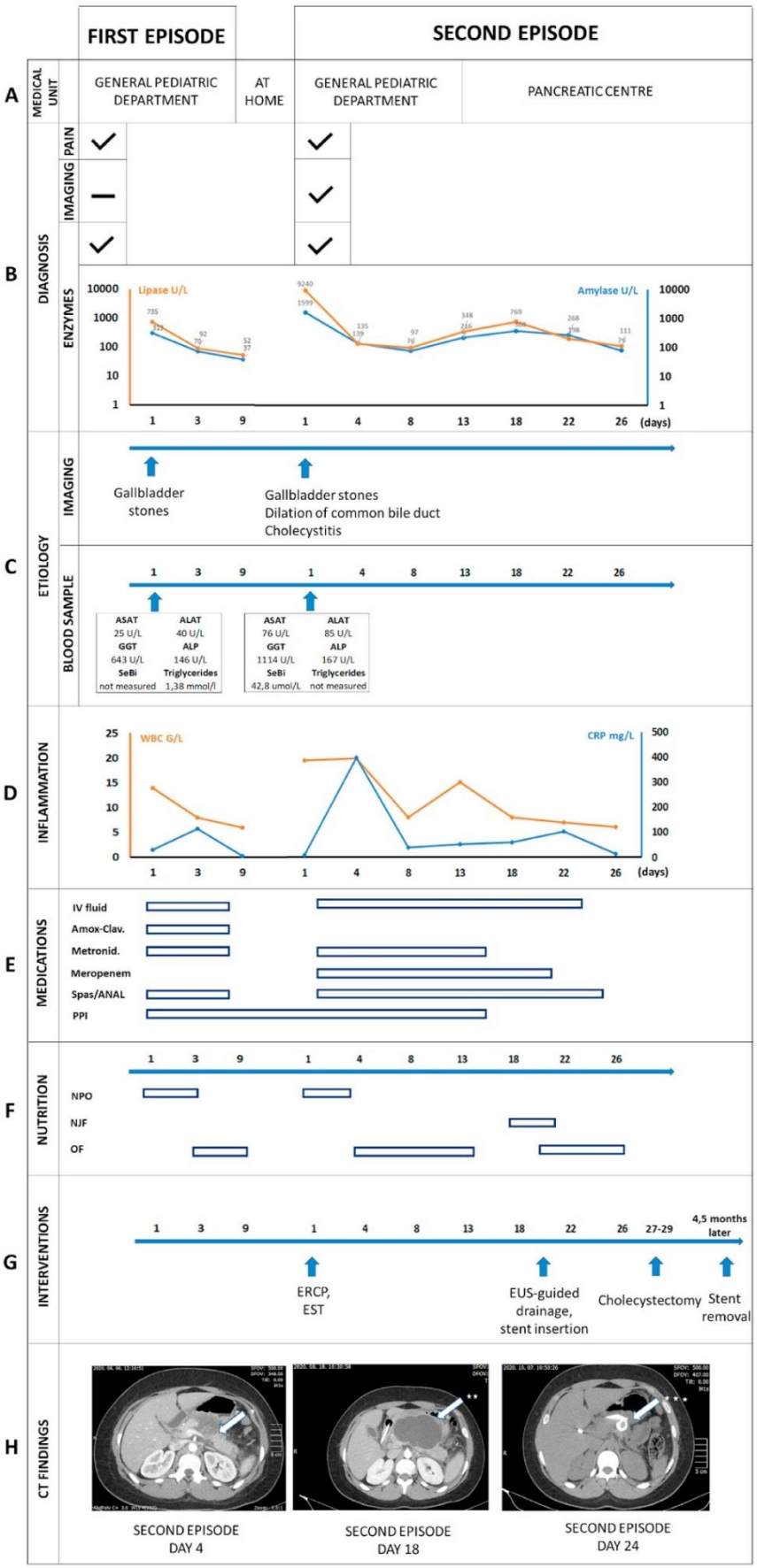
Although pediatric acute pancreatitis (PP) is a relatively rare disease, its incidence has been rising continuously (1, 3). Therefore, experts in the field felt important to develop and publish evidence-based guidelines for PP. Here we provide a case study which clearly demonstrates the importance of the recently published EPC/HPSG evidence-based pediatric pancreatitis guidelines (44).

4.2.2. Case report

Our 17-year-old female patient was admitted to the pediatric 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 pediatric 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 pediatric 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 Centre. 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 (Figure 4.).

Figure 4. Summary of the medical care on a timeline



A. Location of patient care.

B. Determination of diagnosis based on current criteria. According to the EPC/HPSG guideline, a diagnosis of acute pancreatitis (AP) is achieved by meeting at least two of the following three criteria [1]: abdominal pain [2]; serum lipase or serum amylase level at least three times greater than the upper limit of normal [3]; characteristic findings of AP with imaging methods.

C. Aetiology workup. Elevated biliary, cholestatic enzymes and ultrasound findings support a biliary aetiology. ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; GGT: gamma glutamyl transferase; ALP: alkaline phosphatase. D. Inflammatory values on timeline. CRP: C-reactive protein and WBC: white blood cells. E. Medications administered in each department. Amox/clav.: amoxicillin/clavulanic acid; Metronid.: metronidazole, Spas.: spasmolytics; ANAL: analgesics; PPI: proton pump inhibitors.

F. Nutrition management. NPO: nil per os diet; NJF: nasojejunal feeding; OF: oral feeding.

G. Interventions in chronological order. ERCP: endoscopic retrograde cholangiopancreatography, EST: endoscopic sphincterotomy, EUS: endoscopic ultrasound.H. Axial sections of contrast-enhanced computed tomography of the patient's abdomen. The left arrow shows an extended inhomogeneous area in the pancreas, indicating necrosis with fluid collection (∗). The middle arrow shows a large pseudocyst in the region of the pancreas body and tail (∗∗). The right arrow indicates the double-pigtail stent inserted into the pseudocyst (∗∗∗).

4.2.3. Discussion

Some decades ago, clinical practice generally relied on local expertise, often driven by physiological reasoning (2). 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 (45). 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 guidelines (44, 46). 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. Pediatricians 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 pediatric pancreatitis should be treated in a pancreatic center.

Table 2. Adherence to the EPC/HPSG evidence-based guidelines for the management of pediatric 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
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 centres. (Adult evidence level: GRADE 1/C, full agreement).

4.3. Discharge protocol in acute pancreatitis: an international survey and cohort analysis (submitted)

4.3.1. Background

In order to achieve the best treatment for a disease, it is obvious that evidence-based guidelines need to be used (47, 48). The currently used evidence-based medicine guidelines in AP focuses on the diagnosis and management of AP, without clear recommendation on patient discharge (37). Consequently, discharge decisions are made based on local experts' onsite opinions leading to a variety of discharge approaches. A few years ago, the Hungarian Pancreatic Study Group (HPSG) developed a discharge protocol, but it has not been extensively tested and compared with other local protocols.

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

4.3.2. Methods

1. International cohort

To assess the worldwide trends in patient discharge in AP we conducted a multicentre web-based survey by following the Checklist for Reporting of Survey Studies (CROSS) (49). 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. There was no pre-testing period for the questionnaire. In case the collaborators confirmed their participation in the project, we sent a second email with further details and a pre-defined Excel sheet to collect data on gender, age, etiology, length of hospitalization (LOH), mortality and severity of AP, discharge C-reactive protein (CRP) and 1-month readmission rate. Overall, the international data were collected retrospectively. The participants were asked to upload the completed Excel sheet to a private Google Drive folder. The participants did not have access to other collaborators' datasets. The timeframe of the survey took two months. To avoid multiple participation, we carefully checked the participating centers, departments, and affiliations. In case of any questions, the first author was in charge of keeping in contact. For the statistical analysis, we divided the international

centres based on the presence of discharge protocol, creating an international protocol and an international non-protocol cohort, and compared the relevant clinical outcomes, such as LOH, discharge CRP value, and readmission rate.

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 (37). 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 hospitalisation 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.

The CRP value of 50 mg/l has been arbitrarily set based on previous clinical experience and related literature (50-52). As the role of CRP at discharge in acute pancreatitis has not been previously investigated, this is the first time we tested its role and the safety of this cut off value.

Three of the 17 investigated centres used the above-mentioned discharge protocol in Hungary. Therefore, for data analysis, two groups of the Hungarian cohort were identified: 1) centres 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. Diagnosis of acute pancreatitis was defined based on the Atlanta "two of three" classification: abdominal pain, pancreatic enzyme elevation at least three times above the upper limit and morphological changes (53).

3. Statistical analysis

Statistical analyses 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 $p<0.05$.

4. Ethics

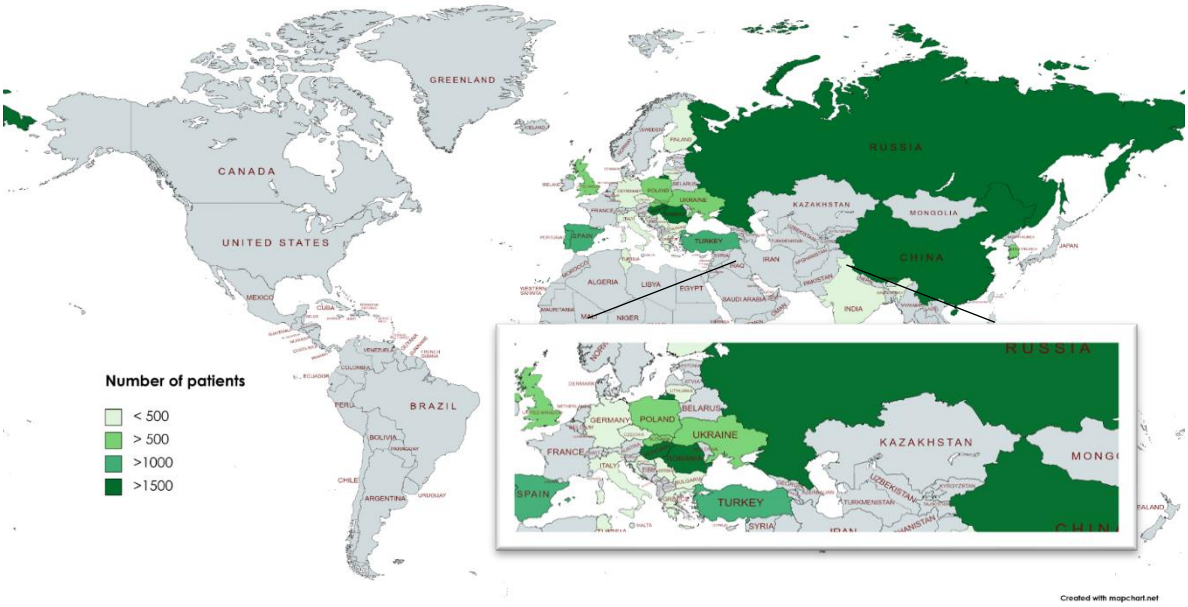
The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council (22254e1/2012/EKU, 17787-8/2020/EÜIG). The study was performed in accordance with the Declaration of Helsinki. Patients' data of foreign centres were treated entirely anonymously. Informed consent was obtained from all subjects and/or their legal guardian(s).

4.3.3. Results

1. Basic characteristics of the international cohorts

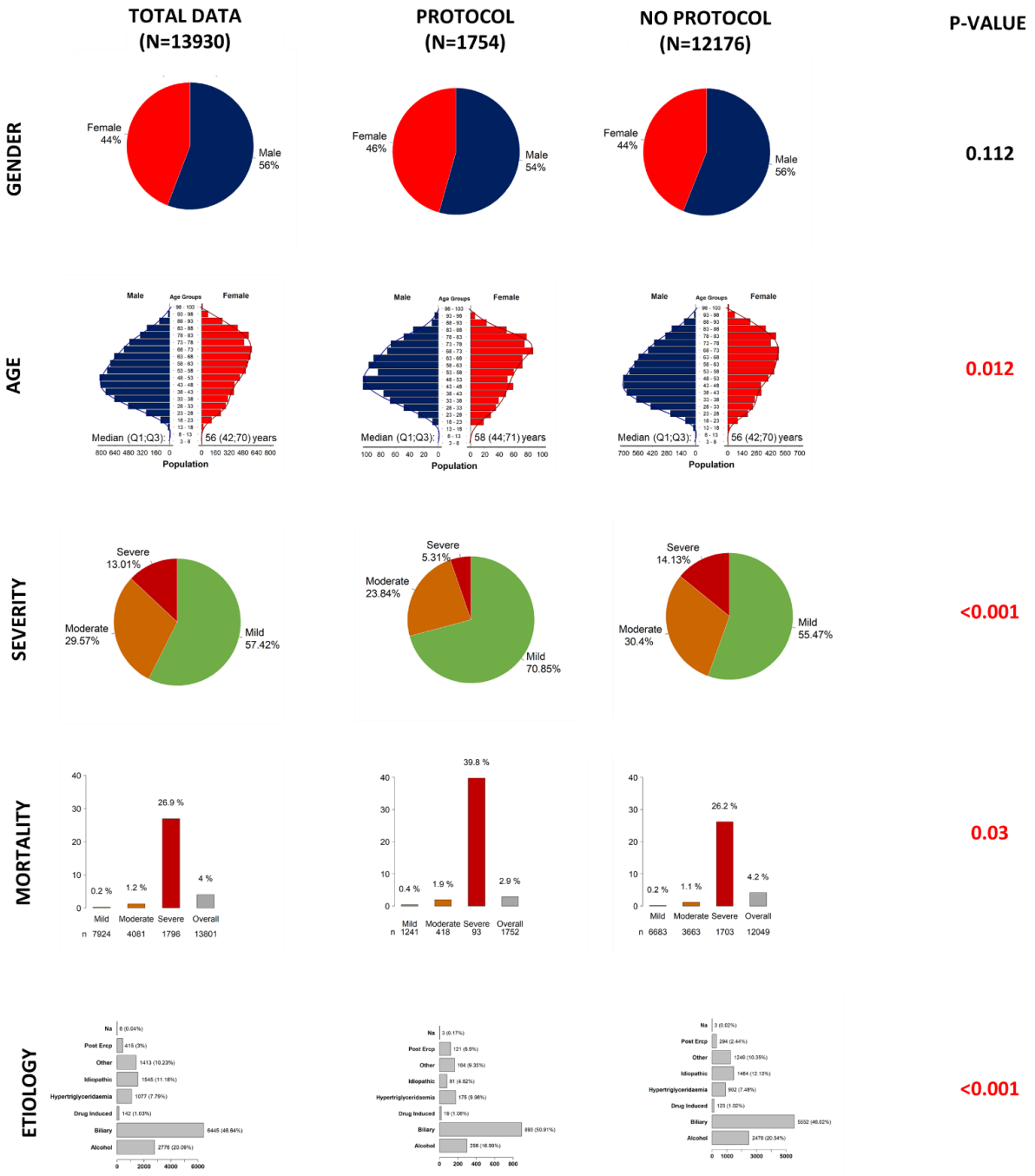
Overall, 13930 cases from 3 continents, 23 countries, 56 centers participated in the survey and were analyzed. Altogether 1754 (12.59%) cases belonged to the international protocol group. The participating countries and the number of uploaded cases are illustrated on a colour-scaled map (Figure 5.). 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 6).

