

Single nucleotide polymorphisms in PRSS1 and CASR genes are associated with chronic pancreatitis in North-Eastern region of India

To the Editor,

The genetic risk factors of chronic pancreatitis (CP) include mutations in several genes, notably serine protease 1 (PRSS1), *serine peptidase inhibitor (SPINK1)*, *cystic fibrosis transmembrane conductance regulator (CFTR)*, *cathepsin B (CTSB)*, *chymotrypsin C (CTRC)* and *calcium sensing receptor (CASR)*. A genome wide association (GWAS) study in European populations revealed that polymorphisms in PRSS1 and claudin 2 (CLDN2) - *MORC family CW-type zinc finger 4 (MORC4)* locus were associated with CP [1]. Replication studies carried out globally, including two studies from north and south India have validated many findings of the GWAS [2, 3]. No genetic data regarding CP were reported for the North-Eastern (NE) Indian population, as this population has a different genetic pattern than north or south India [4]. For the first time, we carried out a candidate gene association study in this population using previously validated markers significantly associated with CP in other populations.

Blood samples from 100 CP patients as well as 110 non-diseased age matched controls without gastrointestinal diseases were collected from Indira Gandhi Memorial Hospital, Agartala. Total genomic DNA was isolated from blood cells, quality checked and targeted sequencing of 17 genes: PRSS1, PRSS2, SPINK1, CTRC, CTSB, CASR, CFTR, CLDN2, *alcohol dehydrogenase (ADH) 2*, *aldehyde dehydrogenase 2 family member (ALDH) 1C*, ALDH3A1, ALDH9A1,

ALDH4A1, *cytochrome P450 family 2 subfamily E member 1 (CYP2E1)*, *methylenetetrahydrofolate reductase MTHFR*, *glucuronosyltransferase family 1 member A7 (UGT1A7)* at desired promoter, exons and UTR regions was done by the in-house Ion Torrent sequencing platform. Quality control steps excluded single nucleotide polymorphisms (SNPs) which were not in the Hardy Weinberg Equilibrium. Association analysis was done using PLINK, finally with 85 CP cases and 78 controls to identify SNPs significantly associated with CP in the NE population by logistic regression after adjusting for confounders like age and sex. Allele-specific odds ratios at 95% CI were calculated. Meta-analysis was done using 'metafor' package in R, using random effects model, publication bias being checked. Phasing of the genotypes was performed using SHAPEITv2, for which the "genetic map" was on build hg-19 from a 1000G database. Post phasing, the files were converted to PLINK input file format. Haplotype association was performed with PLINK-v1.07. The Haploreg and LDpair module of LDlink were used for the validation of linkage disequilibrium (LD) values and haplotype associations.

Association analysis of CP patients vs. controls showed three novel genetic variations in PRSS1 and CASR genes, the association being significant after adjustment for age and sex (Table I). As neither of these two SNPs in PRSS1 (rs6666 and rs6667) was reported before, we carried out haplotype association analysis. Interestingly, as shown in Fig. 1A, rs10273639, the SNP in PRSS1 gene region, reported earlier by GWAS [1] and in both prior Indian studies [2, 3] was found in the same haplotype block together with rs6666 and rs6667. On the other hand, the CASR polymorphism (rs1801726) belongs to a set of polymorphisms clustered at the carboxy-terminal tail

Table I. Details of the SNPs in CASR and PRSS1, found to be associated with chronic pancreatitis

POSITION	SNP	GENE	A1	A2	Frequency of A1 in		OR	SE	STAT	p
					Cases	Controls				
Chr3:122003832	rs1801726	CASR	C	G	0.92	0.96	0.27 (0.08-0.90)	0.61	-2.14	0.03
Chr7:142460313	rs6666	PRSS1	T	C	0.75	0.6	0.56 (0.32-0.97)	0.28	-2.06	0.04
Chr7:142460865	rs6667	PRSS1	T	C	0.75	0.6	0.56 (0.32-0.97)	0.28	-2.06	0.04

