Translating scientific results benefits the community: From pancreatitis to COVID-19

Ph.D. Thesis

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PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

I. Anikó Nagy, Márk Félix Juhász, Anikó Görbe, Alex Váradi, Ferenc Izbéki, et al. Glucose level independently and dose-dependently worsens acute pancreatitis: a prospective, international cohort analysis of 2250 acute pancreatitis cases. Pancreatology 2021. *in press* IF: 3.799

II. Gombos K, Herczeg R, Erőss B, Kovács SZ, Uzzoli A, Nagy T, Kiss S, Szakács Z, Imrei M, Szentesi A, Nagy A, Fábián A, Hegyi P, Gyenesei A. Translating Scientific Knowledge to Government Decision Makers Has Crucial Importance in the Management of the COVID-19 Pandemic. Popul Health Manag. 2021 Feb;24(1):35-45. doi: 10.1089/pop.2020.0159. Epub 2020 Sep 2. PMID: 32882160. IF: 2.145

III. Erőss B, Molnár Z, Szakács Z, Zádori N, Szakó L, Váncsa S, Juhász MF, Ocskay K, Vörhendi N, Márta K, Szentesi A, Párniczky A, Hegyi PJ, Kiss S, Földi M, Dembrovszky F, Kanjo A, Pázmány P, Varró A, Csathó Á, Helyes Z, Péterfi Z, Czopf L, Kiss I, Zemplényi A, Czapári D, Hegyi E, Dobszai D, Miklós E, Márta A, Tóth D, Farkas R, Farkas N, Birkás B, Pintér E, Pethő G, Zsigmond B, Sárközi A, Nagy A, Hegyi P. Personalised health education against health damage of COVID-19 epidemic in the elderly Hungarian population (PROACTIVE-19): protocol of an adaptive randomized controlled clinical trial. Trials. 2020 Sep 29;21(1):809. doi: 10.1186/s13063-020-04733-0. PMID: 32993779; PMCID: PMC7522906. IF: 2.063

SCIENTIFIC METRICS

Number of publications **related to the subject** of the thesis:	3 (1 first author)
Cumulative impact factor of publications related to the thesis:	8.007
D1: 1, Q1: 2, Q2: -, Q3: -, Q4: -	
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Hirsch Index:	4

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I. LIST OF ABBREVIATIONS

AP	Acute pancreatitis
ARP	Acute recurrent pancreatitis
ARDS	Acute respiratory distress syndrome
AUC	Area under the curve (the Receiver Operating Characteristic curve)
BAP	Before acute pancreatitis
CI	Confidence interval
CFTR	Cystic fibrosis transmembrane conductance regulator
CHDI	Complex Health Distance Index
COVID-19	Coronavirus disease 2019
CP	Chronic pancreatitis
CRP	C-reactive protein
CSSE	Center for Systems Science and Engineering
DAP	During acute pancreatitis
DM	Diabetes mellitus
DMC	Data Monitoring Committee
eCRF	Electronic case report form
GDP	Gross Domestic Product
HbA1c	Hemoglobin A1c
HPSG	Hungarian Pancreatic Study Group
HTG	Hypertriglyceridemia
IAP / APA	International Association of Pancreatology / American Pancreatic Association
IQR	Interquartile range
KETLAK	Translational Action and Research Group against Coronavirus
LOH	Length of hospitalization
OAP	On admission with acute pancreatitis
OR	Odds ratio
p	P-value
PCR	Polymerase chain reactionPersonalized Health Education Against COVID-19
PROACTIVE-19	Personalized Health Education Against COVID-19
ROC	Receiver Operating Characteristic
ROS	Reactive oxygen species
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Steering Committee
SD	Standard deviation
SE	Standard error
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
RCT	Randomized controlled trial
TM	Translational medicine
WHO	World Health Organization

II. THESIS INTRODUCTION

II.1. Translating scientific knowledge: Acute pancreatitis and Coronavirus disease 2019

In this day and age, applying a scientific mindset and the prompt utilization of scientific results are vital, for the appropriate functioning and improvement of near all parts of life. However, the number of scientific publications is increasing at a rapid pace: with 291,806 available on MEDLINE in the year of 1995 and 1,064,266 in 2015 – no doubt too much to be handled on a personal or even institutional level (1). In 2016, about 1.5 million people died in the European Union, who were less than 75 years old. Of these deaths, roughly 1 million would have been avoidable, either by applying timely and effective treatment or by better public health interventions (2). While of course, reasons for this astonishingly high number can be sought in economic allocation and education, a major determinant is the inadequate utilization of already acquired scientific results. There is a dire need for a centralized method that aids the incorporation of evidence into daily practice, and that converts it into a language that is understandable and usable not only by scientific professionals, but by governments and the general public as well.

Translational medicine (TM) aims to ensure that scientific results are delivered or 'translated' into general use (3). In medicine for example, this is done by following up promising basic science results with clinical studies, by standardizing the method of reporting in scientific papers, by updating guidelines as often and as thoroughly as possible, and promoting evidence-based patient management (4). And not only in medicine, but in any area of life, knowledge acquired this way should be presented both to decision makers and the general public, in a manner that they can best handle the information. It is also crucial to seek out gaps in the currently available evidence and conduct scientific experiments/systematic reviews to fill them (5). One such field where TM science is greatly needed is acute pancreatitis (AP): since 1965, the proportion of scientific papers focusing on AP among benign GI disorders dropped from 25.7% to 10.7%, and only 5.5% of registered trials were multicentric, making evidence scarce and poorly generalizable (6).

AP is the sudden-onset inflammation of the pancreas, a common reason behind abdominal pain in the adult emergency department (7). In up to 25-30% of cases, severe disease course will occur, with a mortality rate as high as 40% - both severity and mortality could and should be diminished with improved care of these patients (8, 9). Due to remarkable efforts, the treatment of AP has undergone a substantial change in the past decades: instead of a nil per os diet or parenteral nutrition, clinical evidence now clearly prefers enteral feeding, or even

oral intake in case of tolerance (10). Guidelines also discourage the routine use of antibiotics (10, 11). Recent years' basic science and clinical investigations are focusing on commonly encountered laboratory and anamnestic parameters that could help in establishing AP prognosis and the best choice of treatment on admission: pancreatotoxic agents. Pancreatotoxicity, a dose-dependent relationship with worsening clinical outcomes of AP, is already demonstrated in case of bile acids, alcohol and its metabolites, fatty acids and fatty acid ethyl esters (12-16) and presumed in case of smoking and several drugs (17, 18). We set out to examine – in keeping with the mentality of TM – whether such a dose-dependent relationship exists with increasing serum glucose values, since basic science points towards the potential pancreatotoxic effects of hyperglycemia (19).

However, in December 2019 the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic hit, causing the Coronavirus Disease 2019 (COVID-19). It quickly became a humanitarian crisis the likes of which we have not seen perhaps since the Second World War. In little more than one year, there have been around 120 million confirmed cases of COVID-19 worldwide, resulting in almost 3 million deaths, mostly due to respiratory failure (20, 21). The world was struck unprepared for an outbreak and pandemonium of these measures. This made TM more necessary than ever: the scientific evidence, amassed in a hurry, needed to be evaluated and summarized in a hurry so that the government could react promptly and appropriately, minimizing the deleterious effects of the pandemic. It also became essential to assess, more swiftly than usual, where the literature was lacking, and design clinical or basic science experiments to fill the inherent voids. Thus, our focus partly shifted towards applying TM research for improving the COVID-19 pandemic.

II.2. Aims of PhD work

As the Director-General of Heim Pál National Pediatric Institute and the former State Secretary for Health of Hungary, it is of crucial importance to me that scientific results make their way into patient care as soon as possible. This not only improves the quality of care and helps avoid unnecessary deaths, but also greatly contributes towards building a more cost-efficient healthcare system, which ultimately provides the basis for further improvement and better working conditions.

In my PhD work I wanted to focus on different aspects of TM. We set out to analyze a prospective, international cohort of AP patients, and establish whether serum glucose predicts worse clinical outcomes or complications – since this information was yet uninvestigated. During the COVID-19 pandemic we provided systematic literature reviews and performed

mathematical modelling estimations to aid government decision makers. While exploring the available literature, we identified a gap in knowledge – this led to designing and initiating our randomized controlled trial (RCT), Personalized Health Education Against COVID-19 (PROACTIVE-19), which is the first to investigate and provide a personalized, multicomponent lifestyle intervention program in a telephone-based manner, to help avoid the contraction and severe course of COVID-19.

III. GLUCOSE LEVEL INDEPENDENTLY AND DOSE DEPENDENTLY WORSENS ACUTE PANCREATITIS: A COHORT ANALYSIS

III.1. Introduction

AP is the inflammation of the pancreas, most often caused by alcohol consumption and biliary obstruction (22). The incidence of AP is gradually increasing worldwide, now reported to be 4.6-100/100,000 in the general population (23, 24). The severity of the condition varies, with most cases being classified as mild, but in 15-30% and 10-20% of the cases, moderate and severe disease course will occur, resulting in longer hospitalization, organ failure (OF) and higher mortality (up to 40% in severe cases) (9, 25, 26).

Szentesi et al. demonstrated that obesity, hypertension and hyperlipidemia are independent risk factors for several complications in AP. Furthermore, the more components of metabolic syndrome are present, the higher the risk for more severe disease outcomes (27). To acquire more knowledge on how different components of the metabolic syndrome affect the course of AP, the Hungarian Pancreatic Study Group (HPSG) has already investigated on-admission serum triglyceride concentration. This prospective cohort study found that hypertriglyceridemia dose-dependently increases the severity and rate of AP complications (14). As a next step in filling the gaps of knowledge regarding the role of toxic metabolic factors in the clinical course, we set out to examine the outcome parameters of AP in the context of serum glucose concentration.

Hyperglycemia is an established independent risk factor in numerous diseases. It independently predicts long-term mortality and is associated with a worse prognosis in acute myocardial infarction, irrespective of the presence of diabetes mellitus (DM) (28, 29). It is also associated with a higher rate of poor functional outcomes and less successful revascularization after acute ischemic stroke (30, 31). Furthermore, not only the acute elevations in serum glucose are of interest – studies describe chronic glucose dysregulation to be prognostic for mortality after acute myocardial infarction, both in diabetic and non-diabetic patients (32-34). In AP, the exact role of glucose dysregulation and its laboratory indicators is yet to be described. However, of the most widely used AP prognostic scoring systems, two (the Ranson and the Glasgow-Imrie) include a serum glucose concentration above 10 mmol/L, highlighting its potential role and association with severity (35).

Our goal was to examine the presence of dose-dependency between glucose dysregulation and clinically important outcomes of AP in a large, multicenter, prospective cohort. In our current cohort analysis (1) previous glucose homeostasis, as assessed by

glycosylated hemoglobin (HbA1c) levels; and especially (2) serum glucose levels on admission; and (3) the highest glucose levels during hospitalization have shown dose-dependent associations with key clinically important outcomes of AP. We also established hyperglycemia as an independent and dose-dependent risk factor for mortality.

III.2. Methods

Study design, data source

This study presents a post-hoc analysis of a prospective, international, multicenter registry of AP patients, maintained by the HPSG. Participants were enrolled in the AP registry if they fulfilled the diagnostic criteria for AP as per the International Association of Pancreatology / American Pancreatic Association (IAP/APA) and HPSG guidelines (11, 36). They were followed up until the end of their AP associated hospital stay (until oral feeding was reinstated without symptoms and with the normalization of laboratory parameters). A list of study sites can be found in Table 1. Between 2012 and 2019, 2,461 adult (≥18 years old) AP patients' data were collected. To ensure data quality, a four-tier quality control system was applied, described in detail in a previous publication from the registry (37).

Country	City	Institution	n
Belarus	Gomel	Gomel Regional Clinical Hospital	8
Croatia	Rijeka	Clinical Hospital Center Rijeka	11
Czech Republic	Ostrava	Vítkovice Hospital	11
Finland	Helsinki	Helsinki University Central Hospital	25
Hungary	Békéscsaba	Dr. Réthy Pál Hospital	62
	Budapest	Bajcsy-Zsilinszky Hospital	136
		Buda Hospital of the Hospitaller Order of Saint John of God	5
		Military Hospital – State Health Centre	1
	Debrecen	Department of Internal Medicine, University of Debrecen	168
		Department of Surgery, University of Debrecen	7
	Gyula	Pándy Kálmán Hospital of County Békés	31
	Kecskemét	Bács-Kiskun County University Teaching Hospital	8
	Makó	Healthcare Center of County Csongrád	10
	Miskolc	Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital	11
	Pécs	First Department of Medicine, University of Pécs	819
	Szeged	First Department of Medicine, University of Szeged	263
		Second Department of Medicine, University of Szeged	75
		Department of Anesthesiology and Intensive Therapy, University of Szeged	10
	Székesfehérvár	Szent György University Teaching Hospital of County Fejér	383
	Szentes	Dr. Bugyi István Hospital	17
	Szombathely	Markusovszky University Teaching Hospital	17
Japan	Tokyo	Keio University	2
Lithuania	Vilnius	Vilnius University Hospital Santariskiu Klinikos	31

Romania	Bucharest	Central Military Emergency Hospital "Dr Carol Davila"	1
	Targu Mures	Mures County Emergency Hospital	56
Russia	St. Petersburg	Saint Luke Clinical Hospital	28
Spain	Sant Pere de Ribes	General Surgery, Consorci Sanitari del Garrof	26
Turkey	Istanbul	Hospital of Bezmialem Vakif University, School of Medicine, Istanbul	20
Ukraine	Kiev	Bogomolets National Medical University	8
		Total number of patients	**2250**

Table 1: Centre distribution, cities, institutions. n: number of enrolled participants.