Figure 5. 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).

Figure 6. 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 ($p<0.05$).

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 3.). When separately analyzing 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 3). 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, $p=0.002$).

Table 3. Comparison of centres 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 centres 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.

4. 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 7.). 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 4). 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 7. 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%) (Table 4).

Table 4. Table of the readmission rates in the HPSG-Protocol group.

	readmitted		**non-readmitted**	
	N (%)	discharge CRP*	N (%)	discharge CRP
Overall	**35 (5)**	**51.60 (19.95; 66.45)**	**653 (95)**	35.10 (13.40, 68.70)
related to AP etiology	19 (54.29)	38.70 (17.95; 57.2)	NA	
complication of index admission	4 (11.42)	69.15 (66.23; 83.08)	NA	
other causes	12 (34.29)	55.70 (27.8; 61.20)	NA	
discharged < 50 mg/l CRP	17 (48.57)	18.60 (12.00; 38.60)	448 (64.1)	17.25 (8.18; 31.43)
discharged > 50 mg/l CRP	18 (51.43)	66.45 (57.60; 76.60)	205 (35.9)	83.90 (63.35; 112.83)

The table shows the number of readmitted patients due to certain causes. * values are expressed in median (Q1;Q3). unit: mg/l. NA- not applicable, data are not available. Patients readmitted with pseudocyst infection had the highest median discharge CRP value.

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 3). 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).

5. 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).

4.3.4. 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.

In other diseases, there were also positive results from the mindful patient discharge. Naureen et al. implemented a standardized, evidence-based discharge protocol when discharging patients with heart failure and consequently, it was shown that patient education can positively impact self-management after discharge resulting in shorter LOH and lower 30-day readmission rates (54).

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 (44, 46). Furthermore, Whitlock at el. built up a model in which treatment with antibiotics, pain, pancreas necrosis, and

gastrointestinal symptoms were identified as a risk factor for early (within 30 days) readmission (55).

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.

Of course, the prediction of possible readmission is of utmost importance and, therefore, we investigated whether CRP could be a reliable predictive tool. Unfortunately, CRP failed to be useful in this situation. CRP level as a prediction tool for readmission at discharge was investigated in several fields but not in AP. Acute heart failure patients discharged with elevated CRP value (>10 mg/L) value, were shown to have a higher risk of mortality and readmission (56, 57). Furthermore, investigation of the delayed complications after esophagectomy showed that discharge patients with CRP level < 84 mg/L on day 7 proved to be a safe approach, however CRP trend itself could not predict delayed complications (58). In our cohort, neither the absolute CRP value nor the degree of the decline showed a significant relationship with the 1-month readmission, supporting the theory that patient discharge should not depend on the current value or the volume of the decrease but rather on the direction of the tendency.

Strength and limitations

The strength of our study is that we conducted an international survey including 23 countries from 3 continents and extensive data were collected. The data quality, especially in the HPSG registry analysis is remarkably high. However, we have to mention the limitations, such as the retrospective nature of the international cohort analysis. There is no information about the number of tertiary centres in our analysis, which can highly influence the number and characteristics of admitted patients. In the Hungarian cohort analyses, there might be slight differences in the way how the HPSG-discharge protocol was applied in different centres. Furthermore, the fact that those centres that apply protocols probably provide better patient care anyway.

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 readmission. Discharge CRP value is not suitable for predicting the 1-month readmission. There is a particular need for evidence-based recommendations on discharge in guidelines.

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

4.4.1. Background

Monitoring the nutritional status and growth of patients, as well as the prevention and treatment of malnutrition, are demanding components of CF care. Currently, BMI is the generally accepted indicator for monitoring the nutritional status of patients with CF. In children older than 2 years, the target BMI is at least the 50th percentile; in adults, the target BMI is greater than or equal to 22 for women and greater than or equal to 23 for men (59). However, BMI does not distinguish between the major components of the body, namely, fat mass (FM), fat-free mass (FFM), total body water, bone mineral density, and bone mineral content. There is a growing body of evidence highlighting the importance of nutritional status in the diagnostic and therapeutic management of patients with CF, but there is a lack of comprehensive review on patients with a BMI above the target (60-62).

The European Society for Clinical Nutrition and Metabolism; the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; and the European Cystic Fibrosis Society adult and pediatric dietary guideline focuses on nutritional failure with no recommendation on the management of individuals who are overweight or obese (59). However, an analysis of BMI changes found that the prevalence of overweight and obesity in adults with CF is 31.4% and has more than doubled over the past 2 decades in patients with CF (63). However, long-term adherence to the currently recommended high-fat and high-carbohydrate diet in CF also might have controversial effects on body composition and even on some clinical outcomes. 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 (64). 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.

4.4.2. 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-analyses (PRISMA) reporting guideline (65).

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. After each step of the selection process, the rate of agreement was determined and documented by calculating the Cohen κ coefficient. Values may indicate slight (0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect agreement (0.81-1.00). References of each included study were checked, and records that were considered to be eligible were added to the pool.

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 non-underweight group (≥20) and performed subgroup analyses 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 (66). Any disagreement was resolved based on consensus.

Statistical Analysis

A random-effects model was applied in all analyses 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-analyses 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 (67). Sensitivity analyses 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 analyses 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 $P < 0.05$.

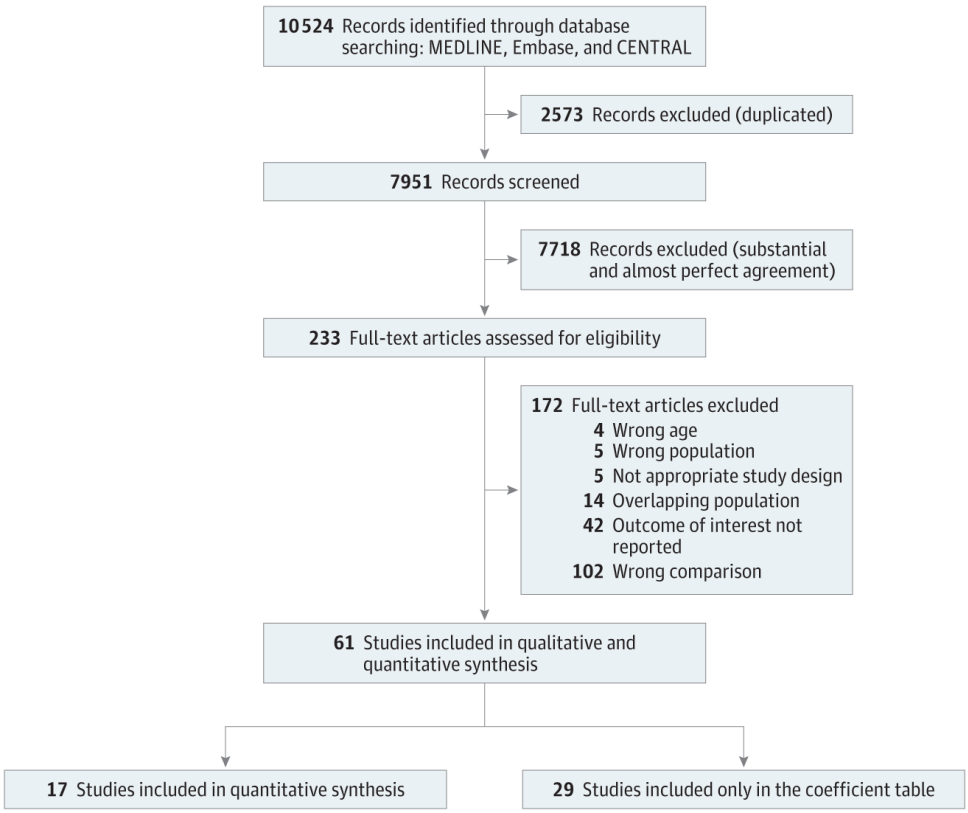
4.3.3. Results

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 8.

Figure 8. Selection flowchart



Preferred Reporting Items for Systematic Reviews and Meta-analyses (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). The major characteristics of the included studies are reported in Table 5.

Table 5. Characteristics of included studies

Source	Characteristic					Setting		
	Patients, No.	**Age group**	**Age, mean (SD), y**	**BMI**	**Pancreatic insufficiency, No. (%)**	**Genotype (DF508)**	**Growth parameter**	**Outcomes**
Altman et al, 2017 (abstract)	224	Adults	32.4 (10.6)	NA	NA	NA	BMI	CFRD, *P aeruginosa* colonization
Alvarez et al, 2016	32	Mixed	26.1 (8.9)	22.1 (2.9)a	31 (96.9)	56.3% Homozygote; 28.1% heterozygote	BMI, percent body fat, FFM	FEV1%, CFRD, FG
Barni et al, 2017b	73	Mixed	25.6 (7.3)	21.0 (3.0)a	66 (90)	17.8% Homozygote; 45.2% heterozygote	BMI	FEV1%, PI, CFRD, *P aeruginosa* colonization
Bodnar et al, 2014b	59	Mixed	14.0 (4.8)	20.4 (2.4)a	NA	50.8% Homozygote	BMI, BMI percentile	FEV1%, *P aeruginosa* colonization
Bonhoure et al, 2020b	290	Adults	25.5 (7.9)	21.7 (2.9)a	232 (79.9)	49.0% Homozygote; 41.3% heterozygote	BMI	FEV1%, PI, CFRD, FG, HbA1c%, TC, TG, HDL-C, LDL-C, FI
Bouma et al, 2020	201	Mixed	13.3 (4.6)	19.9 (3.7)a	NA	51.2% Homozygote; 36.3% heterozygote	BMI, BMI *z* score	FEV1%
Brennan et al, 2010 (abstract)	348	Adults	No data	No data	NA	NA	BMI	FEV1%
Cano Megias et al, 2015b	61	Mixed	26.8 (9.5)	20.3 (3.3)a	NA	24.6% Homozygote; 78.6% heterozygote	BMI, *z* score	FEV1%
Charatsi et al, 2016	71	Mixed	12 (2.7)	18.2 (3.4)c	36 (90)	49.3% Homozygote; 39.4% Heterozygote	FFM *z* score	FEV1%, PI, *P aeruginosa* colonization
Da Silva Garrote et al, 2016 (abstract)	34	Children	10.2 (5.3)	No data	NA	NA	BMI percentile	*P aeruginosa* colonization
Dray et al, 2005b	163	Adults	28.8 (8.4)	19.1 (2.8)a	137 (84)	42.3% Homozygote; 38.6% heterozygote	BMI	PI, CFRD, *P aeruginosa* colonization

Dudina et al, 2017 (abstract)	435	Adults	No data	No data	NA	NA	BMI	FEV1%
Engelen et al, 2012b	77	Mixed	14.8 (2.9)	40.77 (26.4) d	75 (97)	63.6% Homozygote; 25.9% heterozygote	BMI, BMI percentile, FFM, *z* score	FEV1%
Gozdzik et al, 2008b	39	Adults	23.9 (3.7)	19.5 (2.9)a	NA	NA	BMI	FEV1%
Hanna and Weiner,2015b	226	Children	10.6 (4.9)	18.5 (4.2)a	181 (80)	NA	BMI percentile	FEV1%, PI
Harindhanavudhi et al, 2020b	484	Adults	35.2 (11.6)	23.9 (4.4)a	417 (85)	46.9% Homozygote	BMI	FEV1%, PI, CFRD, HbA1c%, HDL-C, LDL-C
Hollander et al,2018 (abstract)	224	Adults	No data	No data	NA	NA	BMI	FEV1%
Ionescu et al, 2003	56	Adults	23 (5.2)	20.9 (1.6)a	29 (100)	NA	FFM	FEV1%
González Jiménez et al, 2012b	109	Children	12.3 (8.8)	21.6 (3.9)a	371 (82)	41.3% Homozygote; 46.7% heterozygote	BMI percentile	FG, HbA1c%, TC, TG, FI
González Jiménez et al, 2017b	451	Mixed	12.7 (3.2)	−0.3 (0.8)e	93 (85)	33.0% Homozygote; 49.8% heterozygote	BMI, *z* score	FEV1%
Kines et al, 2012 (abstract)	114	Mixed	No data	No data	NA	NA	BMI	FEV1%
Kotsifas et al, 2016b (abstract)	44	Adults	No data	No data	NA	NA	BMI	FEV1%
Maksimychev a et al, 2018 (abstract)	51	Children	No data	No data	NA	NA	BMI	FEV1%, *P aeruginosa* colonization
Ochota et al, 2019 (abstract)	226	Adults	No data	23.5 (6.0)a	NA	NA	BMI	FEV1%
Panagopoulou et al, 2008b	43	Mixed	20.1 (8.5)	19.4 (2.6)a	No data	NA	BMI, FFM	FI
Panagopoulou et al, 2014	68	Mixed	19.81(9.0)	19.8 (2.7)a	56 (82)	20.6% Homozygote; 48.5% heterozygote	BMI, BMI percentile	FEV1%, PI, CFRD, FG, TC, TG, *P aeruginosa* colonization

Papalexopoulou et al, 2018	29	Mixed	15 (1.8)	−0.1 (−2.7 – 1.2)e	28 (96.5)	58.6% Homozygote; 31.0% heterozygote	BMI *z* scores, BMI percentile, FFM index *z* score	FEV1%
Proud et al, 2012 (abstract)	117	Adults	28 (9)	No data	NA	NA	BMI, FFM index	FEV1%, PI
Ramírez et al, 2015b	173	Mixed	11.43 (2.3)	No data	145 (83.77)	50.3% Homozygote; 36.9% heterozygote	BMI percentile	FEV1%, PI, *P aeruginosa* colonization
Stephenson et al, 2013b	651	Adults	33.8 (11.4)	22.3 (4.1)a	488 (75)	39.3% Homozygote; 38.2% heterozygote	BMI	FEV1%, PI, CFRD, TC, TG, *P aeruginosa* colonization
Umławska et al, 2014b	89	Children	12.3 (3.5)	–0.8 (0.8)e	80 (90)	51.7% Homozygote; 33.7% heterozygote	BMI percentile	FEV1%, PI
Ziegler et al, 2008	39	Mixed	23.7 (6.4)	20.3 (2.2)a	NA	NA	BMI, BMI percentile	FEV1%

Abbreviations: BMI, body mass index; CFRD, cystic fibrosis–related diabetes; FEV1%, forced expiratory volume in the first second of expiration; FFM, fat-free mass; FG, fasting glucose; FI, fasting insulin; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not assessed; P aeruginosa, Pseudomonas aeruginosa; PI, exocrine pancreatic insufficiency; TC, total cholesterol; TG, triglycerides.