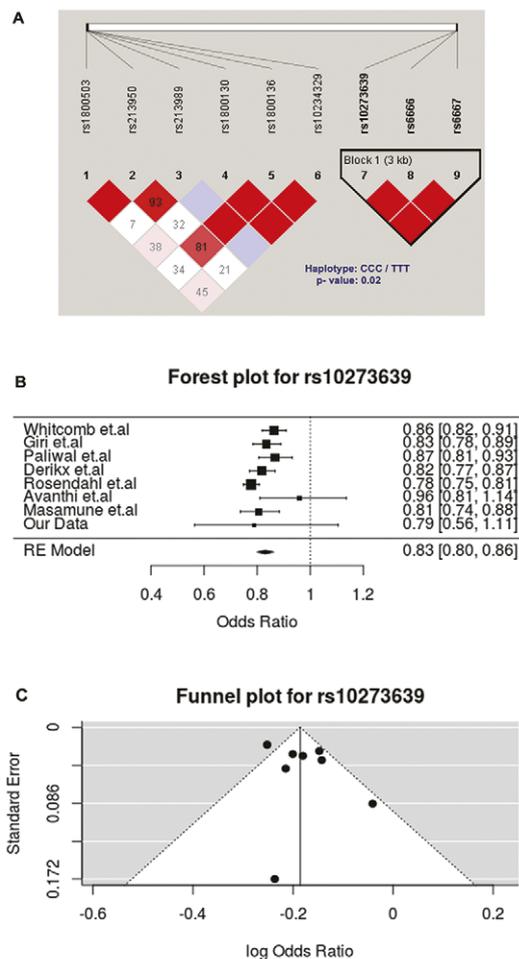


Fig. 1. A: Haplotype analysis with 9 SNPs in Chromosome 7 resulted in two haplotype blocks showing their Linkage Disequilibrium (LD) status. Among them, one haplotype block showing rs66666 and rs66667 is in LD with rs10273639 (as highlighted). B, C: Meta-analysis of rs10273639. B: Forest plot; C: Funnel plot.

where 'cytosine' to 'guanine' nucleotide change is responsible for the loss of function of *CASR* and hence elevation of the serum calcium level, feature of CP. Investigation for SNPs in LD with rs1801726 resulted in the identification of a SNP in 3'-UTR of *CASR* (rs4677948). This SNP is associated with an elevated serum calcium level, as reported in ClinVar. We also found that the risk allele 'A' at rs4677948 created binding sites for three different miRNAs (miR-670-5p, miR-1236-3p and miR-877-3p) at 3'-UTR of *CASR* mRNA. miR-670 expression is upregulated in the pancreatic juice of pancreatic cancer patients and was also reported to promote cell proliferation in other cancers [5]. Interestingly, miR-877-3p also promoted apoptosis and it is known as an anti-autophagy miRNA [6]; both features could have a contributory role in the development of CP. These results indirectly suggest that these miRNAs could have pro-inflammatory role and thereby justify their possible similar function in CP by targeting *CASR* mRNA. HaploReg analysis further showed that the SNP rs1801726 creates a Pdx1 binding site at the coding region of *CASR*, the implication of which is not clear right now.

Furthermore, when alcohol intake was also included as an independent factor in the logistic regression model and its

effect adjusted, rs66666 and rs66667 were no longer significant, indicating that these SNPs are protective mainly for alcoholic CP. Though the GWAS study and other Indian studies found the *PRSS1* polymorphisms to be retained in idiopathic CP patients, yet it was also observed by Whitcomb et al. (2012) [1], that *PRSS1-PRSS2* locus (rs10273639) was associated mainly with alcoholic CP, supporting our result.

In order to compare our association results with similar replication studies [1-3, 7-10], we carried out a meta-analysis of rs10273639. The 'T' allele in rs10273639 was found to be protective whereas 'C' allele in rs10273639 was found to enhance risk in all the studies used for meta-analysis. (Figs. 1B and 1C). Our study followed the same trend with other reports despite small sample size. We did not find any significant association with reported SNPs in *CLDN2* and *SPINK1*. Our results showed OR of 1.88 (1.20-2.96) and 1.27 (0.56-2.86) and allele frequency for risk allele 'C' as 0.68 and 0.08 for rs7057398 in *CLDN2* and rs17107315 in *SPINK1*, respectively, comparable to other studies. The lack of significant association could be due to small sample size.

In conclusion we identified novel single nucleotide polymorphisms in *PRSS1* and *CASR* genes (rs66666, rs66667 and rs1801726) found to be associated with CP in a population of NE India. The SNP rs1801726 was in LD with another SNP in 3'-UTR of *CASR*, creating binding sites for pro-inflammatory miRNAs, miR-670-5p and miR-877-3p.

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Fat droplets on direct cholangioscopy

To the Editor,

Direct cholangioscopy (DC) with or without ancillary anchoring techniques is increasing in clinical use for high-quality visualization of biliary tract diseases and/or instrumentation

under direct endoscopic vision. In this line, the work-up of indeterminate biliary strictures and cholangioscopy-guided treatment of complex stone disease remain first-line indications. By contrast, cholangioscopic assessment of freedom of stones has been reported to be superior to endoscopic retrograde cholangiography (ERC), in particular, in selected patients with diffuse bile duct dilation limiting fluoroscopy-based interpretation as the putative future gold standard. Contrast dye injection prior to cholangioscopy is notorious for interfering with visualization due to the formation of streak-like artifacts [1]. Here, we report on a novel phenomenon observed during DC reminiscent of biliary fat droplets, the distinct provenience and clinical relevance of which remain to be better determined.

Notwithstanding, albeit biliary fat secretion takes place on a “sub-endoscopic” level, it might be tempting to discuss an emulsion of contrast media and bile rich in cholesterol. In an elderly female patient with complex stone disease with status post cholecystectomy, several ERC sessions for papillotomy and presumed complete stone removal presented with increasing laboratory cholestasis and systemic inflammatory parameters, consistent with bacterial cholangitis. After the intake of antibiotics, the clinically stable patient underwent repeat ERC with DC in freehand fashion without CO₂ and/or saline usage on day four. No purulent secretions were noted and an occlusion cholangiogram did not indicate remnant stones in the bile duct measuring > 25 mm. This was confirmed on DC with full-scale visualization of the cystic duct remnant (Fig. 1A) as well as intrahepatic ducts up to a “wedged” position (Fig. 1B). In the common bile duct there were minor amounts of orange-colored bile fluid with intermingled fat droplets (Fig. 1C). Similar findings could be obtained in the right-hepatic ductal system with fat-containing globules flowing out of the deep biliary system (Fig.4D).