Participants

In the present analysis, we included 2,250 patients from the total of 2,461 participants in the AP registry with available data on (1) HbA1c any time during the hospitalization with AP and/or (2) on-admission serum glucose measurement and/or (3) at least two serum glucose measurements during hospitalization.

Three variables were taken into account in dividing our examined cohort into subgroups. To observe the role of the glucose homeostasis preceding the admission with AP – 'before AP' (BAP) – participants were divided into five groups based on their HbA1c: ≤6.50; 6.51-7.00; 7.01-8.00; 8.01-9.00; ≥9.01%. To reflect the on-admission state – 'on-admission AP' (OAP) – seven groups were formed based on on-admission serum glucose levels: ≤3.99, 4.00-5.99, 6.00-7.79, 7.80-11.09, 11.10-14.99, 15.00-19.99, ≥20.00 mmol/L. Seven groups were formed based on peak serum glucose during the hospital stay – 'during AP' (DAP) – among those patients who had at least two glucose measurements: ≤3.99, 4.00-5.99, 6.00-7.79, 7.80-11.09, 11.10-14.99, 15.00-19.99, ≥20.00 mmol/L. These boundaries were chosen to reflect already established cut-offs (6.5% and 7% for HbA1c, 7.8 mmol/L and 11.1 mmol/L for glucose (38), participant and event numbers to maintain statistical power and equal increments to avoid the possibility of arbitrary cut-off selection.

Variables

A complete list of collected variables – including data on laboratory parameters, complications, severity and mortality – is provided in our data quality table (Table 2). Local complications, systemic complications and severity were defined according to the revised Atlanta classification (39).

Glucose measured only within the first 24 hours was accepted as on-admission glucose level. Venous measurements were preferred and accounted for most of the on-admission values, but results from capillary samples were also accepted. HbA1c measured any time

during the hospitalization was accepted for this analysis. 95% of measurements occurred within 48 hours of hospitalization.

EPIDEMIOLOGY, ETIOLOGY	OVERALL	UPLOADED DATA	%
Age	2250	2250	100
Gender	2250	2250	100
Etiology	2250	2250	100
Average uploaded data	*6750*	*6750*	*100*

PERSONAL MEDICAL HISTORY	OVERALL	UPLOADED DATA	%
Acute pancreatitis in the personal history	2250	2185	97
Number of previous episodes among recurrent cases	493	457	93
Chronic pancreatitis in the personal history	2250	2185	97
Average uploaded data	4993	4827	*97*

LABORATORY PARAMETERS	OVERALL	UPLOADED DATA	%
Serum glucose on admission	2250	2129	95
Hemoglobin A1c on admission	2250	752	33
C-reactive protein (CRP)	2250	2197	98
Average uploaded data	*6750*	*5078*	*75*

OUTCOMES	OVERALL	UPLOADED DATA	%
Local pancreatic complications	2250	2232	99
Peripancreatic fluid collection	2250	2232	99
Pancreatic pseudocyst	2250	2232	99
Pancreatic necrosis	2250	2231	99
Organ failure	2250	2245	100
Respiratory failure	2250	2243	100
Heart failure	2250	2244	100
Renal failure	2250	2244	100
Length of hospitalization	2250	2250	100
Severity (mild/moderately severe/severe)	2250	2250	100
Mortality	2250	2250	100
Average uploaded data	*24750*	*24653*	*100*
TOTAL	***43243***	**41308**	***96***

Table 2: Data quality table.

Statistical analysis

For the descriptive analysis of categorical variables, case number and percentage were computed, while in the case of continuous variables, patient number, mean, standard deviation (SD), median, 25% and 75% quartiles (IQR) were calculated. To identify the three subcohorts' representativeness, we used the Chi-squared test in case of categorical data, the Student's t-test for normally distributed variables, and the Mann-Whitney U-test for non-normally distributed variables. In ‘Table 4’, groups with outlying age (Kruskal-Wallis test) and gender distribution (Fisher exact or Chi-squared test) were sought as well as trends in AP recurrence (RAP), chronic pancreatitis (CP), hyperlipidemia, DM in the medical history (Cochran-Armitage test

for trend) and AP episode number among RAP cases (Jonckheere-Terpstra trend test). The dose-dependent effects of HgA1c, on-admission and maximum glucose levels on the investigated outcomes, were tested using the Cochran-Armitage test for trend (in case of categorical variables) and the Jonckheere-Terpstra trend test (in case of continuous variables).

To detect the predictive accuracy of HbA1c, on-admission glucose level and maximum glucose level on the mortality and severity, the Receiver Operating Characteristic Curve (ROC) was applied. To check the performance of the classification, we used Area Under the Curve (AUC) with 95% confidence intervals (CI) (depending on the AUC value, the accuracy of the test can be categorized as followed: 0.5–0.6 fail, 0.6–0.7 poor, 0.7–0.8 fair, 0.8–0.9 good and above 0.9 excellent). We calculated the potential best cut-off value as well. Odds ratios (OR) with 95% CI were calculated for severe AP cases and mortality. Binary logistic regression was used to test the independent prognostic role of the three investigated variables. The model contains the following parameters in all cases: age, gender, DM, AP etiology and HbA1c, on-admission glucose level or maximum glucose level. All calculations were performed with the statistical software R, version 4.0.2 (R Core Team, 2020, Vienna, Austria) using the coin (v1.3-4; Hothorn et. al., 2008), rcompanion (v2.3.27; Mangiafico, 2021), DescTools (v0.99.39; Signorell et. al., 2020), PMCMRplus (v1.9.0; Pohlert, 2021) and pROC (v1.17.0.1; Robin et. al. 2011) packages.

Ethical approval

Ethical approval for the registry was granted in 2012 by the Scientific and Research Ethics Committee of the Medical Research Council (22254–1/2012/EKU). The registry protocol was approved by the institution's human research committee preceding the study initiation. It complies with the ethical guidelines of the Declaration of Helsinki, reaffirmed in 2013. All participants provided written, informed consent for participation.

Study reporting

This study is reported according to the ’Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement’ (40).

III.3. Results

Study population

A total of 2,250 AP cases were analyzed. Table 4 contains the baseline information of participants in each subgroup of all three subcohorts (BAP, OAP and DAP). A statistically

significant trend of increasing proportion of hyperlipidemia and DM in the medical history with increasing HbA1c and glucose values was seen in all subcohorts. Among groups with different on-admission glucose values, significant age differences were noted, with the highest mean ages observed in groups 4-6 (glucose 7.8-19.99 mmol/L) and lowest in group 1 (glucose <4 mmol/L).

BAP – HbA1c						p
Groups, HbA1c%	≤6.50	6.51-7.00	7.01-8.00	8.01-9.00	≥9.01	
n (%)	633 (84.0)	28 (3.7)	32 (4.2)	22 (2.9)	39 (5.2)	
Age (years), mean (SD)	56.50 (16.76)	63.54 (12.20)	58.38 (12.76)	55.23 (11.59)	53.08 (13.86)	*0.068*
Female, n (%)	260 (41)	13 (46)	10 (31)	4 (18)	11 (28)	*0.078*
RAP, n (%)	142 (22)	2 (7)	7 (22)	7 (32)	10 (26)	*0.561*
Episodes, n, median (IQR)	138; 1.00 (1.00, 2.00)	2; 1.00 (1.00, 1.00)	6; 1.00 (1.00, 1.00)	7; 1.00 (1.00, 3.50)	10; 1.50 (1.00, 2.75)	*0.845*
CP, n (%)	48 (8)	3 (11)	3 (9)	2 (9)	2 (5)	*0.882*
DM, n (%)	74 (11.7)	17 (60.7)	28 (87.5)	18 (81.8)	35 (89.7)	***<0.001***
Hyperlip, n (%)	56 (9)	4 (16)	6 (21)	5 (26)	16 (43)	***<0.001***

OAP – on-admission serum glucose								p
Groups, mmol/L	≤3.99	4-5.99	6.00-7.79	7.80-11.09	11.10-14.99	15.00-19.99	≥20.00	
n (%)	21 (1.0)	468 (22.0)	697 (32.7)	613 (28.8)	221 (10.4)	68 (3.2)	41 (1.9)	
Age (years), mean (SD)	45.52 (19.88)	51.40 (17.23)	56.12 (17.62)	59.92 (15.56)	61.20 (14.81)	58.62 (13.91)	53.05 (15.23)	***<0.001***
Female, n (%)	12 (57)	208 (44)	294 (42)	266 (43)	96 (43)	23 (34)	14 (34)	*0.423*
RAP, n (%)	2 (10)	109 (23)	161 (23)	134 (22)	40 (18)	16 (24)	6 (15)	*0.216*
Episodes, n, median (IQR)	2; 1.50 (1.25, 1.75)	102; 1.00 (1.00, 2.00)	152; 1.00 (1.00, 2.00)	124; 1.00 (1.00, 2.00)	35; 1.00 (1.00, 2.00)	16; 1.00 (1.00, 2.50)	6; 2.50 (2.00, 3.75)	*0.227*
CP, n (%)	0 (0)	30 (6)	46 (7)	30 (5)	6 (3)	3 (4)	4 (10)	*0.259*
DM, n (%)	2 (9.5)	24 (5.1)	62 (8.9)	121 (19.7)	105 (47.5)	49 (72.1)	30 (73.2)	***<0.001***
Hyperlip, n (%)	2 (13)	41 (10)	67 (11)	100 (19)	40 (21)	15 (25)	18 (50)	***<0.001***

DAP – peak serum glucose								p
Groups, mmol/L	≤3.99	4.00-5.99	6.00-7.79	7.80-11.09	11.10-14.99	15.00-19.99	≥20.00	
n (%)	6 (1.0)	187 (31.3)	143 (24.0)	123 (20.6)	79 (13.2)	43 (7.2)	16 (2.7)	
Age (years), mean (SD)	60.50 (19.21)	58.03 (18.97)	57.83 (16.13)	59.54 (15.19)	60.82 (13.24)	57.84 (14.44)	61.50 (14.02)	*0.844*
Female, n (%)	4 (67)	88 (47)	63 (44)	50 (41)	29 (37)	19 (44)	8 (50)	*0.611*
RAP, n (%)	3 (50)	37 (20)	34 (24)	27 (22)	19 (24)	8 (19)	3 (19)	*0.868*
Episodes, n, median (IQR)	3; 2.00 (1.50, 2.00)	35; 2.00 (1.00, 2.00)	30; 1.00 (1.00, 2.00)	22; 1.00 (1.00, 3.00)	16; 1.00 (1.00, 3.00)	7; 1.00 (1.00, 1.50)	3; 1.00 (1.00, 1.50)	*0.577*
CP, n (%)	0 (0)	11 (6)	6 (4)	3 (2)	6 (8)	4 (9)	0 (0)	*0.770*

DM, n (%)	0 (0)	13 (7.0)	17 (11.9)	28 (22.8)	46 (58.2)	29 (67.4)	10 (62.5)	***<0.001***
Hyperlip, n (%)	2 (33)	18 (12)	21 (18)	19 (17)	23 (31)	13 (33)	6 (40)	***<0.001***

Table 4: Baseline characteristics of participants in each group of all three subcohorts. AP: acute pancreatitis; BAP: before AP; OAP: on-admission with AP; DAP: during AP; %: percentage; n: number; SD: standard deviation; p: P-value; RAP: recurrent acute pancreatitis; IQR: interquartile range; CP: chronic pancreatitis; DM: diabetes mellitus in the personal medical history; Hyperlip: hyperlipidemia in the personal medical history.

Etiology distribution

Figure 1 shows how different etiologies of AP were distributed across our examined subgroups. While most etiologies showed a balanced distribution, hypertriglyceridemia (HTG) increased in higher HbA1c and serum glucose groups, starting at HbA1c >7% in the BAP, and glucose >11.1 mmol/L in the OAP and DAP subcohorts.