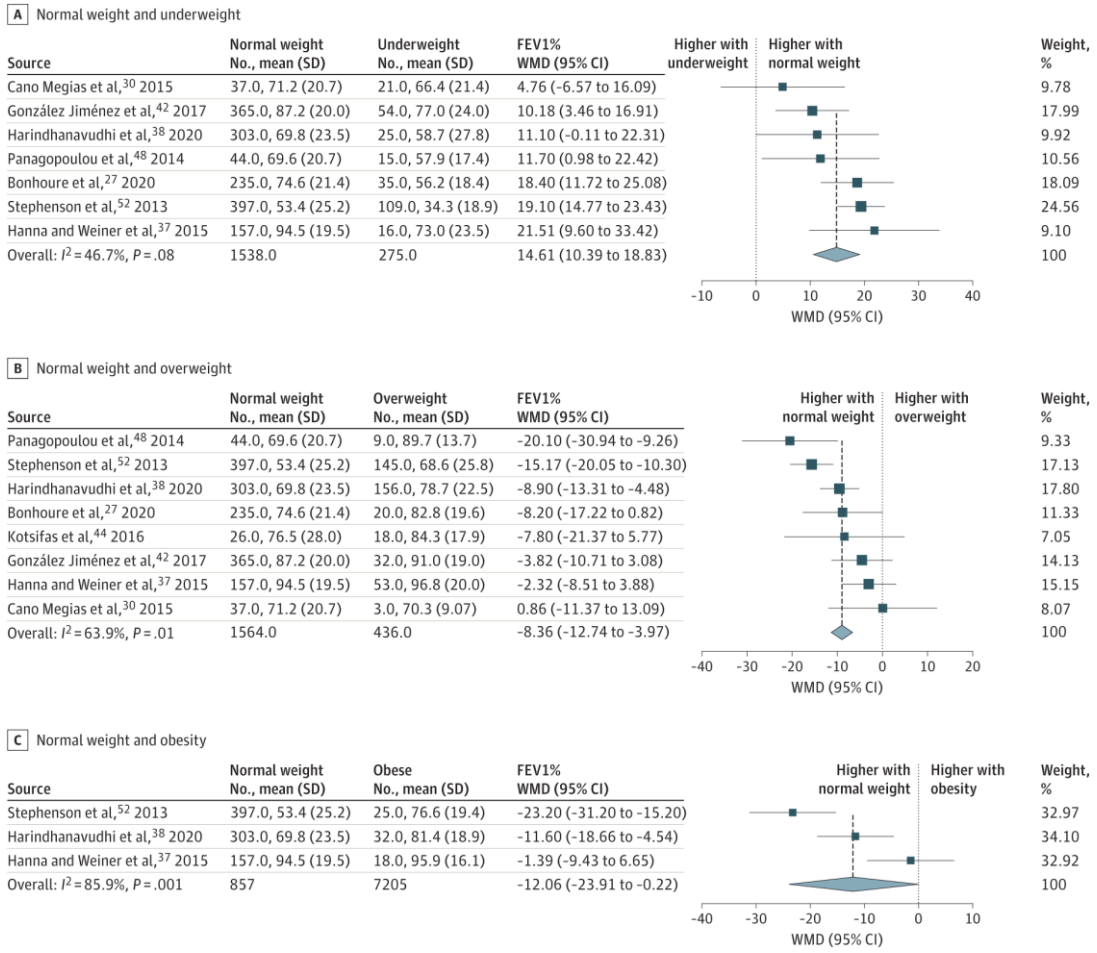
a Value expressed as mean (SD). b Included in the quantitative synthesis. c Value expressed as median (IQR). d Value expressed as mean (SD) percentile. e Value expressed as z score.

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%; WMD, –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 9). High heterogeneity was shown in the analysis of pulmonary function (I^2 = 46.7%-85.9%). In the comparison of patients who were underweight vs not underweight, we found significantly lower FEV_1% in children, adults, and mixed patient populations who were underweight (overall MD, –19.12%; 95% CI, –23.53% to –14.71%).

Figure 9. 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.

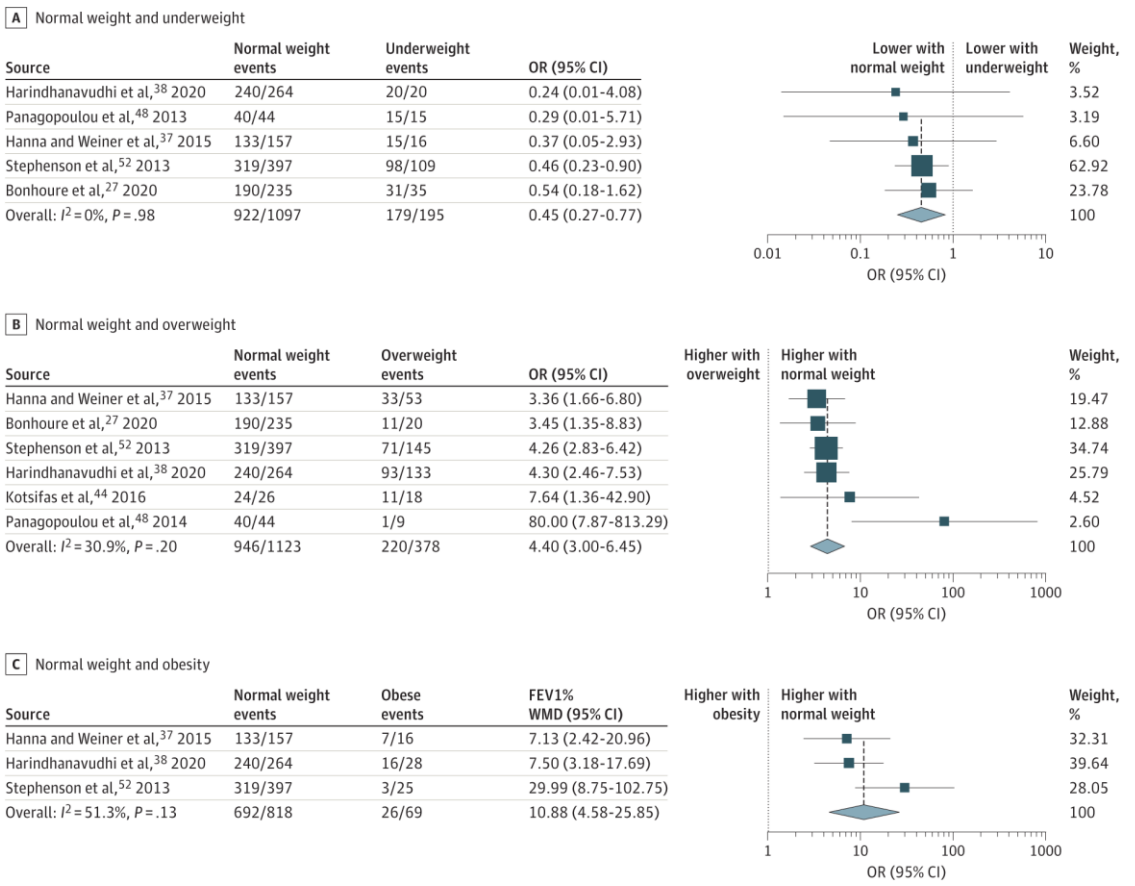
In addition to the 13 records in the quantitative synthesis, 15 studies, including conference abstracts, were added to the qualitative synthesis. The reasons for exclusion of these 15 studies from the quantitative synthesis were either different BMI categorization from the World Health Organization recommendation or insufficient data reporting. Among these 15 studies, 9 studies showed increased FEV_1% values to be associated with higher BMI values in patients with normal BMI or overweight compared with those who were

underweight. Two studies did not report significant differences in pulmonary function when comparing different BMI categories (68, 69). 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 10). 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 10. Odds of Exocrine Pancreatic Insufficiency in Different Body Mass Index Categories



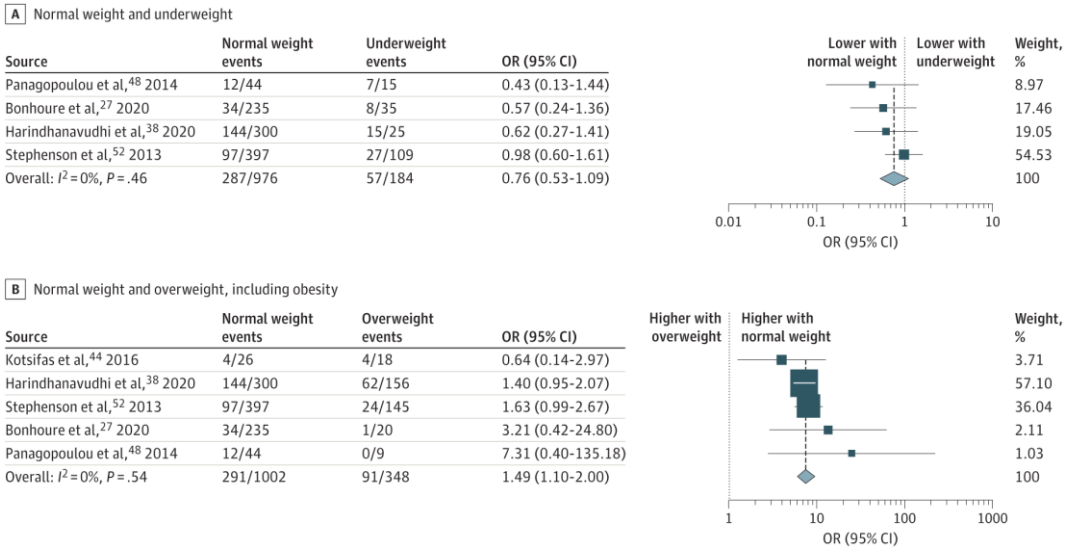
Comparison of patients with normal weight vs underweight (A), normal weight vs overweight (B), and normal weight vs obesity (C). OR indicates odds ratio. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 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 11). 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). The studies of Altman et al. (70) and Alvarez and Stecenko (71) were not included in our quantitative synthesis owing to

inadequate comparison categories; however, none of the studies reported significant differences between BMI groups regarding the CFRD outcome.

Figure 11. 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; WMD, –0.02 0.41 mg/dL; 95% CI, –0.03 to 0.01) and triglyceride levels (0.03 vs 0.02 mg/dL WMD, –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. Bonhoure et al,(72) Harindhanavudhi et al,(73) and Panagopoulou et al., (74) reported high-density and low-density lipoprotein cholesterol values; all of the studies showed significantly higher low-density lipoprotein cholesterol levels and not significantly

lower high-density lipoprotein cholesterol levels in patients who were overweight. However, these results could not be included in the quantitative synthesis owing to insufficient data reporting by Harindhanavudhi et al.(73).

Additional Outcomes and Analysis

The ratio of patients with *P aeruginosa* colonization at the time of assessment was reported in 11 studies; of these, 6 studies were included in our quantitative synthesis. The results showed that patients who were underweight were significantly more likely to have *P aeruginosa* colonization compared with those who were not underweight (OR, 1.86; 95% CI, 1.34-2.59). Of the studies included only in the qualitative synthesis, Maksimycheva et al. (75) and Da Silva Garrote et al. (76) found that underweight is associated with higher odds for *P aeruginosa* colonization, whereas 3 studies did not find significant differences between BMI and FFM categories (70, 77, 78).

The studies by Stephenson et al, (79) Bonhoure et al, (80) and Harindhanavudhi et al, (73) were identified as showing significance regarding PI and CFRD by the leave-1-out sensitivity analysis. Funnel plots were created, and the Egger test was performed to detect publication bias. There was no small-study effect found in our analyses.

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]).

4.4.4. 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 (68, 81-84). The favorable effect of weight gain has also been visible in the past few years as modulator therapy has become available as a novel treatment in CF (85). The continuous spread of modulators that aim to diminish the

influence of *CFTR* dysfunction has been shown to have beneficial effect on body composition (86). In addition to weight gain, the proportion of FFM is increasing, which is associated with the reduction of REE.

Although we intended to include studies that compared patients with CF based not only on BMI but including FFM and FM, there were not enough eligible studies examining FFM and FM for a quantitative synthesis to be performed. All studies included in the qualitative synthesis highlighted the importance of the FFM proportion that leads to better pulmonary function. However, the influence of higher FM on FEV_1% is not obvious. Alvarez et al. (71) reported that FEV_1% is inversely associated with FM, whereas Panagopoulou et al. (74) described a correlation between body fat percentage and pulmonary function.