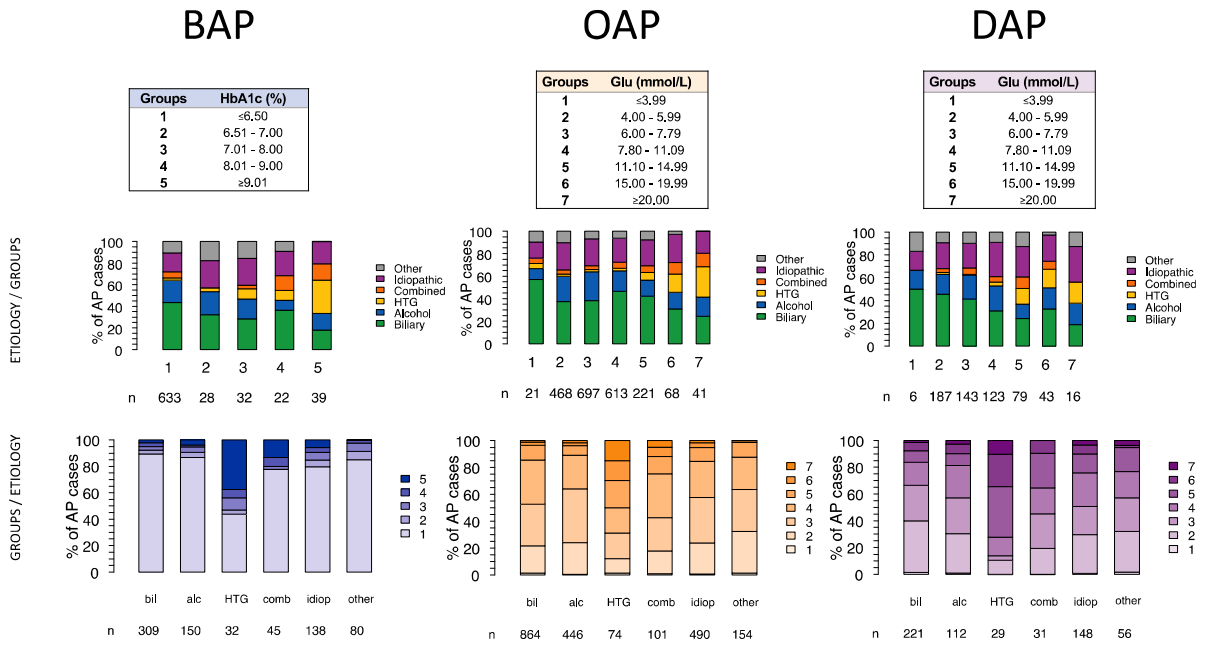

Figure 1: Etiology distribution. The top row shows the classification of groups. The middle row shows how etiologies within each group (etiologies add up to 100%). The bottom row shows group distribution within each etiology (groups add up to 100%). AP: acute pancreatitis; BAP: before AP; OAP: on-admission with AP; DAP: during AP; HbA1c: hemoglobin A1c; Glu: serum glucose; HTG: hypertriglyceridemia; bil: biliary, alc: alcoholic; comb: combined; idiop: idiopathic.

BAP: pre-existing disturbance of glucose metabolism shows a trend of increasing AP severity and local complications.

While no statistically significant differences were noted (p=0.394), a trend of increasing HbA1c and increasing AP severity was observed. AP severity was highest in Group 4 (21.4% moderate, 5.8% severe). HbA1c was directly associated with the length of hospitalization (LOH) (p<0.001) and maximal CRP (p<0.001), both peaking in group 4 probably due to the

higher proportion of moderate cases, but not with mortality, which was the greatest in Group 2 (7.1%) (Figure 2).

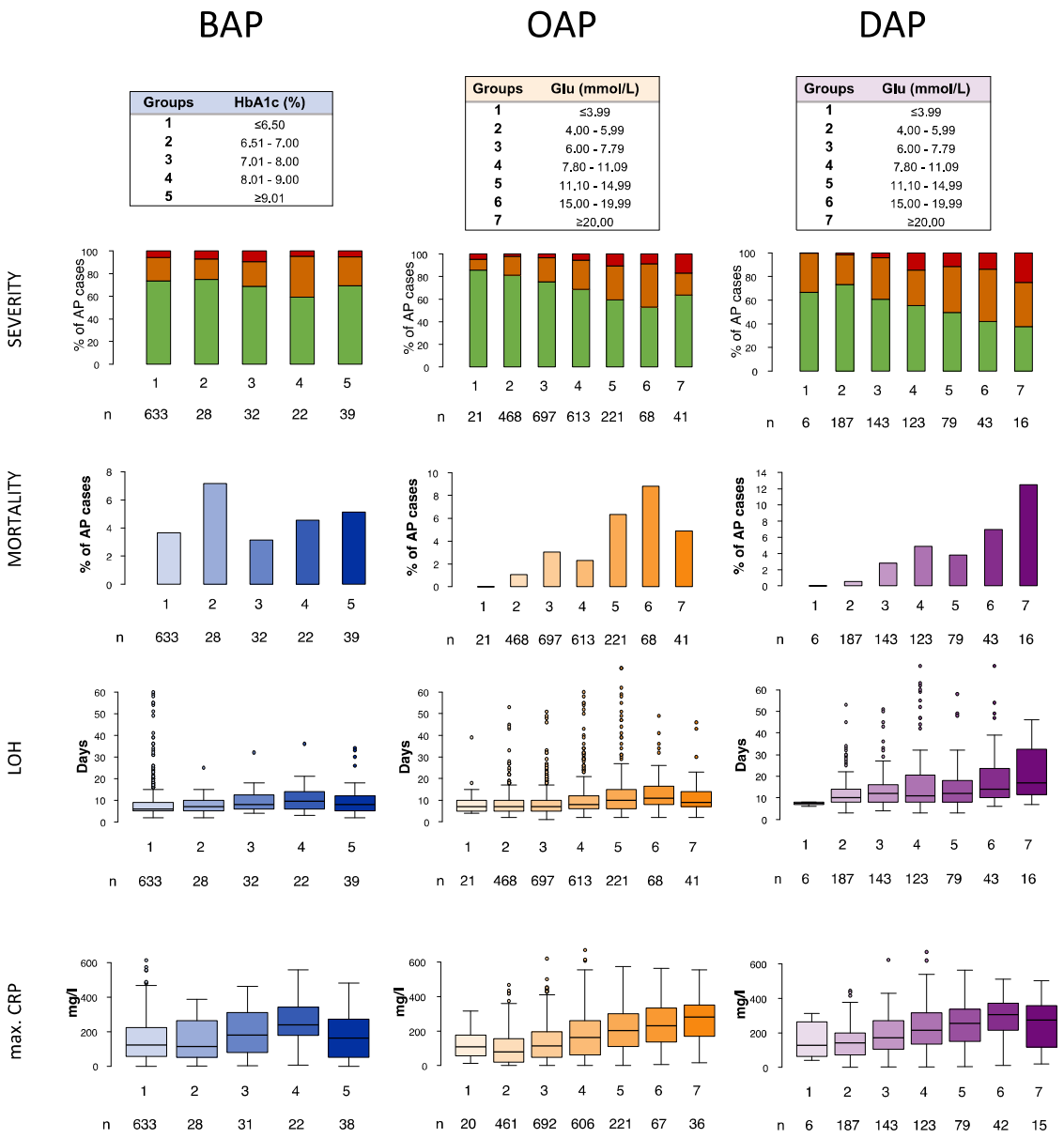

Figure 2: AP severity, mortality, length of AP-associated hospital stay, maximal CRP. AP: acute pancreatitis; BAP: before AP; OAP: on-admission with AP; DAP: during AP; HbA1c: hemoglobin A1c; Glu: serum glucose; LOH: length of AP associated hospitalization; max. CRP: maximal C-reactive protein.

No trends were identified regarding systemic complications (respiratory, renal or heart failure) (p=0.959); the highest rate of organ failures was found in Group 3 (12.5%) (Figure 3). On the other hand, an increasing proportion of local complications (peripancreatic fluid, pancreas pseudocyst, pancreas necrosis) were seen with increasing HbA1c (Figure 4), without statistical significance (p=0.122).

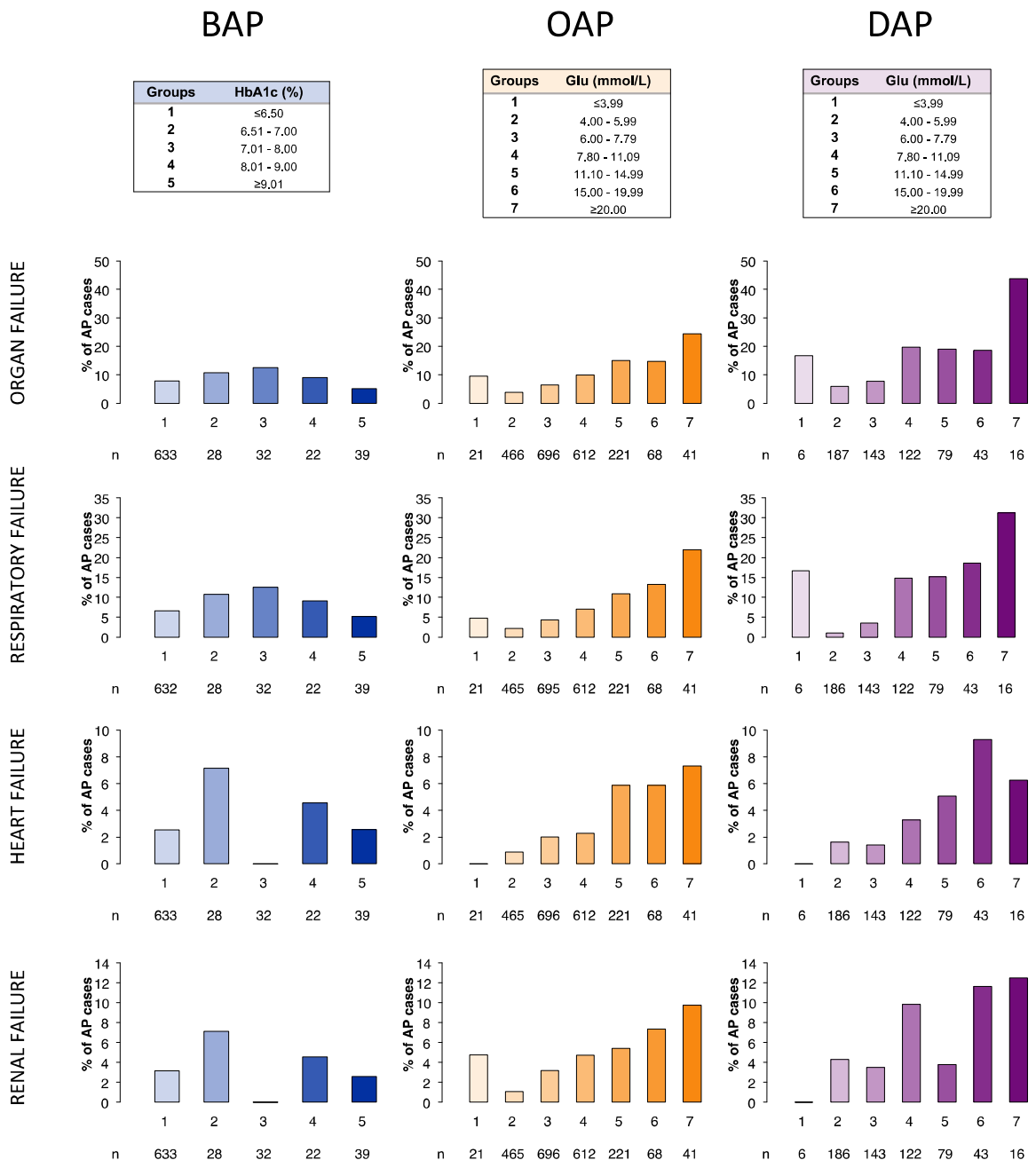

Figure 3: Systemic complications as defined by the revised Atlanta classification and Marshall criteria. The top row shows the classification of groups. The second row shows the percentage of AP cases with organ failure (one or more of lungs, heart and kidney). The third, fourth, and bottom rows show the percentage of AP cases with respiratory, heart and renal failure, respectively, in each group. AP: acute pancreatitis; BAP: before AP; OAP: on-admission with AP; DAP: during AP; HbA1c: hemoglobin A1c; Glu: serum glucose.

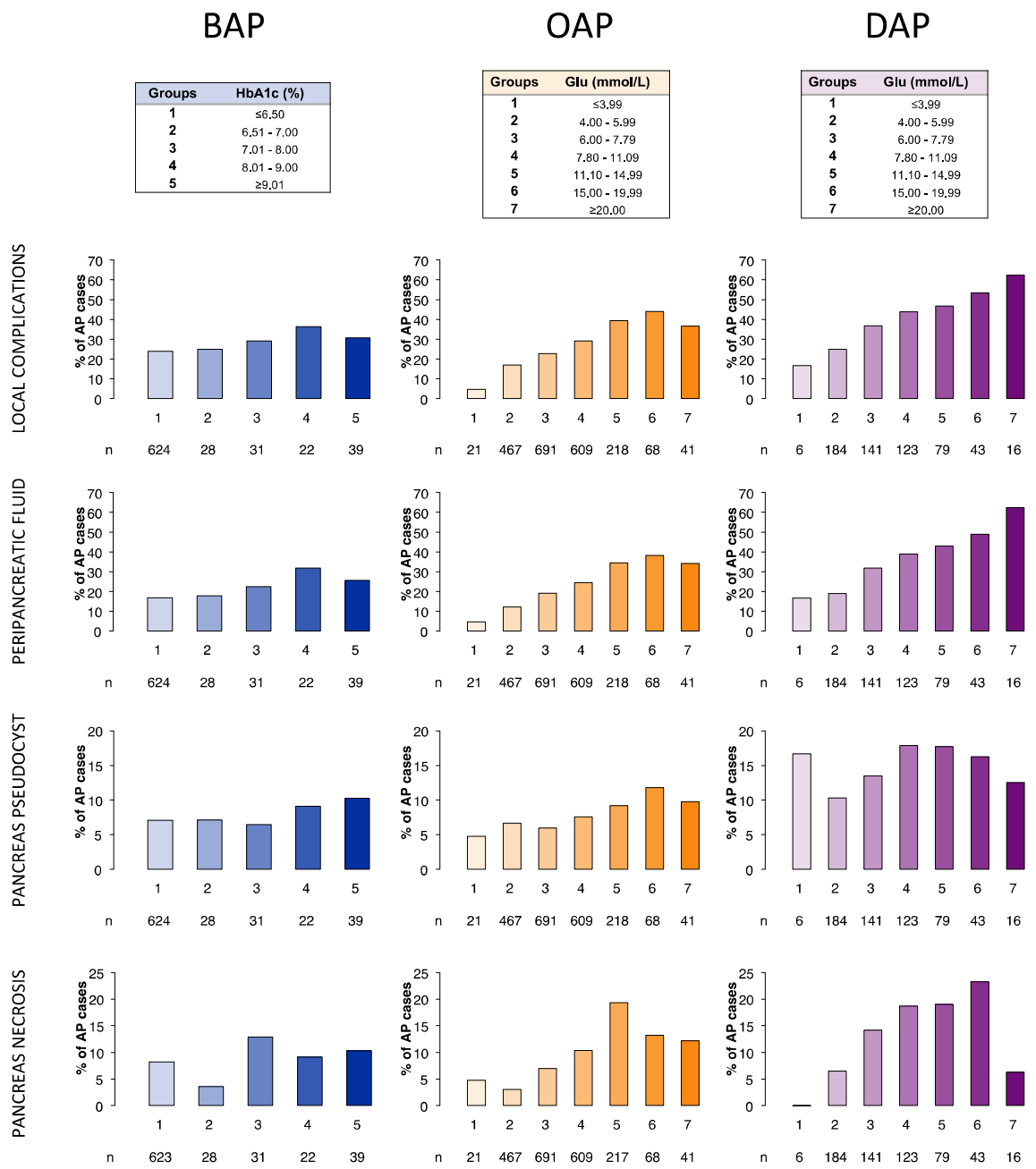

Figure 4: Local pancreatic complications as defined by the revised Atlanta classification. The top row shows the classification of groups. The second row shows the percentage of AP cases with local complications (one or more of acute peripancreatic fluid collection, pancreas pseudocyst, pancreas necrosis – no distinction between acute necrotic collection and walled-off necrosis). The third, fourth, and bottom rows show the percentage of AP cases with acute peripancreatic fluid collection, pancreas pseudocyst and pancreas necrosis, respectively, in each group. AP: acute pancreatitis; BAP: before AP; OAP: on-admission with AP; DAP: during AP; HbA1c: hemoglobin A1c; Glu: serum glucose.

The binary logistic regression did not show HbA1c to be an independent predictor of mortality (OR=1.211 (95% CI: 0.859-1.646), p=0.241) or severity (OR=1.028 (95% CI: 0.768-

1.332), p=0.843) (Tables 7-8). The ROC analysis showed that HbA1c fails to predict mortality (AUC=0.545) and poorly predicts the severity of AP (AUC=0.601).

BAP –HbA1c					
Outcome	p (trend)	p (1 vs 2)	p (1 vs 3)	p (1 vs 4)	p (1 vs 5)
Mortality	*0.602*	*0.919*	*0.919*	*0.919*	*0.919*
Severity	*0.394*	*0.995*	*0.884*	*0.884*	*0.884*
Etiology	***<0.001***	*0.627*	*0.627*	*0.825*	*0.627*
Length of hospitalization	***<0.001***	*0.302*	*0.057*	*0.072*	*0.164*
Maximal C-reactive protein	***<0.001***	*0.136*	*0.802*	*0.820*	*0.988*

OAP – on-admission serum glucose						
Outcome	p (trend)	p (2 vs 3)	p (2 vs 4)	p (2 vs 5)	p (2 vs 6)	p (2 vs 7)
Mortality	***<0.001***	*0.059*	*0.22*	***<0.001***	***<0.001***	*0.084*
Severity	***<0.001***	***0.024***	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Etiology	***<0.001***	*0.465*	*0.113*	*0.843*	*0.873*	*0.992*
Length of hospitalization	***<0.001***	*0.212*	***0.002***	*0.669*	*0.751*	*0.587*
Maximal C-reactive protein	***<0.001***	*0.299*	*0.077*	*0.322*	*0.462*	*0.578*

DAP – peak serum glucose						
Outcome	p (trend)	p (2 vs 3)	p (2 vs 4)	p (2 vs 5)	p (2 vs 6)	p (2 vs 7)
Mortality	***0.001***	*0.239*	*0.059*	*0.16*	***0.027***	***0.002***
Severity	***<0.001***	*0.023*	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Etiology	***<0.001***	*0.899*	*0.260*	*0.069*	*0.899*	*0.330*
Length of hospitalization	***<0.001***	***0.008***	***0.011***	***0.002***	***<0.001***	***<0.001***
Maximal C-reactive protein	***<0.001***	*0.151*	*0.239*	*0.801*	*0.773*	*0.892*

Table 5: P-values corresponding to trends (Cochran-Armitage test for trend and Jonckheere-Terpstra test) and intergroup differences in mortality, severity, etiology, length of hospitalization and maximal C-reactive protein. Values below 0.05 (bold) indicate statistical significance. BAP: before AP; OAP: on-admission with AP; DAP: during AP; p: P-value.

OAP and DAP: on-admission and peak glucose levels demonstrate a dose-dependent association with worse AP outcomes (severity, mortality, complications, LOH, maximal CRP).

A dose-dependent association was seen between on-admission glucose levels, peak in-hospital glucose levels and: severity (p<0.001 in both OAP and DAP), mortality (p<0.001 OAP and DAP), LOH (p<0.001 OAP and DAP), maximal CRP (p<0.001 OAP and DAP) (Figure 2), systemic complications (p<0.001 OAP and DAP; Figure 3) and local complications (p<0.001 OAP and DAP; Figure 4).

The group with a peak in-hospital glucose ≥20 mmol/L (Group 7) noted the highest severity (37.5% moderate, 25.0% severe), mortality (12.5%), systemic (43.8%) and local complications (62.5%). While similarly, on-admission glucose Group 7 saw the highest rate of

local complications (36.6%), Group 6 (serum glucose 15 – 19.99 mmol/L) had the highest severity (38.2% moderate, 8.8% severe), mortality (8.8%), and rate of systemic complications (14.7%).

The binary logistic regression established both on-admission and peak in-hospital serum glucose to be independently associated with mortality (OR=1.133 (95% CI: 1.064-1.204), p<0.001 and OR=1.089 (95% CI: 1.020-1.161), p=0.006, respectively) and severity (OR=1.131 (95% CI: 1.078-1.186), p<0.001 and OR=1.093 (95% CI: 1.039-1.152), p<0.001, respectively) (Tables 7-8). The ROC analysis showed on-admission glucose to be a poor predictor of mortality (AUC=0.636 for an estimated cut-off of 10.635 mmol/l) and severity (AUC=0.671 for an estimated cut-off of 9.435 mmol/l). An on-admission glucose >10 mmol/l had an OR of 3.140 (95% CI: 2.106-4.682) for severe AP and an OR of 2.666 (95% CI: 1.587-4.478) for mortality. The ROC analysis indicated that peak in-hospital glucose is a fair predictor of mortality (AUC=0.703 for an estimated cut-off of 6.665 mmol/l) and severity (AUC=0.732 for an estimated cut-off of 7.355 mmol/l). A peak in-hospital glucose >7 mmol/l had an OR of 14.490 (95% CI: 4.443-47.264) for severe AP and an OR of 4.750 (95% CI: 1.370-16.476) for mortality.

Hypoglycemia (Group 1) was associated with a higher rate of organ failure and maximal CRP in both the OAP and DAP subcohorts and higher severity only in the DAP subcohort. Increased mortality, LOH or local complications were not seen.

Additional trends, intergroup differences

The results of additional trend tests not discussed in the article's main body and P-values corresponding to intergroup differences for all examined outcomes can be found in Tables 5 and 6.

BAP –HbA1c					
Complications	p (trend)	p (1 vs 2)	p (1 vs 3)	p (1 vs 4)	p (1 vs 5)
Local pancreatic complications	*0.122*	*0.892*	*0.892*	*0.892*	*0.892*
Peripancreatic fluid collection	*0.033*	*0.887*	*0.753*	*0.679*	*0.753*
Pancreatic pseudocyst	*0.478*	*0.985*	*0.985*	*0.985*	*0.985*
Pancreatic necrosis	*0.536*	*0.830*	*0.830*	*0.883*	*0.883*
Organ Failure	*0.959*	*0.849*	*0.849*	*0.849*	*0.849*
Respiratory failure	*0.697*	*0.849*	*0.849*	*0.849*	*0.849*
Heart Failure	*0.886*	*0.618*	*0.618*	*0.779*	*0.989*
Renal failure	*0.846*	*0.618*	*0.618*	*0.797*	*0.836*
OAP – on-admission serum glucose					

Complications	p (trend)	p (2 vs 3)	p (2 vs 4)	p (2 vs 5)	p (2 vs 6)	p (2 vs 7)
Local pancreatic complications	***<0.001***	***0.024***	***<0.001***	***<0.001***	***<0.001***	***0.005***
Peripancreatic fluid collection	***<0.001***	***0.003***	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Pancreatic pseudocyst	***0.041***	*0.722*	*0.722*	*0.607*	*0.607*	*0.722*
Pancreatic necrosis	***<0.001***	***0.007***	***<0.001***	***<0.001***	***<0.001***	***0.007***
Organ Failure	***<0.001***	*0.075*	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Respiratory failure	***<0.001***	*0.067*	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Heart Failure	***<0.001***	*0.164*	*0.117*	***0.001***	***0.007***	***0.005***
Renal failure	***<0.001***	*0.062*	***0.002***	***0.002***	***0.002***	***<0.001***
DAP – peak serum glucose						
Complications	p (trend)	p (2 vs 3)	p (2 vs 4)	p (2 vs 5)	p (2 vs 6)	p (2 vs 7)
Local pancreatic complications	***<0.001***	*0.062*	***0.003***	***0.003***	***0.003***	***0.005***
Peripancreatic fluid collection	***<0.001***	*0.023*	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Pancreatic pseudocyst	*0.118*	*0.969*	*0.728*	*0.728*	*0.969*	*0.969*
Pancreatic necrosis	***0.002***	***0.081***	***0.008***	***0.011***	***0.008***	*0.966*
Organ Failure	***<0.001***	*0.643*	***<0.001***	***0.004***	***0.016***	***<0.001***
Respiratory failure	***<0.001***	*0.179*	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Heart Failure	***0.004***	*0.875*	*0.549*	*0.342*	*0.076*	*0.431*
Renal failure	***0.036***	*0.925*	*0.230*	*0.927*	*0.230*	*0.258*

Table 6: P-values corresponding to trends (Cochran-Armitage test for trend) and intergroup differences (Chi-squared or Fisher exact test) in local and systemic complications. Values below 0.05 (bold) indicate statistical significance. BAP: before AP; OAP: on-admission with AP; DAP: during AP; p: P-value.

BAP –HbA1c						
Predictor		β	SE	p	OR	95% CI
Age	per years	0.0524	0.016	***<0.001***	1.054	1.023-1.088
Gender	female (vs. male)	-0.861	0.496	*0.082*	0.423	0.150-1.074
Diabetes Mellitus	<0.001	-1.355	0.710	*0.056*	0.258	0.056-0.934
HbA1c	per 1.0%	0.192	0.163	*0.241*	1.211	0.859-1.646
Etiology	alcoholic (vs. biliary)	0.809	0.705	*0.251*	2.246	0.521-8.857
	HTG (vs. biliary)	2.398	0.849	***0.005***	11.004	1.857-56.432
	Combined (vs. biliary)	2.262	0.686	***<0.001***	9.598	2.407-37.430
	Idiopathic (vs. biliary)	1.689	0.564	***0.003***	5.413	1.824-17.319
	Other (vs. biliary)	-15.169	1160.223	*0.990*	$2.584x10^{-7}$	$0.000-1.545x10^{20}$
OAP – on-admission serum glucose						
Predictor		β	SE	p	OR	95% CI
Age	per years	0.048	0.010	***<0.001***	1.050	1.030-1.071
Gender	female (vs. male)	-0.210	0.303	*0.488*	0.811	0.444-1.463
Diabetes Mellitus	<0.001	-0.984	0.399	***0.013***	0.374	0.162-0.784
On-admission glucose	per 1 mmol/l	0.1252	0.031	***<0.001***	1.133	1.064-1.204
Etiology	alcoholic (vs. biliary)	1.273	0.438	***0.004***	3.570	1.504-8.456

	HTG (vs. biliary)	1.209	0.749	*0.106*	3.351	0.643-12.973
	Combined (vs. biliary)	1.723	0.539	***0.001***	5.603	1.821-15.549
	Idiopathic (vs. biliary)	1.220	0.352	***<0.001***	3.388	1.712-6.872
	Other (vs. biliary)	0.211	0.768	*0.784*	1.235	0.191-4.554
DAP – peak serum glucose						
Predictor		β	SE	p	OR	95% CI
Age	per years	0.025	0.017	*0.142*	1.025	0.993-1.061
Gender	female (vs. male)	-0.125	0.528	*0.813*	0.882	0.305-2.482
Diabetes Mellitus	<0.001	-1.321	0.720	***0.067***	0.267	0.052-0.950
Peak glucose	per 1 mmol/l	0.085	0.031	***0.006***	1.089	1.020-1.161
	alcoholic (vs. biliary)	0.365	0.808	*0.652*	1.440	0.262-6.845
	HTG (vs. biliary)	0.642	1.199	*0.593*	1.900	0.089-15.420
Etiology	Combined (vs. biliary)	1.261	0.896	*0.159*	3.528	0.465-18.498
	Idiopathic (vs. biliary)	0.713	0.593	*0.229*	2.040	0.633-6.802
	Other (vs. biliary)	-15.822	1385.218	*0.991*	$1.344x10^{-7}$	$0.000-3.693x10^{30}$

Table 7: Binary logistic regression for mortality, accounting for age, gender, diabetes mellitus, acute pancreatitis etiology and: on-admission hemoglobin A1c in the BAP grouping, on-admission serum glucose in the OAP grouping, highest in-hospital serum glucose in the DAP grouping. AP: acute pancreatitis; BAP: before AP; OAP: on-admission with AP; DAP: during AP; HbA1c: hemoglobin A1c; HTG: hypertriglyceridemia; β: Beta coefficient; SE: standard error; p: P-value; OR: odds ratio; 95% CI: 95% confidence interval.