Our results regarding the association between higher BMI and the lower odds for PI are consistent with previous research (72, 74, 79). In patients with sufficient exocrine pancreatic function, adequate digestion and absorption are more likely to be present and can lead to higher BMI.

We found underweight to be associated with a higher prevalence of CFRD, which is in accordance with general clinical observations. In patients with CF who are underweight, there are several associated risk factors that contribute to the development of CFRD, such as PI or insulinopenia (87). We assumed that insulin resistance, as the minor component of CFRD, becomes more dominant in individuals who are overweight or obese and may lead to higher odds for diabetes compared with those of normal BMI. However, our results did not confirm this hypothesis, showing significantly lower odds for CFRD in patients with a BMI greater than or equal to 25.

Although our results showed that BMI greater than or equal to 25 does not have a statistically relevant association with glucose homeostasis (fasting glucose, fasting insulin, and HbA_{1c} levels), overweight and obesity are associated with higher total cholesterol and triglyceride levels. However, none of these elevated values exceeded the upper limit of normal.

Based on our results, the higher the BMI, the better the investigated clinical indices; we found no obvious evidence to be associated with harmful effects. However, the assessment of FFM and FM could provide more precise information. Several studies emphasized the

potential usefulness of FFM as a more detailed assessment of body composition compared with BMI. The prevalence of hidden FFM depletion (FFM<5th percentile and normal BMI) is unexpectedly high (10%-20%) among patients with CF and is associated with increased disease severity, including reduced lung function, frequent pulmonary exacerbations, and increased inflammation.

Therefore, measuring body composition in patients with CF may be more informative than the single use of BMI as an indicator of optimal health and nutritional status.

Strengths and Limitations

To our knowledge, this is the first systematic review and meta-analysis assessing body composition in patients with CF in detail, including 3100 patients, with special focus on those who are overweight and obese. Moreover, we performed a meta-analysis regarding 9 outcomes, and subgroup analyses were performed for 3 outcomes.

Our study has limitations. There was substantial heterogeneity in the comparison of patients with normal weight and those who are obese regarding pulmonary function, and the source of substantial heterogeneity could not be identified by subgroup analysis. Furthermore, most of the studies did not report transplant status; thus, we could not perform subgroup analysis, and none of the pediatric studies reported the measurement method of respiratory function in children younger than 6 years.

Conclusions

Our findings suggest that nutritional status plays an important role in maintaining organ function in patients with CF. Higher-than-normal BMI is associated with better clinical parameters. The current nutritional recommendations, including the target BMI in the CF patient population, should be reconsidered. Body composition parameters should be incorporated in the assessment of nutritional status.

6. 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 in the reduction of the differences in clinical approaches worldwide.

We emphasized the importance of adherence to guidelines 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.

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 (11, 40). 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. Although several studies have shown the beneficial effects of BIs on alcoholic patients, their structure and frequency are still debated (42, 88, 89). Nordback et al. found better results with regular interventions at 6-month intervals in the outpatient care compared to a single one during hospitalization. A meta-analysis of Platt et al. showed that brief advice provided by nurses brings the most favorable outcomes and Kaner et al. also confirmed that longer duration of counseling probably has no relevant additional effect (88, 89). The structure and frequency of BIs are still being debated, but psychological approaches have shown promise in reducing alcohol and smoking habits. There are several undergoing randomized clinical trials investigating the effectiveness of psychological approaches on alcohol or smoking habits (28). Our article suggests that incorporating BIs into regular in- and outpatient care could promote abstinence and prevent recurrent episodes.

Based on the findings of another study of ours, 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. It has been reported that patients with CF who are overweight have markedly fewer exacerbations that could contribute to loss of appetite (73), Moudiou et al (90) described a negative correlation between resting

energy expenditure (REE) and BMI *z* score. Resting energy expenditure is the amount of energy that is necessary to maintain basic body functions, such as digestion and breathing, and requires approximately 60% of the total calorie need (91). 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 (19, 20, 91). Based on these data, we hypothesized that excess weight could cover the increased energy requirement during chronic inflammation (84). 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.

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. Sheila Serra et al. showed that discharge patients with mild AP within 48 hours is safe if the CRP level is below 15 mg/dl, the blood urea nitrogen change in 24 h interval is below 5mg/dl and they tolerate oral intake (51). An Australian study examined the possible risk factors which can lead to justified longer LOH than 2 days. Higher body temperature (>38 °C), not tolerating oral diet by day 2, high pain score (VAS>5), and high white blood cell level (>18 G/L) were identified as risk factors. However, 87% of the admitted patients with mild AP could have been discharged at day 2 and transferred to outpatient clinic (92). All these findings raise the question whether the vast majority of the patients do not require several days of hospitalization but an intensive outpatient follow-up. CRP value as a prediction marker has never investigated in AP, literature data availability is restricted to gastrointestinal surgery or cardiology (56-58). In our analysis we proved that CRP level is not suitable for readmission prediction, 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.

7. Implementation for practice

Our case report confirmed the crucial importance of following guidelines. We brought an example from the field of pancreatitis. Pediatricians should not be afraid of following these recommendations irrespective of whether some of the evidence in the guideline came from experience with adults. Implementation of evidence-based discharge protocols will result in shorter LOH and thus, lower costs and also lower risk of hospital-acquired infections When investigating the HPSG discharge protocol it was proved to be usable immediately in practice and resulted in the shortest LOH among the investigated cohorts. Since supposedly, there are further protocols which worth being implemented, new protocols are warranted to investigate.

8. Implementation 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. Since in the CF population the long-term consequences of possible health risk factors have not been investigated thoroughly, studies with long-term follow-up are required to assess 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.

9. Implementation for policy makers

Implementing scientific data in the daily practice have high importance (47, 48). 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. Our case report raises the question of whether specific diseases, such as pediatric pancreatitis should be treated in a pancreatic center. Based on our findings analyzing patients with CF we advise clinicians to reconsider increasing the currently recommended target BMI (22 kg/m2 for women and 23 kg/m2 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. Moreover, careful evaluation of body composition (FFM and FM) should be incorporated into everyday clinical practice.

10. Summary of the novel findings

”In-hospital patient education markedly reduces alcohol consumption after alcohol-induced acute pancreatitis” cohort analysis

- Incorporating psychological interventions, such as BI in the regular in- and outpatient care could promote abstinence and prevent recurrent episodes.

- Communication methods need to be extended among practitioners, especially in the field of gastroenterology and general practice.

- 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.

- 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.

“Revisiting the evidence-based management of pediatric pancreatitis” letter to the editor

- Paediatricians should not be afraid of following the clinical recommendations irrespective of whether some of the evidence in the guideline came from experience with adults.

- Our case report raises the question of whether specific diseases, such as pediatric pancreatitis should be treated in a pancreatic center.

“Discharge protocol in acute pancreatitis: an international survey and cohort analysis”

-

- Only a small portion of the centers apply a protocol when discharging a patient with AP

- Implementation of evidence-based discharge protocols will result in shorter LOH -HPSG discharge protocol resulted in the shortest LOH among the investigated cohorts.

- Discharge decision based on a protocol will probably result in a higher median discharge value compared to centers with no discharge protocol.

- Discharge CRP value is not a reliable marker for predicting hospital readmission

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

- Higher-than-normal BMI is associated with favorable clinical outcomes in patients with CF, including respiratory functions and exocrine and endocrine pancreatic function.

- Patients with CF we advise clinicians to reconsider increasing the currently recommended target BMI (22 kg/m2 for women and 23 kg/m2 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.

- Moreover, careful evaluation of body composition (FFM and FM) should be incorporated into everyday clinical practice.

11. Future perspectives

As part of my Ph.D. program, I completed the Translational Medicine Ph.D. training at both the University of Pécs and Semmelweis University. From the second year of the training I was not only a student in the program, but I also served as a Science Methodology Supervisor for multiple Ph.D. students. Through this role, I provided methodology guide in numerous Ph.D. projects, mainly in the field of pediatrics. In addition, I participated in Pathophysiology training for one year at the Institute of Translational Medicine, which further enhanced my educational skills., Furthermore, during 1 and a half year I started gaining valuable insights into acute pancreatitis care. I enrolled patients in prospective registries and randomized clinical trials. In the near future, I plan to complete my clinical work and research with experience and knowledge in basic research, I have already started

the lab work and learn the basic methodologies. Given that genetic risk factors play an important role in the early onset of diseases in pediatrics, I would like to gain additional knowledge in the field of genetics. Scientific and technological developments are likely to move in the direction of gene therapy, so I will most likely be able to apply the knowledge I acquire to patient care in the future.

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In-Hospital Patient Education Markedly Reduces Alcohol Consumption after Alcohol-Induced Acute Pancreatitis

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Abstract: Although excessive alcohol consumption is by far the most frequent cause of recurrent acute pancreatitis (AP) cases, specific therapy is still not well established to prevent recurrence. Generally, psychological therapy (e.g., brief intervention (BI)) is the cornerstone of cessation programs; however, it is not yet widely used in everyday practice. We conducted a post-hoc analysis of a prospectively collected database. Patients suffering from alcohol-induced AP between 2016 and 2021 received 30 min BI by a physician. Patient-reported alcohol consumption, serum gamma-glutamyl-transferase (GGT) level, and mean corpuscular volume (MCV) of red blood cells were collected on admission and at the 1-month follow-up visit to monitor patients' drinking habits. Ninety-nine patients with alcohol-induced AP were enrolled in the study (mean age: 50 ± 11, 89% male). A significant decrease was detected both in mean GGT value (294 ± 251 U/L vs. 103 ± 113 U/L, $p < 0.001$) and in MCV level (93.7 ± 5.3 U/L vs. 92.1 ± 5.1 U/L, $p < 0.001$) in patients with elevated on-admission GGT levels. Notably, 79% of the patients (78/99) reported alcohol abstinence at the 1-month control visit. Brief intervention is an effective tool to reduce alcohol consumption and to prevent recurrent AP. Longitudinal randomized clinical studies are needed to identify the adequate structure and frequency of BIs in alcohol-induced AP.

Keywords: brief intervention; acute pancreatitis; recurrence; alcohol; gamma-glutamyl transferase

1. Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal-system-related reasons for hospital admission affecting 13–80/100,000 people worldwide, with the primary causes of gallstone and excessive alcohol consumption [1–3]. It is very important to note

that the disease can recur in 20–30% of cases, which can lead to further organ damage even in end-stage diseases such as chronic pancreatitis or pancreatic cancer [4,5]. Therefore, specific therapy for pancreatitis of different etiologies is of utmost importance. A significant proportion of etiologies have specific therapies to avoid recurrence, such as cholecystectomy in biliary etiology or fibrate or statin therapy in hyperlipidemic AP and steroid therapy in the case of autoimmune AP [6–8]. Unfortunately, alcohol-induced pancreatitis stands out in this field, and alcohol-induced AP is by far the most common form of RAP [9,10]; therefore, research on specific therapies for decreasing the number of recurrent alcohol-induced AP is of crucial importance [11,12].

Alcohol misuse is a wide spectrum ranging from binge drinking to alcohol use disorder (AUD), which is determined based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). Heavy drinking (14 or 7 drinks per week for men and women, respectively) and consequent recurrent inflammation can lead to permanent damage to the pancreatic tissue and facilitate the development of chronic pancreatitis [13,14]. Furthermore, excessive alcohol intake itself can decrease life expectancy by 24–28 years compared to the general population, as shown in Nordic countries [15]. Results of Razvodovsky et al. suggested that 63% of all male pancreatitis deaths in Russia could be attributed to alcohol consumption [16]. Despite the fact that heavy drinking and alcohol use disorder (AUD) are continuously spreading worldwide, leading to increased health, economic, and social burdens, there is a lack of intention to encourage patients either to participate in cessation programs or to keep long-term abstinence [17].

Since excessive alcohol consumption is a global emerging healthcare issue, there are several therapeutic options available for the initiation of cessation of alcohol, including psychosocial and pharmacological interventions. Alcohol misuse definitely must be highlighted since alcohol is responsible for 1 out of 7 male and 1 out of 13 female deaths in the age range of 15–64 years in the European Union [18]. Generally, the psychological approach is the cornerstone of cessation programs often combined with pharmacological treatment to achieve the most favorable results [19]. Following motivation assessment, brief intervention is generally the first step provided to patients. Brief interventions (BIs), a type of psychological intervention that ranges from 5 to 30 min, aim to highlight the fact of risky alcohol consumption and its negative effects and emphasize patients' responsibility to quit [20]. One of the commonly used tools in BI is the FRAMES model, which systematically summarizes the main six elements (Feedback, Responsibility, Advice, Menu for change, Empathy, and enhancing Self-efficacy). Brief interventions have already been proven beneficial in clinical practice by several studies [21–23]. A meta-analysis of 52 trials by Platt et al. showed that BIs significantly reduced the amount of alcohol intake; later, this finding was confirmed in a study by the Cochrane Collaboration [22,23]. A randomized clinical trial by Nordback et al. published in 2009 found that repeated BIs can lower the recurrence rate of alcohol-induced AP [21].

To confirm the effectiveness of the applied interventions, in addition to self-reports, objective laboratory parameters are necessary to be followed. Gamma-glutamyl-transferase (GGT) and mean cellular volume (MCV) are known to be traditional and still the most effective and widely available markers for monitoring patients' drinking habits [24]. Although MCV has low sensitivity (40%), it can be a useful marker for screening for alcohol consumption, especially when used in combination with GGT [25].

With this study, we confirm that in-hospital BI reduces alcohol consumption after an alcohol-induced AP episode.

2. Materials and Methods

2.1. Setting and Study Design

This is 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. Patients were enrolled between 2016 and 2021. The list of centers can be seen in Table S1.

2.2. Patients

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

2.2.1. 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 morphological changes [26]. 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 with clear evidence of heavy drinking in their medical history and no other etiology identified were also included in this patient population.

2.2.2. Exclusion Criteria

We excluded patients with alcoholic and biliary mixed etiology 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.