BAP –HbA1c						
Predictor		β	SE	p	OR	95% CI
Age	per years	0.045	0.012	***<0.001***	1.046	1.021-1.074
Gender	female (vs. male)	-0.252	0.361	*0.486*	0.777	0.376-1.565
Diabetes Mellitus	<0.001	-0.310	0.479	*0.518*	0.734	0.273-1.807
HbA1c	per 1.0%	0.028	0.139	*0.843*	1.028	0.768-1.332
	alcoholic (vs. biliary)	0.491	0.519	*0.345*	1.634	0.562-4.414
	HTG (vs. biliary)	2.271	0.624	***<0.001***	9.690	2.737-32.572
Etiology	Combined (vs. biliary)	1.295	0.579	***0.025***	3.651	1.076-10.877
	Idiopathic (vs. biliary)	0.306	0.478	*0.522*	1.358	0.501-3.359
	Other (vs. biliary)	-1.153	1.048	*0.271*	0.316	0.017-1.628
OAP – on-admission serum glucose						
Predictor		β	SE	p	OR	95% CI
Age	per years	0.031	0.007	***<0.001***	1.032	1.017-1.047
Gender	female (vs. male)	0.007	0.232	*0.976*	1.007	0.638-1.587
Diabetes Mellitus	<0.001	-0.626	0.291	***0.031***	0.535	0.295-0.927
On-admission glucose	per 1 mmol/l	0.123	0.024	***<0.001***	1.131	1.078-1.186
	alcoholic (vs. biliary)	0.625	0.335	*0.062*	1.868	0.958-3.581
	HTG (vs. biliary)	1.647	0.438	***<0.001***	5.190	2.130-11.992
Etiology	Combined (vs. biliary)	0.993	0.441	***0.024***	2.699	1.071-6.160
	Idiopathic (vs. biliary)	0.549	0.271	***0.043***	1.732	1.012-2.941
	Other (vs. biliary)	-0.362	0.616	*0.557*	0.697	0.165-2.007

DAP – peak serum glucose						
Predictor		β	SE	p	OR	95% CI
Age	per years	0.009	0.011	*0.422*	1.009	0.988-1.032
Gender	female (vs. male)	-0.096	0.349	*0.783*	0.909	0.454-1.797
Diabetes Mellitus	<0.001	-0.888	0.431	***0.039***	0.412	0.167-0.919
Peak glucose	per 1 mmol/l	0.089	0.026	***<0.001***	1.093	1.039-1.152
Etiology	alcoholic (vs. biliary)	-0.009	0.560	*0.987*	0.991	0.313-2.890
	HTG (vs. biliary)	1.369	0.621	***0.028***	3.932	1.115-13.092
	Combined (vs. biliary)	0.622	0.702	*0.375*	1.862	0.391-6.680
	Idiopathic (vs. biliary)	0.668	0.408	*0.102*	1.951	0.878-4.414
	Other (vs. biliary)	-0.535	0.802	*0.505*	0.586	0.086-2.331

Table 8: Binary logistic regression for severity, accounting for age, gender, diabetes mellitus, acute pancreatitis etiology and: on-admission hemoglobin A1c in the BAP grouping, on-admission serum glucose in the OAP grouping, highest in-hospital serum glucose in the DAP grouping. AP: acute pancreatitis; BAP: before AP; OAP: on-admission with AP; DAP: during AP; HbA1c: hemoglobin A1c; HTG: hypertriglyceridemia; β: Beta coefficient; SE: standard error; p: P-value; OR: odds ratio; 95% CI: 95% confidence interval.

III.4. Discussion

Pancreatic inflammation together with cell death are the end steps of an intricate interplay of events – as described by the model of "multiple hits on multiple targets", various signaling pathways are activated resulting in the clinical entity of AP (41). The main alterations observed inside the acinar cells are the increase in calcium concentration, increase in the number of lysosomes and zymogen granules, leading to mitochondrial dysfunction, endoplasmic reticulum stress and premature trypsinogen activation (24). These changes can be initiated either by ductal obstruction (42, 43) or by the direct acinar effect of various pancreatotoxic agents (12, 44). The most common culprits responsible for pancreatic toxicity are bile acids, alcohol and its metabolites, but fatty acids and fatty acid ethyl esters are also described to initiate the above-mentioned pathways in a dose-dependent manner (12, 13, 15, 16, 45). And observations go beyond basic science – cohort studies also describe hypertriglyceridemia to be dose-dependently associated with increasing severity and rate of complications (14).

There is a layered relationship between DM and AP. In severe AP cases with substantial pancreatic necrosis, β-cell loss can lead to the development of DM (46). But even in moderate and mild AP, impaired β-cell function and insulin resistance are observed in more than 30% of the cases (47), leading to a two-fold risk for developing diabetes after experiencing a single episode (48, 49). At the same time, cohort studies described a 1.5-3 times higher risk of AP among type 2 diabetic individuals – a possible reason behind this are the overlapping risk

factors (e.g., obesity and hypertriglyceridemia) (27, 50-52). Another key point in the many intersections between these two conditions is the higher severity of AP in individuals with pre-existing DM. A meta-analysis of cohort studies described a significantly higher risk of complications, intensive care unit (ICU) admission, and mortality as compared to non-DM individuals (53). In a pancreatitis rat model, streptozotocin-induced hyperglycemia significantly reduced the pancreatic amylase content, which the investigators believed to be due to the direct harmful effects on acinar cells (19). This indicates that glucose itself could be involved in AP as a potential pancreatotoxic agent. So far, clinical investigations were limited to discussing the role of DM – and neglected the glycemic state.

Our study is the first to focus on how alterations of the glucose homeostasis affect clinically relevant outcomes of AP. We found on-admission and peak in-hospital serum glucose concentrations to have a statistically significant dose-dependent relationship with AP severity, mortality, LOH, maximal CRP, systemic and local complications. Both these variables are independently (accounting for DM, age, gender and etiology) associated with AP severity and mortality, a peak in-hospital glucose >7 mmol/l making severe AP almost 15 times and death almost five times more likely. While statistically significant dose-dependency was only identified with LOH and maximal CRP in case of HbA1c, a trend of increasing severity and rate of local complications was also noted. In light of the currently available scientific literature on the matter, these findings strongly suggest that glucose has a direct pancreatotoxic effect.

The main step in glucose-mediated cytotoxicity is the intracellular increase in reactive oxygen species (ROS) (54). ROS also have a central role in the process of pancreatic inflammation, promoting pathways towards mitochondrial dysfunction, cell death and inflammation in a self-amplifying manner (55, 56). Another way in which glucose could potentially harm the pancreas is via influencing its vasculature. Increased ROS production inside endothelial cells in hyperglycemia causes microvascular endothelial dysfunction by decreasing nitric oxide availability and increasing permeability, leukocyte adhesion and procoagulant activity (57). Such microvascular disturbances contribute to the inflammation of the ischemia-sensitive pancreas (58).

While we demonstrated dose-dependency and independent association with AP severity and mortality, the whole extent of worsening AP outcomes should not exclusively be attributed to glucose. As hyperglycemia often presents in the context of DM and metabolic syndrome, the prevalence of these conditions accumulates with increasing glucose concentration. Here, an increased rate of hypertriglyceridemia, cholelithiasis and possibly β-cell hypertrophy facilitate the formation of AP (59-62), with hypertriglyceridemia also being associated with a

more severe disease course (63). Accordingly, in our cohort, we observed a growing proportion of hypertriglyceridemia with increasing serum glucose and HbA1c values. Severity and mortality however, only increased parallelly with on-admission and peak glucose, but not HbA1c. This might partly be due to the low participant and event numbers in the higher HbA1c groups – 83.9% of cases had HbA1c values below 6.5% - and partly because HbA1c indicates the preceding three months' glucose homeostasis, not necessarily reflecting glucose levels at the time of the AP. All in all, the fact that the proportion of hypertriglyceridemia increased with all three variables, but severity and mortality only did so with serum glucose further reinforces the results of our binary logistic regression, underlining the potential pancreatotoxic nature of hyperglycemia.

Apart from signaling a transient dysregulation, on-admission and especially peak in-hospital hyperglycemia could also be caused by new-onset pancreatogenic DM. A common concern is that AP episodes that are more severe might have a higher likelihood of substantial β-cell death; this could increase the proportion of severe cases among those with high glucose values. However, clinical studies do not support the association between AP severity and newly diagnosed DM (64). DM and thus pathological serum glucose values can be overrepresented in CP cases, 25-80% of CP patients develop DM (65). Acute exacerbations in people with CP are known to be less severe (66), possibly decreasing severity and mortality in higher HbA1c and glucose groups, but we found a balanced distribution of CP among groups.

Strengths and limitations

Strengths: To our knowledge, this is the first clinical study focusing on the role of glucose homeostasis in AP, observing the presence of dose-dependency with its clinically important outcomes. We succeeded in demonstrating dose-dependency and independent association with AP severity and mortality for both on-admission and peak in-hospital serum glucose. The data source is a prospective cohort, boasting an impressive number of patients from multiple centers worldwide, enhancing the applicability of our results. As described in the 'Methods' section we also applied a rigorous quality control system, to ensure the validity of our data.

Limitations: A limitation to our study is that glucose values cannot be separated from the underlying DM and metabolic comorbidities, possibly influencing outcomes. Nevertheless, we feel that they should not be separated: although more likely in diabetic patients, hyperglycemia can occur and elicit pancreatotoxicity in any subpopulation. Distinguishing exactly what causes the dysregulation in each patient was beyond the scope of this clinically oriented cohort analysis – an interesting question nonetheless for future studies. Another limitation is that DM

is overrepresented in the BAP subcohort (23.0% of HbA1c measurements happened in known diabetic participants). Only 26.5% of patients had at least two glucose measurements during their hospitalization, predominantly those with abnormal on-admission values (44.7%). As mentioned in the 'Methods' section, capillary glucose values (although representing the minority of cases) were also accepted. In an attempt to form groups based on established cut-offs and equal increments, some groups ended up having relatively low participant numbers, weakening statistical power.

Implications

Prevention: Increased HbA1c was associated with higher severity and a higher rate of local complications. Maintaining a normal glucose homeostasis might reduce the risk of these events.

Prognosis: Increased on-admission glucose has a dose-dependent association with increasing severity, mortality, LOH and complications of AP.

Prompt treatment: High peak glucose is dose-dependently associated with a higher rate of severe cases, mortality, systemic complications and increased LOH. Hyperglycemia does not necessarily present on admission, monitoring serum glucose during the course of AP is crucial. Adequate in-hospital control of hyperglycemia can greatly contribute to the treatment of AP.

IV. TRANSLATIONAL MEDICINE IN THE COVID-19 PANDEMIC

The arrival of the COVID-19 pandemic and the ensuing humanitarian crises immediately shifted our focus. Through tremendous efforts, we formed an interdisciplinary team applying the methods of TM. Our ultimate goal was to aid the Hungarian government in this desperate and seemingly hopeless situation to best handle the pandemic, so together, we can achieve the best possible medical and economical results. We mathematically modelled intensive care unit (ICU) capacity, regional differences, Gross Domestic Product (GDP) loss, etc. and forwarded the information to policy-makers. During our systematic review of the available literature, we noted the need for RCTs testing telephone-based lifestyle interventions. We designed and initiated the PROACTIVE-19 trial to fill this void.

IV.1. TRANSLATING SCIENTIFIC KNOWLEDGE TO GOVERNMENT DECISION MAKERS: MATHEMATICAL MODELLING STUDY

IV.1.1. Introduction

TM is an enterprise that aims to translate scientific evidence for community benefits in order to elevate the health level of a society (67, 68). It is essential to find a way to translate scientific findings into digestible information for the general public, healthcare professionals, insurance companies, leaders of institutions and governmental policymakers (69-72). This latter has particular importance in times of epidemics and humanitarian crises, when government officials have a short time to make critical decisions (73, 74). The foretelling of future scenarios and forwarding evidence-based information for policymakers are paramount during pandemics (75-78).

Unsurprisingly, countries like Israel, Switzerland, Germany, Canada, South Korea (79-82), handled the COVID-19 outbreak with better outcomes, where the science level is high and the government listened to scientists. In Italy and Spain, where the scientific activity is lower (83) and in the USA where the governments failed to listen to scientists early enough, the initial consequences of the pandemics were more devastating (84).

In Hungary, the first COVID-19 patient was identified on the 4th of March, 2020. Wisely, the Hungarian government immediately started a conversation with expert scientists and health care professionals to assess the potential future scenarios before decisions on the epidemic were taken. Our Translational Action and Research Group against Coronavirus so called KETLAK released and handed two documents directly to the National Epidemiological Policy-Making Body which was lead by the Prime Minister of Hungary to help the decision making process related to the Easter holidays and gradual normalization of public life. Here we summarize the scientific methodology, results, and suggestions which had a vital impact on the Hungarian government's decisions.

IV.1.2. Methods

To support the epidemiological decision-making process, we performed several scientific data analyses and formulated them into three chapters: 1) results, 2) problems, 3) suggestions. The two materials were submitted on the 9th and 19th of April and one of the members of KETLAK introduced the conclusions personally (85).

Modeling the ICU bed capacity in Hungary.

In our mathematical model we calculated that above 3,000 beds, due to the significant decrease of human capacity, i.e., the effectiveness of treatments, the mortality rate will significantly increase as we saw it in Wuhan, Italy or New York (86-88). Therefore up to 3,000

ICU beds we calculated with 30% mortality, whereas above 3,000 ICU beds with 60% mortality.

Mathematical modeling of the COVID-19 epidemic in Hungary

To predict the possible outcome over time for various R metrics, data was collected on the 8th of April 2020 from the official Hungarian data resource site (koronavirus.gov.hu). Input parameters of the model included the actual R metric, the total numbers of infected cases up to the 8th of April and the available and occupied ICU beds. The model was generated both for the whole country and separately for all its main regions. In the case of Budapest, for example, R was estimated to be 1.25, the number of reported infected cases 552, and the available ICU beds is 750. Additional parameters were set based on the available international data such as the rate of how many of infected cases would end up in the intensive care unit (2-4%), the number of days one patient would spend there (~2 weeks) and the total death rate of ICU patients (30%) (87).

Modeling the regional differences in Hungary: the complex health distance index (CHDI)

For the measurement of the regional differences of health status in Hungary, we adopted and restructured the approach of the functional distance index from the economic analyses (89, 90). Our *Complex Health Distance Index (CHDI)* in addition to the availability of the health care institutions (physical distance component) takes into account, the social, economic and institutional characteristics of the analyzed regional units (settlement, district, county etc.) and the main indicators of the health status of the local (91).

Modeling the GDP loss, economic crisis management, and competitiveness

Our mathematical model focuses on quantifiable variables, and takes into account data of the previous years and currently available data. It means that it works with the average per-capita GDP, the population of the given region and the healthcare data related to morbidities and fatalities. To model the GDP loss for the five main Hungarian regions, GDP was corrected and normalized by the estimated death rate, predicted by the first model, for all the main Hungarian regions separately.

Modelling the impact of closing and reopening elementary schools

Classic SIR (susceptible-infected-recovered) simulation using EpiFire 3.34 API software was applied to model contact network of epidemic transmission using the ‘small-

world-like' model to compare epidemic scenarios for closing and reopening schools in the current COVID-19 pandemic. This model was developed by Carrat et al. and used as a flexible tool to determine interventions in influenza pandemic (92). The model captures changing disease transmission dynamics (93).

Modeling the optimal screening strategy in Hungary

A Hungarian-specific model was developed to estimate the optimal screening strategies, i.e. the number of screening tests needed for recommendations to keep R under a required level. These were calculated for all regions, the individual counties of the region, and the whole country under various cases of lifting the socio-economic lockdown. The calculation was made in R software (94).

IV.1.3. Results

First we modeled different scenarios to the decision-makers in which we estimated the number of deaths in relation to the predicted number of new cases (number of people infected) together with the modeled numbers of available and occupied ICU beds. The best case scenario for the whole country, using R metrics estimated on the 8th of April, shows that maintaining the restriction would result in a total of 20,000 new cases at its peak, there would still have enough number of ICU beds to cover the needs for the most serious cases, and therefore, the total death would be kept under 1,500 (Figure 5A). The worst case scenario was modeled for higher R metrics (R=2.2), i.e., what would happen for the whole country in case of removing all the restrictions. The numbers indicate that within three weeks there would not be enough ICU beds, as we would have been sort of 40,000 at the peak, the number of infected cases would have reached 550,000 and the number of deaths was predicted to be 70,000 (Figure 5B).

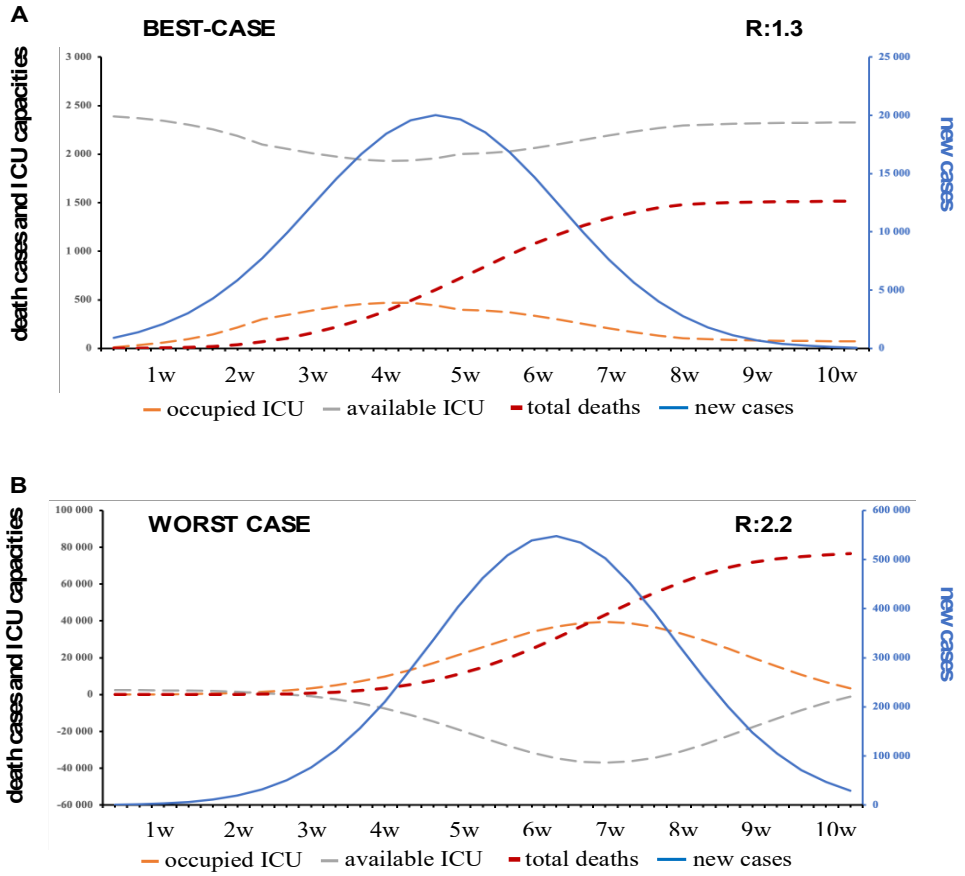

Figure 5. Mortality scenarios for the whole country with 2 different R metrics. (A) Best-case scenario with R set to 1:3. (B) Worst-case scenario with R set to 2.2. In both cases, the left side of the y-axis stands for numbers presented by the dashed-line curves, such as the total death, occupied and available ICU beds (in red, orange and gray, respectively), the right side of the y-axis stands for the numbers presented by the single normal line curve (ie, the predicted new cases [in blue]). The numbers of available and occupied ICU beds are in close connection and if one is decreasing, the other is increasing by the same number. When no more ICU beds are available, the number will go to less than zero, showing the lack of ICU beds. ICU: intensive care unit

Then we investigated the regional differences in Hungary. Our mathematical models clearly indicated that Hungary could not be handled as a whole, but rather regional differences should be taken into account. It was clearly seen when we looked for each region separately the regional distribution of people over 65 years, the differences between the ICU capacities, the estimated GDP loss due to lack of labor force, and the inequalities in CHDI. Therefore the earier modeled best case scenario was also modeled for each region separately. Although we can see big differences between the regions, there would be enough hospital capacity in case of maintaining the socio-economic lockdown. The worst case scenario for each region separately indicates that none of the region would have enough ICU bed capacity. Moreover, clear differences can be seen in how many weeks a region can survive with the available

number of ICU beds. As expected, regions where these numbers reach earlier the limits would suffer the most in mortality.

Next we provided disease transmission simulations to help crucial decisions on closing and reopening elementary schools. The disease transmission simulation model of Budapest can be seen in Figure 6. According to our calculations for Budapest in the case of the R=2.2 or higher, large epidemic size classes are prone to face fast disease transmission with relatively high frequency. In this case, the chance for an effective health policy intervention to suppress or mitigate the epidemic cycle is very low. Thereby we don't suggest early or complete release of school closures, moreover we support a prolonged and stepwise opening towards the contact education in the elementary schools. The epidemic size estimations for the county seats seem to be more controllable with smaller subgroups develop the epidemic outbreak with higher frequency even in our baseline R=2.2 scenario. Thus there is a real likelihood to carry out the proper intervention at the level of the Hungarian public health and health care capacities.

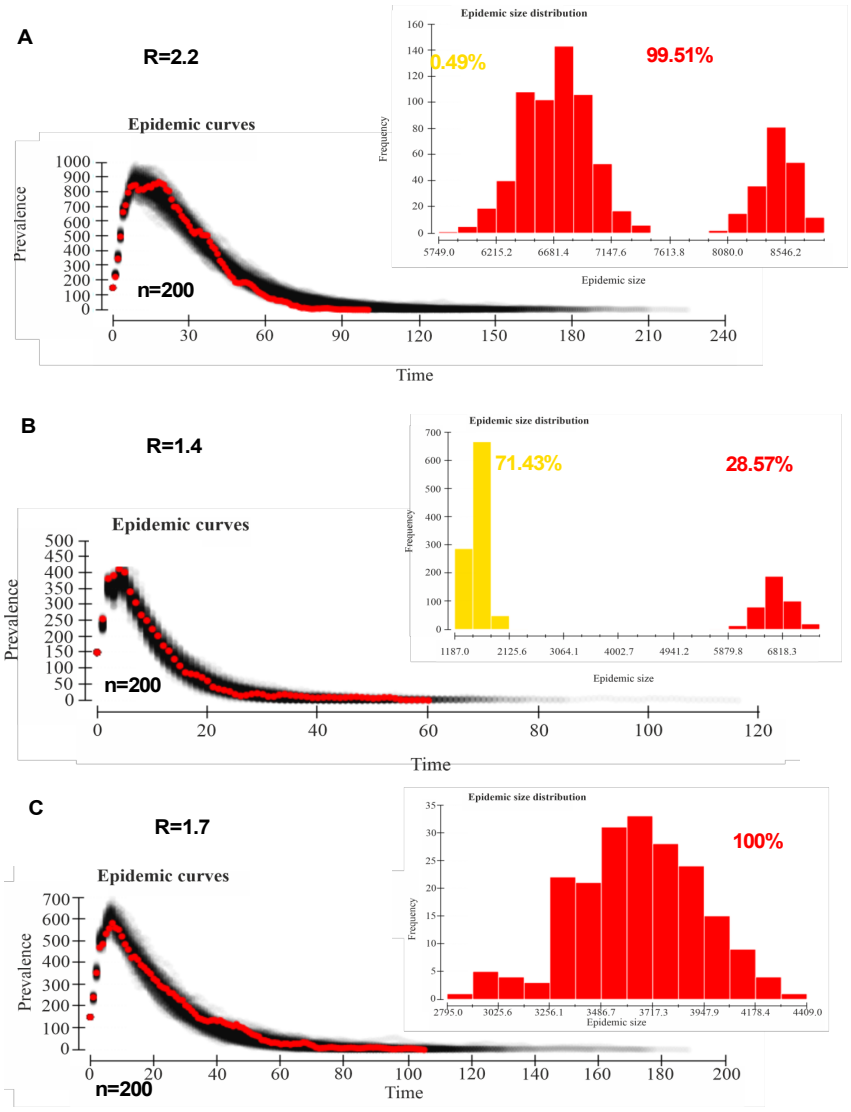

Figure 6. Impact of closing and reopening elementary schools in Budapest. Simulation models of disease transmission dynamics to demonstrate the COVID-19 outbreak in Hungary with the reproduction rate (R) = 2.2 (A) and the effect of closing (R= 1.4) (B) and reopening (R= 1.7) (C) elementary educational institutions in Budapest. (n = 200 simulations were run for each R scenario.)

Since it was earlier suggested that higher number of tests results in a lower rate of mortality, we compared the number of tests performed in different countries. We can clearly conclude that the amount of daily testing highly determines the rate of subsequent mortality

Figure 7A show that the amount of tests are very low in Hungary. Internationally available data show that Germany is one of the most efficient European countries to keep the mortality rate low. Using this number as a reference point, we have estimated the optimal number of tests needed in Hungary. Figure 7B. After that, numbers from Figure 7B were corrected for each county by regional hospital capacities, such as ICU beds, the GDP, and the CHDI (Figure 7C). Using these parameters, Figure 7D and 7E show how many tests would be needed in case of easing the restrictions by reopening the primary schools and completely reopening the whole country, respectively.