2.3. 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, emphasizing the patients' responsibility for their health [27]. After the assessment of the root causes of alcohol consumption, e.g., anxiety, bad thoughts, and/or boredom, the communication strategy was adapted accordingly. The interventions took 20–30 min. Additionally, leaflets were available to provide information in relation to excessive alcohol consumption, its impact on health, and options for professional help.

2.4. Investigated Parameters

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

2.5. Outcome Parameters

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

2.6. Analysis

2.6.1. Subgroups

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.

2.6.2. Statistical Analysis

Statistical analyses were performed using R 4.1 software (R Core Team; 2020.) For descriptive statistics, mean, standard deviation (SD), median, and IQR values were calculated for continuous variables, and the Wilcoxon–Mann–Whitney U test or the Kruskal–Wallis

rank sum test were conducted, as applicable. For categorical variables, the Chi-square test and Fisher's 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 the two variables. The level of significance was considered $p \leq 0.05$.

2.7. Ethical Approval

The study was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (17787–8/2020/EÜIG) and conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all subjects involved in the study.

3. Results

3.1. 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. Details are shown in Table 1. Information on the quality of data is provided in Table S2. The investigated cohort represented the total cohort of patients with alcohol-induced AP. Representativity analysis can be seen in Figure S1.

Table 1. Summary of patient characteristics and laboratory values.

	Unit	Overall	Elevated Admission GGT	Non-Elevated Admission GGT
Patients	*n*	99	79	20
Epidemiology				
Gender				
Male	*n* (%)	88 (89)	68 (86)	20 (100)
Female	*n* (%)	11 (11)	11 (14)	0
Age (year)	Mean ± SD	50.05 ± 11.37	48.84 ± 11.21	54.85 ± 10.96
	Median (IQR)	50 (44–57)	50 (41–56)	54 (49–59)
Outcomes				
Length of hospitalization (days)	Mean ± SD	9.94 ± 10.53	9.56 ± 9.65	11.45 ± 13.66
	Median (IQR)	6 (5–9)	6 (5–9)	7 (4–10)
Severity				
Mild	*n* (%)	61 (62)	50 (63)	11 (55)
Moderate	*n* (%)	28 (28)	21 (27)	7 (35)
Severe	*n* (%)	8 (8)	6 (8)	2 (10)
Medical history				
Previous acute pancreatitis	*n* (%)	40 (40)	31 (39)	9 (45)
Chronic pancreatitis	*n* (%)	14 (14)	9 (11)	5 (25)
Hypertriglyceridemia	*n* (%)	17 (17)	15 (20)	2 (10)
Alcohol consumption (frequency)				
None	*n* (%)	6 (6)	5 (6)	1 (5)
Occasionally	*n* (%)	24 (24)	14 (18)	10 (50)
Monthly	*n* (%)	2 (2)	2 (3)	0 (0)
Weekly	*n* (%)	13 (13)	9 (11)	4 (20)

Table 1. *Cont.*

	Unit	Overall	Elevated Admission GGT	Non-Elevated Admission GGT
Daily	*n* (%)	54 (54)	49 (62)	5 (25)
Alcohol consumption (gram/occasion)	Mean ± SD	81.06 ± 65.26	84.43 ± 69.25	67.55 ± 44.88
Laboratory parameters				
Admission GGT (U/L)	Mean ± SD	364.57 ± 471.14	448.58 ± 493.43	32.7 ± 10.34
	Median (IQR)	166 (64–493)	263 (115.5–571)	34 (28.5–39)
Discharge GGT (U/L)	Mean ± SD	255.28 ± 248.88	294 ± 250.75	36.79 ± 23.78
	Median (IQR)	194 (70–399)	229 (108–419)	30.50 (21.25–40.25)
1-month GGT (U/L)	Mean ± SD	88.55 ± 105.80	103.2 ± 113.5	30.65 ± 20.90
	Median (IQR)	91 (87.3–94)	53 (41–108)	28 (18–35.25)
Admission MCV (fL)	Mean ± SD	91.45 ± 6.04	92.51 ± 5.69	97.29 ± 5.70
	Median (IQR)	166 (87.8–94.65)	92 (89–95.90)	35 (28.5–39)
Discharge MCV (fL)	Mean ± SD	92.58 ± 5.79	93.73 ± 5.3	97.74 ± 5.34
	Median (IQR)	92.5 (88.93–96.25)	93.4 (89.95–97.03)	87.85 (84.25–90.95)
1-month MCV (fL)	Mean ± SD	91.02 ± 5.34	92.07 ± 5.10	86.9 ± 4.22
	Median (IQR)	90.9 (87.3–94)	91.5 (88.35–95)	87.6 (83.92–90.33)
1-month GGT change (U/L)	Mean ± SD	152.67 ± 195.94	190 ± 202.16	2.05 ± 17.69
1-month GGT change (U/L; %)	Mean ± SD	40.92 ± 71.13	49.25 ± 74.50	8.04 ± 43.42
1-month MCV change (fL)	Mean ± SD	1.50 ± 2.95	1.79 ± 2.93	0.38 ± 2.83
1-month MCV change (fL; %)	Mean ± SD	1.53 ± 3.16	1.85 ± 3.12	0.31 ± 3.06
Self-reporting				
1-month abstinence	*n* (%)	74 (79)	60 (80)	14 (70)

GGT—gamma-glutamyltransferase; MCV—mean corpuscular volume.

3.2. Acute Pancreatitis Is Often Followed by Another Episode

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

3.3. Frequent Alcohol Drinkers Have 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 g. There was a significant difference in the admission GGT values between the occasional and daily drinker groups (210 ± 268 U/L vs. 267 ± 470 U/L, respectively, $p = 0.01$). More than half of the patients (66%) in the E subgroup reported daily intake, while only 5 patients (25%) reported daily consumption in the 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 ($p = 0.23$). Further details are shown in Table 1.

3.4. Significant Decrease Is 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% ($p < 0.001$) (Table S1, Figures 1 and 2). In Group N, out of 20, only 2 patients' GGT levels increased above the normal level at the 1-month control visit. Comparing patients based on sex, slightly more male patients reported avoiding alcohol entirely (80% vs. 72%); however, the GGT level decrease was slightly more relevant in women (decreased by 70% vs. 65%) The effectiveness of BI on serum GGT levels in patients with elevated or non-elevated admission GGT levels is visualized in Figure 1.

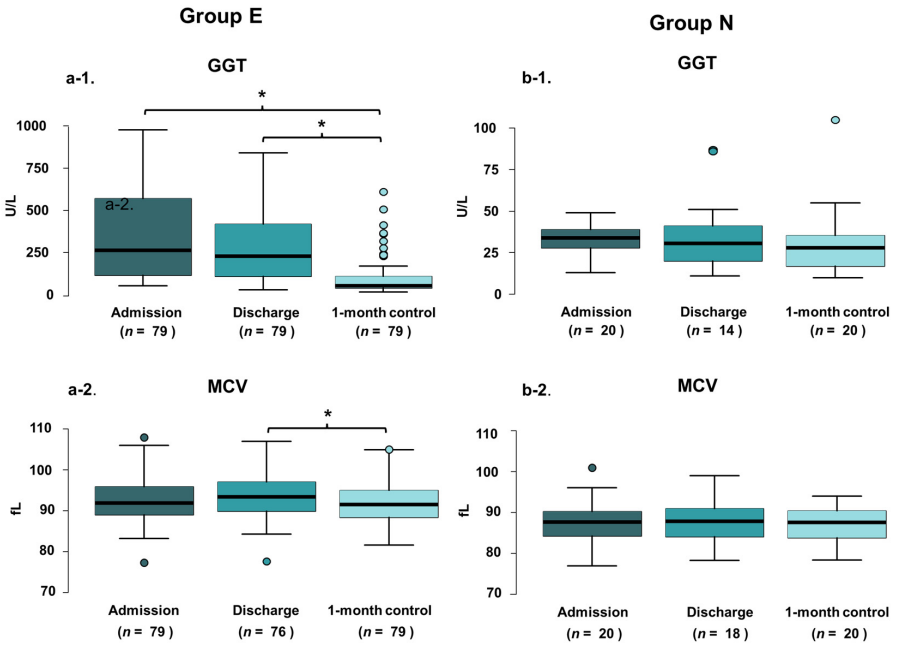
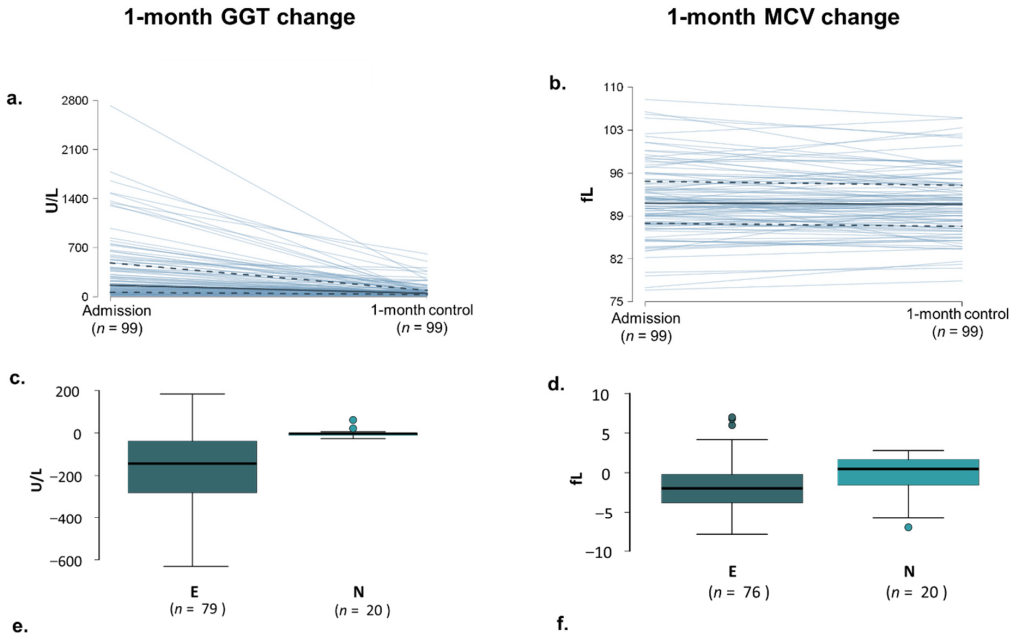


Figure 1. GGT and MCV values of patients in Groups E and N in different time points visualized by boxplots. E-patients with elevated on-admission GGT level (**a**); N-patients with non-elevated on-admission GGT level (**b**); GGT—gamma-glutamyltransferase; MCV—mean corpuscular volume. * $p < 0.001$.



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

Figure 2. Analysis of the change in GGT and MCV levels. Figures show the change in laboratory values between discharge and the 1-month control visit. (**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.

3.5. 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 control visit, which means an average 1.85 ± 3.12% decrease ($p < 0.001$) (Table 1, Figures 1 and 2). No one had macrocytosis (MCV > 95 fL at the control visit).

3.6. 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 Group E and 15/20 (75%) in Subgroup N, kept abstinence from alcohol. Out of the 99 analyzed patients, 3 (all belonging to Group E) were readmitted due to alcohol-induced RAP.

4. Discussion

Excessive alcohol consumption has a negative effect on almost every organ, causing a variety of disorders. It is generally known that alcohol abuse can lead to liver cirrhosis, but it is less common worldwide that alcoholic pancreatitis is one of the most painful and serious consequences of alcohol abuse and can subsequently lead to CP [5].

Studies investigating RAP episodes have shown that the prevalence of RAP ranges from 25 to 45% (the follow-up periods were highly different), and 80% of recurrences happen within 4 years [4,28]. In our cohort, 40% of the admitted patients had a previous AP episode, and 14% had the diagnosis of chronic pancreatitis on admission, which is consistent with a Dutch cross-sectional analysis [29]. Three patients were readmitted due to recurrence, all of whom were diagnosed with CP.

The aim of the preventive approach is to reach abstinence in this population, since the biggest risk factor of having RAP is the continuous alcohol intake in a dose-dependent manner [21]. Based on a recent cohort analysis, not only the entire abstinence but also a lower amount of alcohol consumption is related to better outcomes [12]. Pelli et al. found that none of the patients had RAP during the 24-month period and stayed totally abstinent [30]. Our results showed that among patients who reported abstinence (75%), there was no readmission due to RAP within 1 month, and the majority of these patients (95%) had decreased GGT levels on the control visit compared to the discharge value.

However, abstinence cannot be achieved as simply as it may seem at first. Therefore, particular efforts are needed to be brought into patient care in order to diminish regular alcohol consumption. Although several studies have shown the beneficial effects of BIs on alcoholic patients, their structure and frequency are still under debate [21–23]. Nordback et al. found better results with regular interventions at 6-month intervals in outpatient care compared to single care during hospitalization. A meta-analysis by Platt et al. showed that brief advice provided by nurses brings the most favorable outcomes, and Kaner et al. also confirmed that a longer duration of counseling probably has no relevant additional effect [22,23]. There are several undergoing randomized clinical trials investigating the effectiveness of the psychological approach on alcohol or smoking habits [11].

4.1. Strengths and Limitations

The strengths of our study are the multicentric uniform data collection and high data quality. The limitations are the retrospective nature of the analysis, the short follow-up time, the absence of the control group, and that we also have to consider the possible differences between BI methods since psychological interventions were performed by physicians in different centers.

4.2. Implications for Patients

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

4.3. Implications for Research

Longitudinal studies and RCTs are needed to identify the adequate structure and frequency of BIs to achieve alcohol abstinence and minimize the risk of alcohol-induced RAP [11].

5. Conclusions

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 episode [25,31].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu14102131/s1, Table S1. Participating centers; Table S2. Data quality; Figure S1. Data quality.