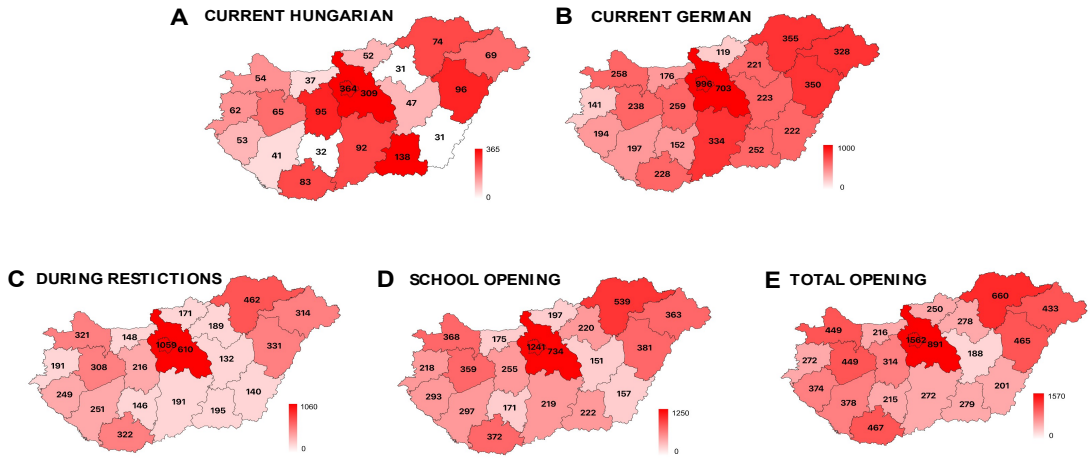

Figure 7. Current testing in Hungary and in Germany. (A) Number of tests for all counties (for 100,000 people) in Hungary on April 8, 2020. (B) Required number of tests for the regions if the German testing rate (50,000 tests per day) is taken as a reference. Suggested testing in Hungary calculated from the German testing number modified by the Hungarian ICU capacity, GDP and CHDI. The optimal number of tests based on the German testing rate, corrected by ICU capacity, GDP, and CHDI, in case of maintaining the restrictions (C), reopening primary schools (D), and removing all the restrictions except for the elderly (E). All numbers are corrected to the population of the given county. CHDI: Complex Health Distance Index; GDP: gross domestic product; ICU: intensive care unit.

IV.1.4. Discussion

The tasks of the scientific community include recognizing challenges in specific circumstances, conducting high quality research based on scientific methodology, preparing

evidence-based summaries of scientific results and communicating them in understandable language to the target groups where the knowledge can be utilized. The latter includes two-way communication between the scientific community and government decision makers as well. An excellent example of this is the European Commission's Scientific Advice Mechanism system, in which the High Level Group of Scientific Advisors and Academies provide timely, independent scientific advice to the highest policy level in Europe and for the wider public to support their decision making (95, 96). This is especially important in situations where there is a short time to make key decisions that affect the daily lives and health of the population. In this article we present the preparation and summary of two important scientific materials and their effects in Hungary.

There were recent epidemics caused by members of the coronavirus family. These epidemics had different dynamics and characteristics. The deadly outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 in Toronto, which claimed 43 lives among 253 infected patients, was successfully contained by a rapid and efficient response by scientists and politicians fighting it shoulder to shoulder (97-99). The successful strategy against the current SARS-CoV-2 pandemics of South Korea stemmed from their recent bitter experience with the Middle East respiratory syndrome (MERS) outbreak. They learned the lesson that only scientific evidence could guide political decisions in an epidemic (100).

Here we show direct scientific evidence that there is a large difference between the territorial patterns and the economic, social and healthcare structures in Hungary, which can have an impact on the spread of the pandemic. Therefore, besides using the available international data we counted the major influencing factors such as age differences, ICU bed availability, and the differences between the CHDI separately in our later analysis. Since a pandemic is not only health but also a socio-economic crisis, we took the regional GDP differences into account as well. It was also important since the socio-economic crisis structures that evolve after the pandemic ends will also display various patterns deriving from pre-crisis specificities and the dynamic variables observed during the crisis. The former can be changed with a slow process, while the latter, once understood, may play a key role in spatial organization.

Previous modeling studies from the 2003 SARS outbreak in mainland China, Hong Kong and Singapore, the 2009 H1N1 influenza pandemic in Taiwan as well as limited information from clinical reports from the 1957 Asian influenza pandemic, where R was estimated to be similar to COVID-19 provide different results and divergent aspects of effect estimation (101-105). Even using mathematical models for the very same SARS outbreak in

2005, the estimated effect of school closure was calculated to be very different from the disease transmission reduction (106). Studies modeling the COVID-19 pandemic (107-110) support the restriction measures including the closure of educational institutions at national levels, however literature data is gappy on the estimation of school closure intervention separately from other strict and the general social distancing control.

Here we could draw conclusions that education institution closure as well as contact management strategies in schools populations cannot be seized or estimated as a homogenous effect on disease transmission. Different urban models with differing school population size, contact density and dynamics and additional different inhabitant population in the background can shape the infection transmissibility and its impact on epidemic progression significantly.

In addition to the results gained from the modeling of the mitigation and suppression-based strategies and the disease transmission network dynamics had a dire message too. If we can't reduce the R value, we have no chance of finding a good solution to restart the lives of the population. Therefore, we concentrated on the methods which can help to decrease the R value. We revealed that the number of screening and testing could have large effects on mortality. Data showed that Germany is one of the most efficient European countries to keep the mortality rate low. Therefore we used their numbers as a reference point to estimate the optimal number of tests needed in Hungary. However, in order to be specific to the conditions of the regions, the number of tests likely to be required was corrected for each county by regional hospital capacities, such as ICU beds, the GDP, and the CHDI index. We must admit that our CHDI will need further modifications in the future.

To provide the most detailed assistance to decision makers, we also analyzed the numbers of tests required to resolve the restrictions by region. In the current phase of the COVID-19 pandemic the proper diagnostic tool to identify individuals who can potentially communicate the infection is the polymerase chain reaction (PCR) based molecular assay which detects RNA target regions of the SARS-CoV-2 pathogen's nucleic acid (111-113).

Considering the capacities available for PCR 4,000-6,000 testing is the maximum limit of the successful feasibility calculated on the 18th of April, 2020. During the elaboration of a complex testing and screening strategy we aimed to fit it close to the accessibility rather than aiming to reach perfection. However, we would like to highlight that continuous effort should be made to strategically enhance the throughput of COVID-19 PCR testing and screening at this stage. Serological testing should also be a testing issue as the COVID-19 begins to subside to detect the immunized state of the population. Therefore, we recommended testing

approaches for symptomatic patients, healthcare professionals and highlighetd the importance of residential base representative screening.

Similar to the European Commission, 4-5 high level groups of scientific advisors help the decision-makers in Hungary, so it is challenging to judge which analysis has a decisive impact on the final decisions. There were several similarities and differences in the analyses of the research groups. While, for example, the ITM Network Mathematical Epidemiology Group was primarily unique in the analysis of contact numbers, our multidisciplinary KETLAK consortium highlighted (1) the need for regional thinking and (2) the calculation of the effect of real health capacities on mortality scenarios.

Importantly, it seems that the analyses described here and presented to the National Epidemiological Policy-Making Body could have major impact on governmental decision-making since several of these suggestions has already taken effect before the submission of this article for publication. For example:

(1) previous considerations of the possible lifting of restrictions during the Easter holidays were rejected and lifting the restrictions were postponed for approximately a month (114),

(2) regional variations of the epidemic have been introduced; restrictions will be eased in less densely populated areas while Budapest and surrounding area will remain under a more strict control,

(3) the importance of increasing the number of testing has been recognized by the authorities,

(4) a representative population screening study was recently initiated which involves more than 10000 volunteers and the concerted effort of the country's four medical university (115).

In conclusion, in times of epidemics, the formation of interdisciplinary research groups is essential for policymakers, as none of the disciplines can model the complex problems that arise during an epidemic alone. The establishment, research activity and participation in decision-making of the KETLAK group can serve as a model for other countries, researchers and policymakers not only in managing the challenges of COVID-19, but in future pandemics as well.

IV.2. PERSONALIZED HEALTH EDUCATION AGAINST COVID-19 (PROACTIVE-19): PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL

IV.2.1. Introduction

World Health Organization (WHO) announced the COVID-2019 outbreak pandemic in the morning of 12 March 2020 (116). At the time of writing this study protocol, there are more than 770,000 confirmed cases with 37,000 fatalities across 178 countries, according to the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University, including 447 cases and 15 deaths in Hungary. The tendency predicts that the epidemic is far from its peak (117).

As often seen in the case of other epidemics, most cases can be asymptomatic or develop only mild symptoms and remain undiagnosed. Therefore, it is difficult to estimate the true incidence and the disease outcomes precisely (118) (119). However, early reports indicate that it may require ICU admission in 5-26%, due to acute respiratory distress syndrome (ARDS) in 17-20%, and overall mortality can rise to 11% of the recognised cases, mostly affecting the elderly (120-123).

Significant efforts have been invested in research and development to re-target existing and discover new pharmacological treatments and preventive strategies against COVID-19 (124), as indicated by the number of submitted protocols of the currently recruiting randomized trials on ClinicalTrials.gov. Nevertheless, it must be noted that we lack evidence-based targeted pharmacological therapy for prevention and treatment alike (125). None of the registered studies investigates the effects of lifestyle interventions in the prevention of poor outcomes in the COVID-19 epidemic. Advanced age and pre-existing comorbidities, such as cancer, cardiovascular disease, or diabetes mellitus, predispose to a more severe disease course and ICU admission (121, 126-128).

The high risk of being infected with SARS-CoV-2 as well as the social distancing and quarantining as primary recommendations for the suppression of virus transmission may generate a high level of anxiety and mental stress (129, 130). In infected patients, better mental health might even have a positive impact on disease progression and survival (131, 132). Therefore, efforts for better coping with the aversive psychological states caused by the COVID-19 outbreak have high importance in mental health resilience. The role of lifestyle factors and fitness in the severity of COVID-19 has remained unexplored except for two recent studies. The history of smoking is independently associated with disease progression (OR=14.3, 95% CI: 1.6-25.0) in a Chinese cohort of 78 patients (133). Body mass index was >25 kg/m^2 in 88% of patients who died as compared to 19% in survivors in another Chinese cohort of 112 patients (134). The latter seemingly contradicts the results of a very recent registry analysis of almost 100,000 participants where higher body mass index (indirectly,

better nutritional status) proved to be neutral or even preventive although against non-COVID-19 upper airway infections (135). These suggest that personalized lifestyle interventions via education or counselling could be beneficial for COVID-19 outcomes.

Our main objective is to evaluate the effects of a personalized multicomponent lifestyle intervention aiming to improve the outcomes of COVID-19 infection in the population over 60 years in a randomized clinical trial. The main hypothesis of PROACTIVE-19 is that the personalized multicomponent lifestyle intervention reduces the rate of our composite outcome consisting of the need for intensive therapy, hospitalisation, and mortality in the COVID-19 population.

IV.2.2. Methods

Design

The study protocol is structured following SPIRIT 2013 (136). PROACTIVE-19 is a pragmatic, randomized controlled clinical trial with adaptive "sample size re-estimation" design. This design allows interim analyses and necessary modifications of the sample size of the ongoing trial to ensure adequate power (137).

Legislative amendment and ethical approval

In Hungary, Act CLIV of 1997 on Health and Decree No. 23/2002 (of 9 May 2002) of the Minister of Health on Biomedical research on human individuals (as amended) stipulates the procedure for non-interventional investigation, according to which: 1) the leader of the investigation or the investigator shall inform the subject both verbally and in writing, before obtaining the consent of the subject to participate in the clinical research; 2) the participants' informed consent shall be written. This Act and Decree would not have allowed commencing the clinical trial as it would have amounted to a criminal offence. Based on our request sent to the Prime Minister of Hungary to amend the Decree, the Government of Hungary, issued Government Decree No. 63/2020 of 24 March 2020, according to which the new decree amends: 1) in addition to Section 159 of Act CLIV of 1997 on Health, subjects with full disposing capacities can be informed about the non-interventional investigation qualified as clinical research on coronavirus via means of telecommunications; 2) subjects may consent to participate in the clinical research through telecommunications; 3) subjects may withdraw their consent through telecommunications.

Ethical approval: Scientific and Research Ethics Committee of the Hungarian Medical Research Council (IV/2428- 2 /2020/EKU).

Study population

Inclusion and exclusion criteria

The inclusion criteria of our selective primary prevention programme are: (1) age over 60 years (that is, high-risk individuals), (2) informed consent to participate. The exclusion criteria are: (1) confirmed COVID-19 (active or recovered); (2) hospitalisation at screening for eligibility; (3) someone was already enrolled in the study from the same community/household (to avoid potential crosstalk between the study arms).

Flow and timing

A toll-free phone number will be available for all interested in participation. By dialling this number, the participant will be informed about the trial through a pre-recorded voice message, including the study rationale, conditions of participation, the process of the study, and the information on data protection. Willing participants will be redirected to an available operator, who will ascertain eligibility. Following verbal consent and randomization, the operator will obtain key personal information of the participants and all study-related information (Fig.1.). The allocation will not and can not be concealed from the operator, but it will be concealed from everyone else (participants, caregivers, outcome assessors).

Interventions

Participants will be randomized into two groups: (A) general health education; (B) personalized health education. They will go through questioning and recommendations in 5 domains: (1) mental health, (2) smoking habits, (3) physical activity, (4) dietary habits, and (5) alcohol consumption. Both groups will receive the same line of questioning to assess habits concerning these domains.

Group A: questioning will be done in the order as mentioned above, followed by a general health education aiming towards improvement of these factors with general recommendations (the expected mean duration is approximately 10 min).

Group B: questioning will be done in the same structured order, but an assessment of each domain will be followed by personalized recommendations (the expected mean duration is approximately 20 min).

After the first contact, there will be follow-up calls in both groups, with a matching schedule: every week in the first month, every second week in the second month, then monthly. During these encounters, all change in all five domains since the last call will be assessed.

The operators will have received any healthcare education. Before enrolling participants, the operators will have to complete a standard training program consisting of seminars on the interventions held by medical professionals, followed by practice of scenarios. The operators will be trained not to give additional healthcare advice, and we will not secure other information sources, including electronic and printed material.