Author Contributions: R.N.: conceptualization, data curation, writing the original draft; P.H.: conceptualization, methodological guidance, writing the original draft, supervision; K.O.: conceptualization, methodological guidance, writing the original draft; A.P.: conceptualization, methodological guidance, writing the original draft, supervision; A.V.: statistical analysis, visualization; M.P., Z.V., F.I., E.B., L.G., A.S., B.E., P.J.H., Á.V., J.B., P.S., A.M., K.M. and D.P.: interpretation of data, revising the draft. All authors have (1) contributed to the concept of the study, (2) revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board at University of Pécs and Semmelweis University.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Access to sequencing data is available on request.

Conflicts of Interest: The authors declare no conflict of interest.

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Revisiting the evidence-based management of paediatric pancreatitis

Keywords:
Acute pancreatitis
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Dear Editor,

In the past decade the concept of evidence-based medicine (EBM) has been clearly defined [1]. Implementation of EBM offers standards that potentially provide the best quality of medical care at a reasonable cost avoiding clinical decisions based on local expert opinions [2]. Although paediatric acute pancreatitis (PP) is a relatively rare disease, its incidence has been rising continuously [3,4]. 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. Our 17-year-old female patient was admitted to the paediatric ward of a local county hospital due to her first AP episode (Fig. 1). 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 centre 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 Centre. 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.

Some decades ago, clinical practice generally relied on local expertise, often driven by physiological reasoning [5]. 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 [6]. 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 1). 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 guidelines [7,8]. 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 centre.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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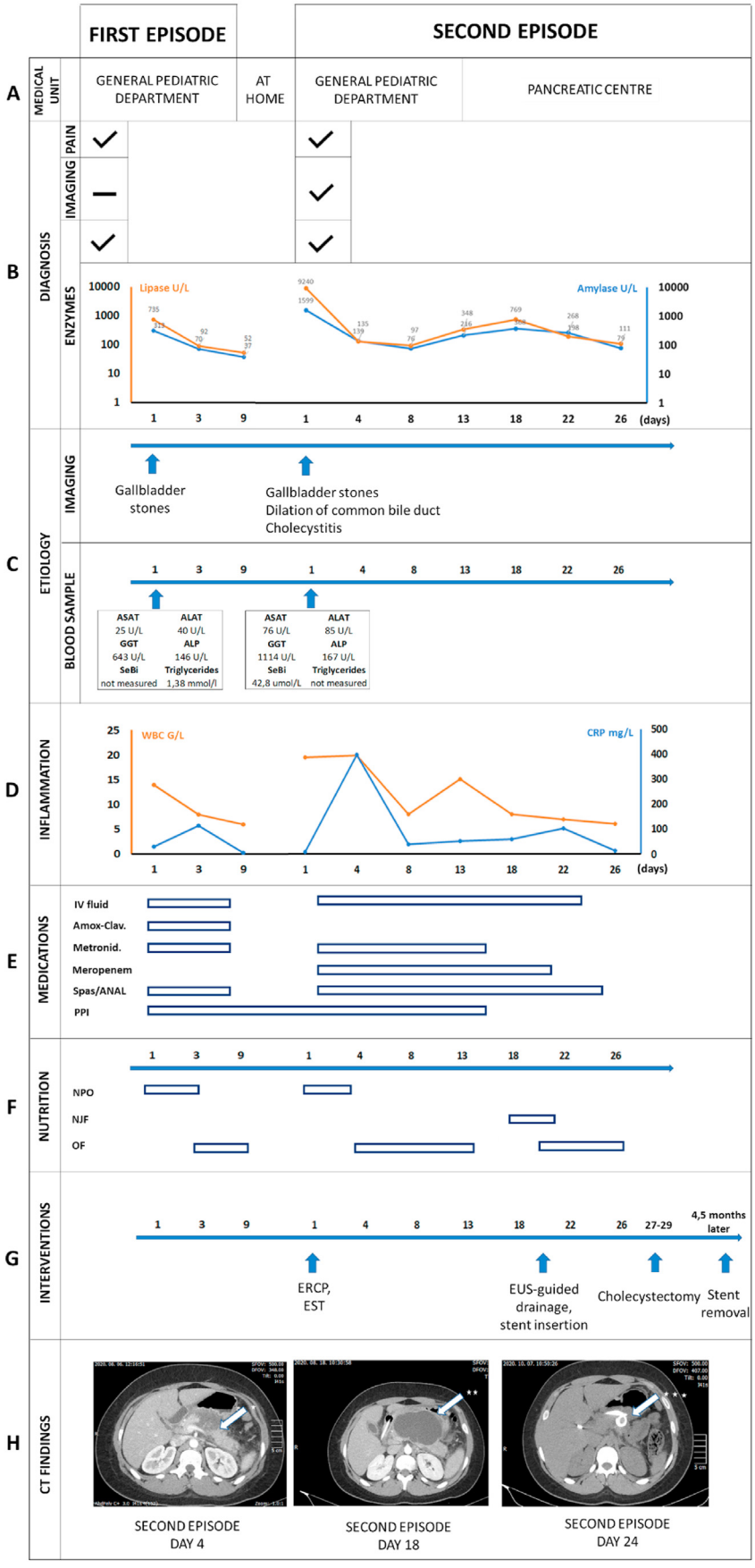
FIRST EPISODE
SECOND EPISODE
A
MEDICAL UNIT
GENERAL PEDIATRIC DEPARTMENT
AT HOME
GENERAL PEDIATRIC DEPARTMENT
PANCREATIC CENTRE
B
DIAGNOSIS
PAIN
IMAGING
ENZYMES
Lipase U/L
Amylase U/L
(days)
C
ETIOLOGY
IMAGING
Gallbladder stones
Gallbladder stones
Dilation of common bile duct
Cholecystitis
BLOOD SAMPLE
ASAT 25 U/L
ALAT 40 U/L
GGT 643 U/L
ALP 146 U/L
SeBi not measured
Triglycerides 1,38 mmol/l
ASAT 76 U/L
ALAT 85 U/L
GGT 1114 U/L
ALP 167 U/L
SeBi 42,8 umol/L
Triglycerides not measured
D
INFLAMMATION
WBC G/L
CRP mg/L
(days)
E
MEDICATIONS
IV fluid
Amox-Clav.
Metronid.
Meropenem
Spas/ANAL
PPI
F
NUTRITION
NPO
NJF
OF
G
INTERVENTIONS
4,5 months later
ERCP, EST
EUS-guided drainage, stent insertion
Cholecystectomy
Stent removal
H
CT FINDINGS
SECOND EPISODE DAY 4
SECOND EPISODE DAY 18
SECOND EPISODE DAY 24

Fig. 1. Summary of the medical care on a timeline.
A. Location of patient care.
B. Determination of diagnosis based on current criteria. According to the EPC/HPSG guideline, a diagnosis of acute pancreatitis (AP) is achieved by meeting at least two of the following three criteria [1]: abdominal pain [2]; serum lipase or serum amylase level at least three times greater than the upper limit of normal [3]; characteristic findings of AP with imaging methods.
C. Aetiology workup. Elevated biliary, cholestatic enzymes and ultrasound findings support a biliary aetiology. ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; GGT: gamma glutamyl transferase; ALP: alkaline phosphatase. D. Inflammatory values on timeline. CRP: C-reactive protein and WBC: white blood cells. E. Medications administered in each department. Amox/clav.: amoxicillin/clavulanic acid; Metronid.: metronidazole, Spas.: spasmolytics; ANAL: analgesics; PPI: proton pump inhibitors.
F. Nutrition management. NPO: nil per os diet; NJF: nasojejunal feeding; OF: oral feeding.
G. Interventions in chronological order. ERCP: endoscopic retrograde cholangiopancreatography, EST: endoscopic sphincterotomy, EUS: endoscopic ultrasound.H. Axial sections of contrast-enhanced computed tomography of the patient's abdomen. The left arrow shows an extended inhomogeneous area in the pancreas, indicating necrosis with fluid collection (*). The middle arrow shows a large pseudocyst in the region of the pancreas body and tail (**). The right arrow indicates the double-pigtail stent inserted into the pseudocyst (***).

Table 1
Adherence to the EPC/HPSG evidence-based guidelines for the management of paediatric pancreatitis. NA* - not applicable.

	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
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 centres. (Adult evidence level: GRADE 1/C, full agreement).

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

A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE The prevalence of overweight (body mass index [BMI] = 25-29.9 [calculated as weight in kilograms divided by height in meters squared]) and obesity (BMI ≥30) is increasing among patients with cystic fibrosis (CF). However, it is unclear whether there is a benefit associated with increasing weight compared with the reference range (ie, normal) in CF.

OBJECTIVE To evaluate the association of altered BMI or body composition and clinical outcomes in patients with CF.

DATA SOURCES For this systematic review and meta-analysis, the literature search was conducted November 2, 2020, of 3 databases: MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials.

STUDY SELECTION Patients older than 2 years diagnosed with CF with altered body composition or BMI were compared with patients having the measured parameters within the reference ranges. Records were selected by title, abstract, and full text; disagreements were resolved by consensus. Cohort studies and conference abstracts were eligible; articles with no original data and case reports were excluded.

DATA EXTRACTION AND SYNTHESIS Two authors independently extracted data, which were validated by a third author. Studies containing insufficient poolable numerical data were included in the qualitative analysis. A random-effects model was applied in all analyses.

MAIN OUTCOMES AND MEASURES Pulmonary function, exocrine pancreatic insufficiency (PI), and CF-related diabetes (CFRD) were investigated as primary outcomes. Odds ratios (ORs) or weighted mean differences (WMDs) with 95% CIs were calculated. The hypothesis was formulated before data collection.

RESULTS Of 10 524 records identified, 61 met the selection criteria and were included in the qualitative analysis. Of these, 17 studies were included in the quantitative synthesis. Altogether, 9114 patients were included in the systematic review and meta-analysis. Overweight (WMD, −8.36%; 95% CI, −12.74% to −3.97%) and obesity (WMD, −12.06%; 95% CI, −23.91% to −0.22%) were associated with higher forced expiratory volume in the first second of expiration compared with normal weight. The odds for CFRD and PI were more likely in patients of normal weight (OR, 1.49; 95% CI, 1.10 to 2.00) than in those who were overweight (OR, 4.40; 95% CI, 3.00 to 6.45). High heterogeneity was shown in the analysis of pulmonary function (I^2 = 46.7%-85.9%).

(continued)

Key Points

Question Is higher-than-normal body mass index (BMI) associated with better clinical outcomes in patients with cystic fibrosis?

Findings In this systematic review and meta-analysis of studies including 9114 patients with cystic fibrosis, BMI indicating overweight and obesity were associated with better pulmonary function and lower chance for exocrine pancreatic insufficiency and cystic fibrosis–related diabetes compared with normal BMI.

Meaning The findings of this study suggest that guidelines should be updated to recommend a higher target BMI in patients with cystic fibrosis.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE The findings of this systematic review and meta-analysis suggest that the currently recommended target BMI in patients with CF should be reconsidered. Studies with long-term follow-up are necessary to assess the possible adverse effects of higher BMI or higher fat mass in patients with CF.

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Introduction

Cystic fibrosis (CF) is a common, often lethal inherited disorder caused by recessive genetic variants in the CF transmembrane conductance regulator (*CFTR*) gene affecting 1 in 3300 neonates of White race.[1] The variants result in diminished function of chloride, sodium, and bicarbonate ion transport, leading to thick mucus production that causes functional derangement of multiple organs (eg, lungs, gastrointestinal system, and reproductive system).[2] Consequential frequent airway infections, chronic inflammation, exocrine pancreatic insufficiency (PI), and complications, such as CF-related diabetes (CFRD) and CF-related liver disease, result in general unease and poor quality of life.[3]

Among patients with CF, malnutrition is commonly seen, mainly caused by the combination of the following mechanisms: (1) nutrient malabsorption and fecal energy loss due to PI, (2) increased energy expenditure predominantly related to chronic inflammation and breathing efforts,[4-6] and (3) loss of appetite caused by inflammation-related anorexia.[7] Malnourishment may accelerate the progression of the disease; nevertheless, underweight (body mass index [BMI]<15th percentile, with BMI calculated as weight in kilograms divided by height in meters squared) is known to be associated with worse pulmonary function and increased morbidity and mortality in patients with CF.[8]

Monitoring the nutritional status and growth of patients, as well as the prevention and treatment of malnutrition, are demanding components of CF care. Currently, BMI is the generally accepted indicator for monitoring the nutritional status of patients with CF. In children older than 2 years, the target BMI is at least the 50th percentile; in adults, the target BMI is greater than or equal to 22 for women and greater than or equal to 23 for men.[9] However, BMI does not distinguish between the major components of the body, namely, fat mass (FM), fat-free mass (FFM), total body water, bone mineral density, and bone mineral content. There is a growing body of evidence highlighting the importance of nutritional status in the diagnostic and therapeutic management of patients with CF,[10-12] but there is a lack of comprehensive review on patients with a BMI above the target.

The European Society for Clinical Nutrition and Metabolism; the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; and the European Cystic Fibrosis Society adult and pediatric dietary guideline focuses on nutritional failure with no recommendation on the management of individuals who are overweight or obese.[9] However, an analysis of BMI changes found that the prevalence of overweight and obesity in adults with CF is 31.4% and has more than doubled over the past 2 decades in patients with CF.[13] However, long-term adherence to the currently recommended high-fat and high-carbohydrate diet in CF also might have controversial effects on body composition and even on some clinical outcomes. 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.[14] 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.

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-analyses (PRISMA) reporting guideline.[15]

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. Further details regarding the strategy of the literature search and selection can be found in the eMethods in the Supplement.

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. After each step of the selection process, the rate of agreement was determined and documented by calculating the Cohen κ coefficient. Values may indicate slight (0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect agreement (0.81-1.00).[16] References of each included study were checked, and records that were considered to be eligible were added to the pool.

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.[17]

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 analyses 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.). Data collected included sex distribution, age distribution, genotype, patient numbers, and mean or median values of outcomes of interest. Correlation coefficients were also extracted regarding the association of BMI or body composition and clinical outcomes. Further details regarding data

extraction can be found in the eMethods in the Supplement. Most of the eligible studies were cross-sectional. For longitudinal studies, we collected only baseline data. 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.[19] Any disagreement was resolved based on consensus.

Statistical Analysis

A random-effects model was applied in all analyses using the DerSimonian-Laird estimation.[20] 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-analyses are displayed in forest plots. Statistical heterogeneity was analyzed using the I^2 and χ^2 tests to gain probability values; $P < .10$ 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.[21] Sensitivity analyses 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.[22] Statistical analyses 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 $P < .05$.

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. These records and coefficients are included in the eTable in the Supplement. The selection process is shown in **Figure 1**.

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). The major characteristics of the included studies are reported in the **Table**.

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 (WMD, 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%; WMD, −8.36%; 95% CI, −12.74% to −3.97%) or obese (84.63% vs 72.57%; WMD,

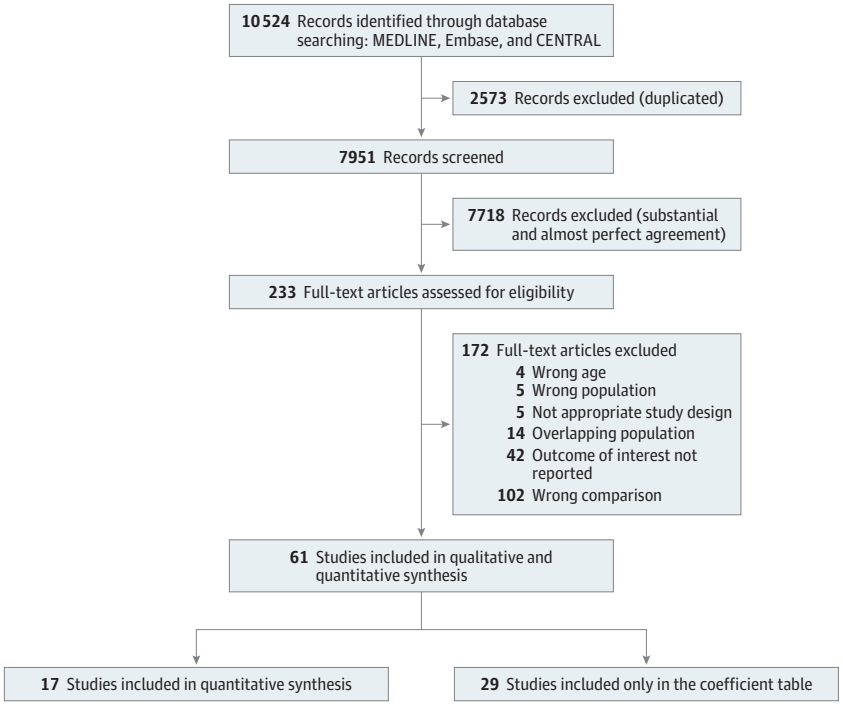
−12.06%; 95% CI, −23.91% to −0.22%) (**Figure 2**). High heterogeneity was shown in the analysis of pulmonary function (I^2 = 46.7%-85.9%). In the comparison of patients who were underweight vs not underweight, we found significantly lower FEV_1% in children, adults, and mixed patient populations who were underweight (overall WMD, −19.12%; 95% CI, −23.53% to −14.71%) (eFigure 1 in the Supplement).

In addition to the 13 records in the quantitative synthesis, 15 studies, including conference abstracts, were added to the qualitative synthesis. The reasons for exclusion of these 15 studies from the quantitative synthesis were either different BMI categorization from the World Health Organization recommendation or insufficient data reporting. Among these 15 studies, 9 studies showed increased FEV_1% values to be associated with higher BMI values in patients with normal BMI or overweight compared with those who were underweight. Two studies did not report significant differences in pulmonary function when comparing different BMI categories.[49,54] 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% CI, 4.58-25.85) (**Figure 3**). 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) (eFigure 2 in the Supplement). The studies of Ramírez et al[51] reported a nonsignificant result and were not included in our quantitative synthesis owing to inadequate data reporting.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses Flowchart



CENTRAL indicates Cochrane Central Register of Controlled Trials.

Table. Characteristics of Included Studies

Source	Characteristic					Setting		
	Patients, No.	Age group	Age, mean (SD), y	BMI	Pancreatic insufficiency, No. (%)	Genotype (DF508)	Growth parameter	Outcomes
Altman et al,[23] 2017 (abstract)	224	Adults	32.4 (10.6)	NA	NA	NA	BMI	CFRD, *P aeruginosa* colonization
Alvarez et al,[24] 2016	32	Mixed	26.1 (8.9)	22.1 (2.9)[a]	31 (96.9)	56.3% Homozygote; 28.1% heterozygote	BMI, percent body fat, FFM	FEV_1%, CFRD, FG
Barni et al,[25] 2017[b]	73	Mixed	25.6 (7.3)	21.0 (3.0)[a]	66 (90)	17.8% Homozygote; 45.2% heterozygote	BMI	FEV_1%, PI, CFRD, *P aeruginosa* colonization
Bodnar et al,[26] 2014[b]	59	Mixed	14.0 (4.8)	20.4 (2.4)[a]	NA	50.8% Homozygote	BMI, BMI percentile	FEV_1%, *P aeruginosa* colonization
Bonhoure et al,[27] 2020[b]	290	Adults	25.5 (7.9)	21.7 (2.9)[a]	232 (79.9)	49.0% Homozygote; 41.3% heterozygote	BMI	FEV1%, PI, CFRD, FG, HbA_{1c}%, TC, TG, HDL-C, LDL-C, FI
Bouma et al,[28] 2020	201	Mixed	13.3 (4.6)	19.9 (3.7)[a]	NA	51.2% Homozygote; 36.3% heterozygote	BMI, BMI *z* score	FEV_1%
Brennan et al,[29] 2010 (abstract)	348	Adults	No data	No data	NA	NA	BMI	FEV_1%
Cano Megias et al,[30] 2015[b]	61	Mixed	26.8 (9.5)	20.3 (3.3)[a]	NA	24.6% Homozygote; 78.6% heterozygote	BMI, *z* score	FEV_1%
Charatsi et al,[31] 2016	71	Mixed	12 (2.7)	18.2 (3.4)[c]	36 (90)	49.3% Homozygote; 39.4% Heterozygote	FFM *z* score	FEV_1%, PI, *P aeruginosa* colonization
Da Silva Garrote et al,[32] 2016 (abstract)	34	Children	10.2 (5.3)	No data	NA	NA	BMI percentile	*P aeruginosa* colonization
Dray et al,[33] 2005[b]	163	Adults	28.8 (8.4)	19.1 (2.8)[a]	137 (84)	42.3% Homozygote; 38.6% heterozygote	BMI	PI, CFRD, *P aeruginosa* colonization
Dudina et al,[34] 2017 (abstract)	435	Adults	No data	No data	NA	NA	BMI	FEV_1%
Engelen et al,[35] 2012[b]	77	Mixed	14.8 (2.9)	40.77 (26.4)[d]	75 (97)	63.6% Homozygote; 25.9% heterozygote	BMI, BMI percentile, FFM, *z* score	FEV_1%
Gozdzik et al,[36] 2008[b]	39	Adults	23.9 (3.7)	19.5 (2.9)[a]	NA	NA	BMI	FEV_1%
Hanna and Weiner,[37] 2015[b]	226	Children	10.6 (4.9)	18.5 (4.2)[a]	181 (80)	NA	BMI percentile	FEV_1%, PI
Harindhanavudhi et al,[38] 2020[b]	484	Adults	35.2 (11.6)	23.9 (4.4)[a]	417 (85)	46.9% Homozygote	BMI	FEV_1%, PI, CFRD, HbA_{1c}%, HDL-C, LDL-C
Hollander et al,[39] 2018 (abstract)	224	Adults	No data	No data	NA	NA	BMI	FEV_1%
Ionescu et al,[40] 2003	56	Adults	23 (5.2)	20.9 (1.6)[a]	29 (100)	NA	FFM	FEV_1%
González Jiménez et al,[41] 2012[b]	109	Children	12.3 (8.8)	21.6 (3.9)[a]	371 (82)	41.3% Homozygote; 46.7% heterozygote	BMI percentile	FG, HbA_{1c}%, TC, TG, FI
González Jiménez et al,[42] 2017[b]	451	Mixed	12.7 (3.2)	−0.3 (0.8)[e]	93 (85)	33.0% Homozygote; 49.8% heterozygote	BMI, *z* score	FEV_1%
Kines et al,[43] 2012 (abstract)	114	Mixed	No data	No data	NA	NA	BMI	FEV_1%
Kotsifas et al,[44] 2016[b] (abstract)	44	Adults	No data	No data	NA	NA	BMI	FEV_1%
Maksimycheva et al,[45] 2018 (abstract)	51	Children	No data	No data	NA	NA	BMI	FEV_1%, *P aeruginosa* colonization
Ochota et al,[46] 2019 (abstract)	226	Adults	No data	23.5 (6.0)[a]	NA	NA	BMI	FEV_1%
Panagopoulou et al,[47] 2008[b]	43	Mixed	20.1 (8.5)	19.4 (2.6)[a]	No data	NA	BMI, FFM	FI
Panagopoulou et al,[48] 2014	68	Mixed	19.81(9.0)	19.8 (2.7)[a]	56 (82)	20.6% Homozygote; 48.5% heterozygote	BMI, BMI percentile	FEV_1%, PI, CFRD, FG, TC, TG, *P aeruginosa* colonization
Papalexopoulou et al,[49] 2018	29	Mixed	15 (1.8)	−0.1 (−2.7-1.2)[e]	28 (96.5)	58.6% Homozygote; 31.0% heterozygote	BMI *z* scores, BMI percentile, FFM index *z* score	FEV_1%
Proud et al,[50] 2012 (abstract)	117	Adults	28 (9)	No data	NA	NA	BMI, FFM index	FEV_1%, PI
Ramírez et al,[51] 2015[b]	173	Mixed	11.43 (2.3)	No data	145 (83.77)	50.3% Homozygote; 36.9% heterozygote	BMI percentile	FEV_1%, PI, *P aeruginosa* colonization
Stephenson et al,[52] 2013[b]	651	Adults	33.8 (11.4)	22.3 (4.1)[a]	488 (75)	39.3% Homozygote; 38.2% heterozygote	BMI	FEV_1%, PI, CFRD, TC, TG, *P aeruginosa* colonization

(continued)

Table. Characteristics of Included Studies (continued)

Source	Characteristic					Setting		
	Patients, No.	Age group	Age, mean (SD), y	BMI	Pancreatic insufficiency, No. (%)	Genotype (DF508)	Growth parameter	Outcomes
Umławska et al,[53] 2014[b]	89	Children	12.3 (3.5)	-0.8 (0.8)[e]	80 (90)	51.7% Homozygote; 33.7% heterozygote	BMI percentile	FEV_1%, PI
Ziegler et al,[54] 2008	39	Mixed	23.7 (6.4)	20.3 (2.2)[a]	NA	NA	BMI, BMI percentile	FEV_1%

Abbreviations: BMI, body mass index; CFRD, cystic fibrosis–related diabetes; FEV_1%, forced expiratory volume in the first second of expiration; FFM, fat-free mass; FG, fasting glucose; FI, fasting insulin; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not assessed; *P aeruginosa*, *Pseudomonas aeruginosa*; PI, exocrine pancreatic insufficiency; TC, total cholesterol; TG, triglycerides.

[a] Value expressed as mean (SD).

[b] Included in the quantitative synthesis.

[c] Value expressed as median (IQR).

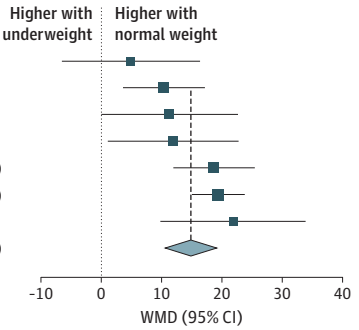
[d] Value expressed as mean (SD) percentile.

[e] Value expressed as *z* score.

Figure 2. Pulmonary Function in Different Body Mass Index (BMI) Categories of Patients With Cystic Fibrosis

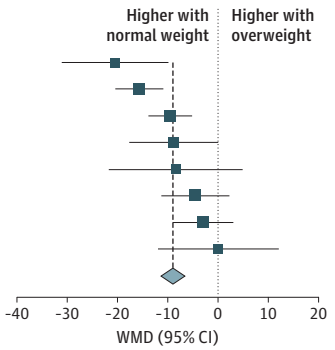
A Normal weight and underweight

Source	Normal weight No., mean (SD)	Underweight No., mean (SD)	FEV1% WMD (95% CI)	Weight, %
Cano Megias et al,[30] 2015	37.0, 71.2 (20.7)	21.0, 66.4 (21.4)	4.76 (-6.57 to 16.09)	9.78
González Jiménez et al,[42] 2017	365.0, 87.2 (20.0)	54.0, 77.0 (24.0)	10.18 (3.46 to 16.91)	17.99
Harindhanavudhi et al,[38] 2020	303.0, 69.8 (23.5)	25.0, 58.7 (27.8)	11.10 (-0.11 to 22.31)	9.92
Panagopoulou et al,[48] 2014	44.0, 69.6 (20.7)	15.0, 57.9 (17.4)	11.70 (0.98 to 22.42)	10.56
Bonhoure et al,[27] 2020	235.0, 74.6 (21.4)	35.0, 56.2 (18.4)	18.40 (11.72 to 25.08)	18.09
Stephenson et al,[52] 2013	397.0, 53.4 (25.2)	109.0, 34.3 (18.9)	19.10 (14.77 to 23.43)	24.56
Hanna and Weiner et al,[37] 2015	157.0, 94.5 (19.5)	16.0, 73.0 (23.5)	21.51 (9.60 to 33.42)	9.10
Overall: I^2 = 46.7%, P = .08	1538.0	275.0	14.61 (10.39 to 18.83)	100