Outcomes

Based on literature data (120, 138), **the primary endpoint** will be defined as the composite of any of the followings in COVID-19 cases (an accredited laboratory should verify positivity) the rate of:

1. ICU admissions
2. hospital admissions (longer than 48 hours) for the following reasons
    - arrhythmia (causing hemodynamic instability and requiring continuous monitoring and/or cardiac support, as indicated by mean arterial pressure <65 mm Hg, and/or serum lactate >2 mmol/L) and/or
    - ARDS (severe hypoxemic respiratory failure indicated by a PaO_2/FiO_2 <300 mm Hg according to the Berlin definition) (139) and/or
    - circulatory shock (the requirement of continuous vasopressor support to maintain mean arterial pressure ≥65 mmHg and/or serum lactate ≤2 mmol/L) and/or
3. deaths.

Secondary endpoints are the followings:

1. the number of general practitioner visits,
2. the number of emergency, hospital, and intensive care admissions;
3. the LOH and ICU stay,
4. the number of organ dysfunctions and failures (central nervous system, cardiovascular, respiratory, renal, liver, hematological),
5. the measurable lifestyle changes (including physical and mental health),
6. the costs of care.

The primary and secondary outcomes will be assessed upon the conclusion of the trial, at least one year after the enrollment of the last participant.

Randomization and blinding

Computer-generated random sequence randomization (central) will be performed, after giving informed consent. Due to the expected large sample size, we will use simple randomization. The allocation ratio will be 1:1. No stratification or blocking will be applied. In the study, participants will be blinded to the knowledge of the details of differences between the interventions. Everyone else (outcome assessors, caregivers, and data analysts) will be blinded regarding the allocation.

Sample size calculation, interim and final analyses

The primary outcome is estimated to occur in 20% of COVID-19-infected cases (≥60 years of age) receiving the standard of care based on Chinese reports (120). Due to the lack of data, we hypothesised that our intervention would result in a 50% risk reduction. Considering one interim analysis on efficacy (with the Pocock correction), 90% power, 5% alpha (superiority design, two-sided), a dropout rate of 20% (140, 141) and assuming 10% incidence of COVID-19 in the target population, the estimated sample size is 3788 (rounded up to 3800) subject per study arm. The calculation was performed by Stata (version 15, Philadelphia, the USA).

We plan to hold three interim analyses: the first for sample size re-estimation at 5% of the target sample size due to the dropout rate, the second for safety assessment at 10% of the target sample size and a third for efficacy assessment and sample size-reestimation at 50% of the target sample size. Early stopping will be executed if (1) safety concerns arise during the interim analysis, (2) the statistical power reaches at least 90% and $p<0.05$ at the efficacy interim analysis (stopping for benefit), (3) the statistical power does not reach 10%, $p>0.05$, and the event number does not reach the assumed 10% for the whole population at the efficacy interim analysis (that is, 380 events for the primary outcome - otherwise, the interim analysis is postponed and repeated when the event number reaches 380 events) (stopping for futility), (4) the consequences of the pandemic make further recruitment or follow-up impossible (stopping for unfeasibility).

In the final analysis, the intention-to-treat analysis will be favoured over per-protocol (or "as-treated") analysis. We expect a full dataset for the primary endpoint (since the Hungarian Ministry of Interior will provide these data). If for any reason, data will be missing for the primary outcome, we will use available case analysis. The "last observation carried forward" strategy will be followed to impute missing data for other outcomes measured during the study. Missing more than one consecutive interventions after the initial assessment or

withdrawal of consent during follow-up result in the dropout of the patients unless hospitalisation is required in the meantime.

In descriptive statistics, the count and percentage will be provided for each treatment arm for binary outcomes. For continuous outcomes, n, mean, median, interquartile (Q3–Q1), standard deviation, minimum, and maximum values will be provided for each treatment arm. In a univariate comparative analysis, we will calculate relative risk with 95% confidence interval (CI) when comparing the primary endpoint between two groups (alpha=5%) with a reference arm using non-repeated intervention complemented with chi-square or Fisher's exact test (the same strategy will be followed for binary secondary outcomes). For continuous variables, we will use t-test assuming unequal variances or the Mann-Whitney test. We will perform univariate (Kaplan-Meier and Cox-regression) and multivariate (Cox-regression) survival analysis for binary outcomes. An adjustment will be carried out at least for age, sex, and education. Mixed effect logistic regression will be conducted to estimate the effect of the multicomponent intervention on the outcomes, where the subject IDs will be used as a random subject. The model will be adjusted for changes in smoking habits, alcohol consumption, physical activity, and dietary habits (or body mass index).

All analyses will be carried out with SPSS version 26 and Stata version 15.

Study duration

The planned starting date of the study is 1 April 2020, and the anticipated finishing date is the end of the pandemic or development of the vaccine, but no more than one year from the enrolment of the last participant.

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	0	0	0	Weekly in the 1st month	Every second week in the 2nd month	Monthly from the 3rd month	1 year*
ENROLMENT							
Eligibility screen	X						
Informed consent	X						
Randomization		X					
INTERVENTIONS:							
Intervention A General guidance			X	X	X	X	X
Intervention B Personalized guidance			X	X	X	X	X
ASSESSMENTS:							
Questionnare			X	X	X	X	X

Table 9: Schedule of enrollment, interventions, and assessments according to the SPIRIT statement. The asterisk indicates that the anticipated finishing date is the end of the pandemic or development of the vaccine, but no more than 1 year from the enrolment of the last participant

Data management

Data handling

Confidential and anonymous data handling will be performed by the Data Monitoring Committee (DMC). To be able to trace data to an individual subject, a subject identification code list will be used. A Personal Identification Number will be generated to identify the data of the participant. This Personal Identification Number will be present on all forms and documents of each individual. Electronic case report forms (eCRFs) will be used. The Investigator will ensure that the data in the eCRFs are accurate, complete, and legible. Detailed data flow will be described in a Data Management Plan. Data from completed eCRFs will be validated under the direction of the Data Manager on the DMC according to a Data Cleaning Plan. Any missing, implausible, or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form. They will be documented for each subject before clean file status is declared. All changes to eCRFs will be recorded.

The DMC will perform an independent assessment of trial-related documents and activities to ensure respect for subjects' right, safety and well-being and to guarantee the plausibility of clinical data. The similarity of groups at baseline will also be checked.
Written informed consent had to be replaced, due to the specific circumstances (the need to maintain social distance during the pandemic), by verbal consent obtained during the first call on recruitment. The verbal consent to participate in such clinical research had not been permitted by the law previously. Therefore, the bill was amended on 24/03/2020 upon the request of our study consortium. This amendment enabled us to conduct this trial.

After verbal consent of the subjects, the data will be recorded by the investigator. Clinical research data are processed separately from participants' data under pseudonyms. Data may only be accessed by persons acting under the authority of the controller and in accordance with the authorisation system established within the controller's organisational structure, only to the extent and in the manner necessary for the performance of tasks. Personal data are not accessible to third parties.

Safety

Due to the nature of the multicomponent moderate-intensity lifestyle intervention, we do not expect serious adverse events. However, minor or moderate adverse events may develop, such as alcohol and nicotine withdrawal, weight change exceeding the optimum, and the need for change in regular medications (antihypertensive or antidiabetic drugs). Participants will be advised to consult their primary care physician if any non-lifestyle-related health issue arises except for COVID-19-related concerns when the call will be transferred to the COVID-19-specific national helpline immediately. If a participant develops a potentially serious health problem, the chairman of the Safety Monitoring Board (LC) will be notified. After the first interim analysis for safety at 10% of the target number, the board will revise the charts of all visits to health facilities and assess if any event is related to the interventions (see, early stopping for safety).

IV.2.3. Discussion

Neither the worldwide climax of the COVID-19 pandemic can be foreseen nor the potential repeated outbreaks (117). Although efforts of primary prevention (i.e. vaccine development) are promising, it is expected to take 12-18 months from now on (142). Better lifestyle has its unquestionable advantages not only for infectious but also for common chronic diseases including diabetes mellitus, chronic heart failure or malignant tumours. Considering the recent low numbers of reported cases and the expected trajectory of the epidemic in Hungary, it seems that we are still on time to seek for personalized and easily available public health interventions applicable for the target population.

While in the United States, "remote" consent via telecommunication may be possible, the Hungarian laws have not allowed such initiatives until now. An outbreak imposes new challenges to the process of ethical approval (143). Most importantly, the instant reaction of both the researchers and the ethical committees is essential, while preserving the validity of scientific content (144).

Based on the results of the current study, such strategies could be introduced in other countries. Lifestyle counselling is expected to reduce mental distress, smoking and alcohol consumption, increase physical activity and favourably change the body mass (along with the body composition). As the main results of all these, the interventions may boost the body's cardiovascular and pulmonary reserve capacities, leading to improved resistance against the damage caused by COVID-19. Consequently, lifestyle changes can reduce the incidence of life-threatening conditions and attenuate the detrimental effects of the pandemic seriously affecting the older population.

Strengths and limitations

We aim to apply lifestyle interventions considered to be safe in a broad population of subjects exposed at high risk of a severe course of COVID-19. The expected health benefits of the interventions considerably exceed its potential harms. With this study design, we can evaluate the effectiveness of (1) the offer of lifestyle intervention vs (2) that of the actual uptake of or compliance to the lifestyle intervention. We expect that the moderate intensity of the personalized multicomponent lifestyle intervention will maximise the effectiveness and, at the same time, prevents low adherence. In addition to the expected beneficial effects regarding the infection, other protective changes are likely regarding cardiovascular and malignant morbidity and mortality on the long-term. The interventions are easy to be delivered while being affordable and implementable for the vast majority of the population.

We expect that there will be limitations in this study (145). We define cross-contamination that participants on different arms deliberately and unknowingly communicate with each other, leading to the loss of the true effect of lifestyle interventions. To minimise the risk of cross-contamination, we decided to include only one subject from communities with multiple potential candidate participants. Although we can evaluate the actual uptake of the lifestyle interventions, its validity is uncertain due to the patient-reported nature of the data. We cannot anticipate the climax of the epidemics so that the infection rate of the target population may deviate from the assumed 10%. To overcome this, we use sample size-readjustment adaptive design, which may settle the problem with the unpredictable dropout rate as well (although this method cannot counteract chronological changes in the dropout rate throughout the evolution of the pandemic). All data on secondary outcomes are provided by participants and other, less reliable indirect data sources. We anticipate that volunteers give a representative sample of the target population, but we cannot exclude that our study population will be somewhat better educated and highly motivated. Despite the thorough training of the operators, inter-operator variability may be present.

Additional information and plans

A follow-up study (PROACTIVE-19 PLUS) is planned to follow up patients, in which blood samples (serum and plasma) from every patient will be stored to analyse immunoglobulins later if required and to build a biobank for a future clinical study. We also intend to publish the study protocol.

V. SUMMARY AND NEW DISCOVERIES

Chapter III. Glucose level independently and dose-dependently worsens acute pancreatitis: A cohort analysis

- We established that increasing on-admission and peak in-hospital glucose is associated with increasing AP severity and mortality, independently of age, gender, DM and AP etiology.
- We saw a dose-dependent association not only with severity and mortality, but also with LOH and complications. In light of the available literature, this suggests that serum glucose might be a pancreatotoxic agent.
- A trend was seen with increasing HbA1c and AP severity and complications
- Based on these conclusions, we formulated the following implications for practice:
    - 1. Prevention: Maintaining a normal glucose homeostasis might reduce the risk of severe AP and local complications.
    - 2. Prognosis: Increased on-admission glucose has a dose-dependent association with increasing severity, mortality, LOH and complications of AP.
    - 3. Prompt treatment: High peak glucose is dose-dependently associated with a higher rate of severe cases, mortality, systemic complications and increased LOH. Hyperglycemia does not necessarily present on admission, monitoring serum glucose during the course of AP is crucial. Adequate in-hospital control of hyperglycemia can greatly contribute to the treatment of AP.

Chapter IV. Translational medicine in the COVID-19 pandemic

- We formed an interdisciplinary team (KETLAK) to help contain the COVID-19 pandemic in Hungary – we think that formation of such teams is crucial to aid government decision makers. No single discipline can tackle such a complex problem alone.
- We analyzed the international state of the COVID-19 pandemic, performed mathematical models for the course and dynamics, also accounting for territorial patterns, economic, social and healthcare related factors.
- These information were regularly delivered to the government and policy makers to help combat the pandemic.
- The KETLAK group could serve as a model for other countries and for future epidemics as well.

- Noticing a gap in the available evidence, we planned and initiated a RCT. The PROACTIVE-19 trial will show the benefits of a telephone-based, personalized, multicomponent lifestyle intervention in COVID-19.
- Based on positive results, a similar strategy could be applied in other countries, not only for COVID-19, but for other diseases as well.

VI. AUTHOR'S OWN CONTRIBUTIONS

In all three articles used in the thesis, the author played a key role in designing the concept and structure of the investigations, in performing the analyses and writing the manuscript. Additional contributions:

VI.1. Nagy et al. Pancreatology, 2021

The author drafted the original concept, and conducted the majority of data interpretation, wrote the manuscript.

VI.2. Gombos et al. Popul Health Manag, 2020

The author played a central role in coordinating the interdisciplinary team and in maintaining a continuous channel of communication with the governing body's pandemic board, led by the prime minister. The author also made significant contributions in interpreting and analyzing the data and writing the manuscript.

VI.3. Erőss et al. Trials, 2020

Next to a key role in designing the study structure, wiriting and providing critical revisions for the manuscript, the author took part in overviewing the available literature and registered trials in the field of question.

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