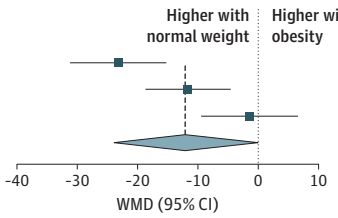
B Normal weight and overweight

Source	Normal weight No., mean (SD)	Overweight No., mean (SD)	FEV1% WMD (95% CI)	Weight, %
Panagopoulou et al,[48] 2014	44.0, 69.6 (20.7)	9.0, 89.7 (13.7)	-20.10 (-30.94 to -9.26)	9.33
Stephenson et al,[52] 2013	397.0, 53.4 (25.2)	145.0, 68.6 (25.8)	-15.17 (-20.05 to -10.30)	17.13
Harindhanavudhi et al,[38] 2020	303.0, 69.8 (23.5)	156.0, 78.7 (22.5)	-8.90 (-13.31 to -4.48)	17.80
Bonhoure et al,[27] 2020	235.0, 74.6 (21.4)	20.0, 82.8 (19.6)	-8.20 (-17.22 to 0.82)	11.33
Kotsifas et al,[44] 2016	26.0, 76.5 (28.0)	18.0, 84.3 (17.9)	-7.80 (-21.37 to 5.77)	7.05
González Jiménez et al,[42] 2017	365.0, 87.2 (20.0)	32.0, 91.0 (19.0)	-3.82 (-10.71 to 3.08)	14.13
Hanna and Weiner et al,[37] 2015	157.0, 94.5 (19.5)	53.0, 96.8 (20.0)	-2.32 (-8.51 to 3.88)	15.15
Cano Megias et al,[30] 2015	37.0, 71.2 (20.7)	3.0, 70.3 (9.07)	0.86 (-11.37 to 13.09)	8.07
Overall: I^2 = 63.9%, P = .01	1564.0	436.0	-8.36 (-12.74 to -3.97)	100



C Normal weight and obesity

Source	Normal weight No., mean (SD)	Obese No., mean (SD)	FEV1% WMD (95% CI)	Weight, %
Stephenson et al,[52] 2013	397.0, 53.4 (25.2)	25.0, 76.6 (19.4)	-23.20 (-31.20 to -15.20)	32.97
Harindhanavudhi et al,[38] 2020	303.0, 69.8 (23.5)	32.0, 81.4 (18.9)	-11.60 (-18.66 to -4.54)	34.10
Hanna and Weiner et al,[37] 2015	157.0, 94.5 (19.5)	18.0, 95.9 (16.1)	-1.39 (-9.43 to 6.65)	32.92
Overall: I^2 = 85.9%, P = .001	857	7205	-12.06 (-23.91 to -0.22)	100



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.

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 4**). 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) (eFigure 3 in the Supplement). The studies of Altman et al[23] and Alvarez and Stecenko[24] were not included in our quantitative synthesis owing to inadequate comparison categories; however, none of the studies reported significant differences between BMI groups regarding the CFRD outcome.[24]

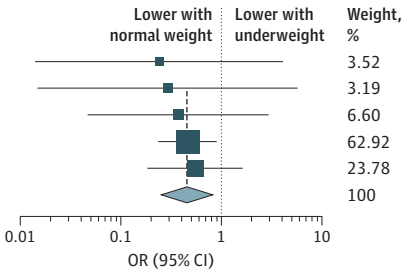
Secondary Outcomes

Glucose metabolic status indicators, such as fasting glucose, fasting insulin, and HbA_{1c} levels did not significantly differ between BMI categories (eFigures 4-6 in the Supplement). 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; WMD, −0.02 0.41 mg/dL; 95% CI, −0.03 to 0.01) and triglyceride levels (0.03 vs 0.02 mg/dL WMD, −0.005; 95% CI, −0.009 to 0.0005 [to convert to millimoles per liter, multiply by 0.0113]) (eFigure 7 and eFigure 8 in the Supplement). In the comparison of patients with normal weight vs underweight,

Figure 3. Odds of Exocrine Pancreatic Insufficiency in Different Body Mass Index Categories

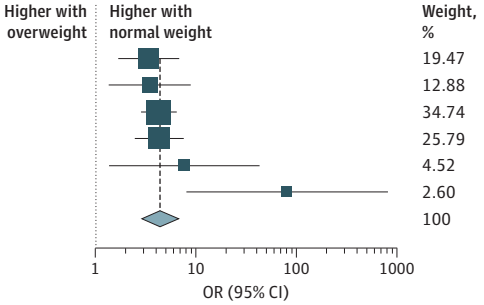
A Normal weight and underweight

Source	Normal weight events	Underweight events	OR (95% CI)
Harindhanavudhi et al,[38] 2020	240/264	20/20	0.24 (0.01-4.08)
Panagopoulou et al,[48] 2013	40/44	15/15	0.29 (0.01-5.71)
Hanna and Weiner et al,[37] 2015	133/157	15/16	0.37 (0.05-2.93)
Stephenson et al,[52] 2013	319/397	98/109	0.46 (0.23-0.90)
Bonhoure et al,[27] 2020	190/235	31/35	0.54 (0.18-1.62)
Overall: I^2 = 0%, P = .98	922/1097	179/195	0.45 (0.27-0.77)



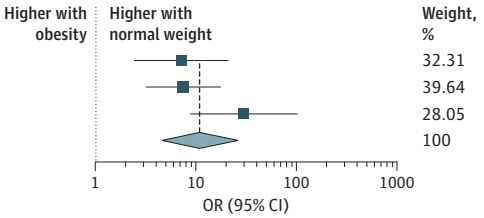
B Normal weight and overweight

Source	Normal weight events	Overweight events	OR (95% CI)
Hanna and Weiner et al,[37] 2015	133/157	33/53	3.36 (1.66-6.80)
Bonhoure et al,[27] 2020	190/235	11/20	3.45 (1.35-8.83)
Stephenson et al,[52] 2013	319/397	71/145	4.26 (2.83-6.42)
Harindhanavudhi et al,[38] 2020	240/264	93/133	4.30 (2.46-7.53)
Kotsifas et al,[44] 2016	24/26	11/18	7.64 (1.36-42.90)
Panagopoulou et al,[48] 2014	40/44	1/9	80.00 (7.87-813.29)
Overall: I^2 = 30.9%, P = .20	946/1123	220/378	4.40 (3.00-6.45)



C Normal weight and obesity

Source	Normal weight events	Obese events	FEV1% WMD (95% CI)
Hanna and Weiner et al,[37] 2015	133/157	7/16	7.13 (2.42-20.96)
Harindhanavudhi et al,[38] 2020	240/264	16/28	7.50 (3.18-17.69)
Stephenson et al,[52] 2013	319/397	3/25	29.99 (8.75-102.75)
Overall: I^2 = 51.3%, P = .13	692/818	26/69	10.88 (4.58-25.85)



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.

both cholesterol levels (WMD, 0.008 mg/dL; 95% CI, 0.004 to 0.013) and triglyceride levels (WMD, 0.003 mg/dL; 95% CI, 0.001 to 0.006) were significantly higher in the normal weight group (eFigures 7-8 in the Supplement). Bonhoure et al,[27] Harindhanavudhi et al,[38] and Panagopoulou et al[48] reported high-density and low-density lipoprotein cholesterol values; all of the studies showed significantly higher low-density lipoprotein cholesterol levels and not significantly lower high-density lipoprotein cholesterol levels in patients who were overweight. However, these results could not be included in the quantitative synthesis owing to insufficient data reporting by Harindhanavudhi et al.[38]

Additional Outcomes and Analysis

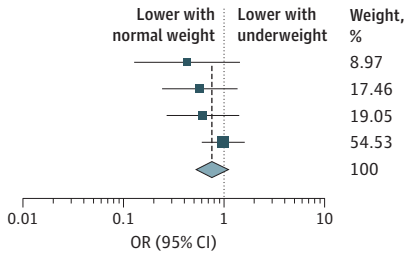
The ratio of patients with *P aeruginosa* colonization at the time of assessment was reported in 11 studies; of these, 6 studies were included in our quantitative synthesis. The results showed that patients who were underweight were significantly more likely to have *P aeruginosa* colonization compared with those who were not underweight (OR, 1.86; 95% CI, 1.34-2.59) (eFigure 9 in the Supplement). Of the studies included only in the qualitative synthesis, Maksimycheva et al[45] and Da Silva Garrote et al[32] found that underweight is associated with higher odds for *P aeruginosa* colonization, whereas 3 studies did not find significant differences between BMI and FFM categories.[23,31,51]

The studies by Stephenson et al,[52] Bonhoure et al,[27] and Harindhanavudhi et al[38] were identified as showing significance regarding PI and CFRD by the leave-1-out sensitivity analysis (eFigures 10-13 in the Supplement). Funnel plots were created, and the Egger test was performed to detect publication bias. There was no small-study effect found in our analyses (eFigure 14 and eFigure 15 in the Supplement).

Figure 4. Odds for Cystic Fibrosis–Related Diabetes in Different Body Mass Index Categories

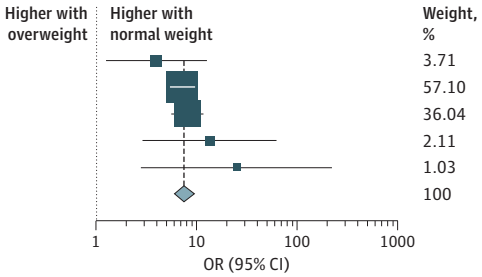
A Normal weight and underweight

Source	Normal weight events	Underweight events	OR (95% CI)
Panagopoulou et al,[48] 2014	12/44	7/15	0.43 (0.13-1.44)
Bonhoure et al,[27] 2020	34/235	8/35	0.57 (0.24-1.36)
Harindhanavudhi et al,[38] 2020	144/300	15/25	0.62 (0.27-1.41)
Stephenson et al,[52] 2013	97/397	27/109	0.98 (0.60-1.61)
Overall: I^2 = 0%, P = .46	287/976	57/184	0.76 (0.53-1.09)



B Normal weight and overweight, including obesity

Source	Normal weight events	Overweight events	OR (95% CI)
Kotsifas et al,[44] 2016	4/26	4/18	0.64 (0.14-2.97)
Harindhanavudhi et al,[38] 2020	144/300	62/156	1.40 (0.95-2.07)
Stephenson et al,[52] 2013	97/397	24/145	1.63 (0.99-2.67)
Bonhoure et al,[27] 2020	34/235	1/20	3.21 (0.42-24.80)
Panagopoulou et al,[48] 2014	12/44	0/9	7.31 (0.40-135.18)
Overall: I^2 = 0%, P = .54	291/1002	91/348	1.49 (1.10-2.00)



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.

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]). Detailed results of risk of bias assessments are shown in eFigures 16 to 24 in the Supplement.

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.[35,40,49,55,56] It has also been reported that patients with CF who are overweight have markedly fewer exacerbations that could contribute to loss of appetite.[38] Moudiou et al[57] described a negative correlation between resting energy expenditure (REE) and BMI *z* score. Resting energy expenditure is the amount of energy that is necessary to maintain basic body functions, such as digestion and breathing, and requires approximately 60% of the total calorie need.[58] 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.[5,6,58] Based on these data, we hypothesized that excess weight could cover the increased energy requirement during chronic inflammation.[56] The favorable effect of weight gain has also been visible in the past few years as modulator therapy has become available as a novel treatment in CF.[59] The continuous spread of modulators that aim to diminish the influence of *CFTR* dysfunction has been shown to have beneficial effect on body composition.[60] In addition to weight gain, the proportion of FFM is increasing, which is associated with the reduction of REE.

Although we intended to include studies that compared patients with CF based not only on BMI but including FFM and FM, there were not enough eligible studies examining FFM and FM for a quantitative synthesis to be performed. All studies included in the qualitative synthesis highlighted the importance of the FFM proportion that leads to better pulmonary function. However, the influence of higher FM on FEV_1% is not obvious. Alvarez et al[61] reported that FEV_1% is inversely associated with FM, whereas Panagopoulou et al[48] described a correlation between body fat percentage and pulmonary function.

Our results regarding the association between higher BMI and the lower odds for PI are consistent with previous research.[27,48,52] In patients with sufficient exocrine pancreatic function, adequate digestion and absorption are more likely to be present and can lead to higher BMI.

We found underweight to be associated with a higher prevalence of CFRD, which is in accordance with general clinical observations. In patients with CF who are underweight, there are several associated risk factors that contribute to the development of CFRD, such as PI or insulinopenia.[62] We assumed that insulin resistance, as the minor component of CFRD, becomes more dominant in individuals who are overweight or obese and may lead to higher odds for diabetes compared with those of normal BMI. However, our results did not confirm this hypothesis, showing significantly lower odds for CFRD in patients with a BMI greater than or equal to 25.

Although our results showed that BMI greater than or equal to 25 does not have a statistically relevant association with glucose homeostasis (fasting glucose, fasting insulin, and HbA_{1c} levels), overweight and obesity are associated with higher total cholesterol and triglyceride levels. However, none of these elevated values exceeded the upper limit of normal.

Based on our results, the higher the BMI, the better the investigated clinical indices; we found no obvious evidence to be associated with harmful effects. However, the assessment of FFM and FM could provide more precise information. Several studies emphasized the potential usefulness of FFM as a more detailed assessment of body composition compared with BMI. The prevalence of hidden FFM depletion (FFM<5th percentile and normal BMI) is unexpectedly high (10%-20%) among patients with CF and is associated with increased disease severity, including reduced lung function,

frequent pulmonary exacerbations, and increased inflammation.[31,35,40,55] Therefore, measuring body composition in patients with CF may be more informative than the single use of BMI as an indicator of optimal health and nutritional status.

Strengths and Limitations

To our knowledge, this is the first systematic review and meta-analysis assessing body composition in patients with CF in detail, including 3100 patients, with special focus on those who are overweight and obese. Moreover, we performed a meta-analysis regarding 9 outcomes, and subgroup analyses were performed for 3 outcomes.

Our study has limitations. There was substantial heterogeneity in the comparison of patients with normal weight and those who are obese regarding pulmonary function, and the source of substantial heterogeneity could not be identified by subgroup analysis. Furthermore, most of the studies did not report transplant status; thus, we could not perform subgroup analysis, and none of the pediatric studies reported the measurement method of respiratory function in children younger than 6 years.

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.

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SUPPLEMENT.