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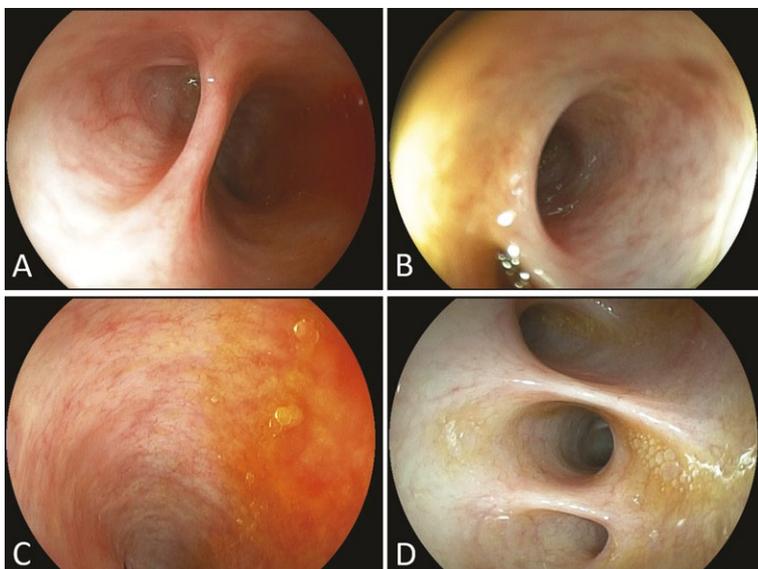


Fig. 1. (A) Direct cholangioscopic (DC) visualization of the cystic duct remnant (left) and the common hepatic duct (right) as well as (B) intrahepatic ducts (right anterior system) in a “wedged” position excluding remnant bile duct stone disease. (C) During advancement fat droplets were noted in the common bile duct (CBD) and (D) active flow of fat particles from deeper intrahepatic ducts was noted during intrahepatic cholangioscopy.

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Sustained virological response following an 11-day course of direct acting antiviral therapy for hepatitis C infection

To the Editor,

Direct acting anti-viral (DAA) medications have revolutionized the treatment of chronic hepatitis C (HCV) [1]. Sustained virological response (SVR) can now be accomplished following 8-12 weeks of treatment in the majority of patients. Here we present a novel report of HCV eradication following only 11 days of treatment.

An asymptomatic 63-year-old non-cirrhotic female was referred for chronic HCV treatment at the liver clinic of Soroka University Medical Center. Medical history was significant for dyslipidemia, for which she stated that she was not taking medication. Laboratory workup showed elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) of up to two times the normal upper limit. Virologic examination showed genotype 1b and a viral load of 3,679,847 IU/ml. Serologic workup was significant to past exposure to hepatitis B virus (HBV) with development of protective immunity. The patient was prescribed treatment with Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir for 12 weeks. On day 11 of treatment the patient began suffering from severe weakness and muscle rigidity and discontinued the treatment. On day 13 she presented to the emergency department after her muscle rigidity worsened. Blood tests revealed a creatinine kinase (CK) level of 8690 U/L, AST of 759 U/L, ALT of 457 U/L. The patient was admitted with a working diagnosis of rhabdomyolysis and supportive care with intravenous fluids was initiated. Upon further evaluation the patient recalled she had been concomitantly taking simvastatin for the past few weeks. Repeat testing did not disclose evidence of HBsAg reversion. After stopping simvastatin, CK, AST and ALT showed gradual decline. Following discharge, a HCV RNA test performed 30 days after treatment initiation was found to be negative and AST, ALT and CK were all within normal limits. Repeated HCV RNA testing at 12- and 24-weeks post treatment cessation were also negative. It was therefore concluded that the patient had obtained SVR.

This case report highlights HCV eradication following an ultra-short treatment course of only 11 days. Early discontinuation of treatment was mandated due to the well-known drug-drug interaction between medications included in this regimen and simvastatin [2]. OATP/CYP3A4 inhibition by paritaprevir and ritonavir increases systemic simvastatin exposure which can subsequently lead to the development of myopathy and rhabdomyolysis. Simvastatin use was not

disclosed by the patient at the time of DAAs initiation, which resulted in a potentially life-threatening outcome. The underlying mechanism for the rapid viral clearance seen in this case is not quite clear. One possible explanation is that the systemic inflammation induced by rhabdomyolysis triggered a hepatic inflammatory reaction which in turn enhanced HCV viral clearance. Alternatively, the abrupt elevation in liver enzymes could be determined to the development of an idiosyncratic DAA-induced liver injury leading to accelerated viral clearance.

This report adds to accumulating data in the literature of HCV eradication following ultra-short DAAs therapy [3-5]. Further investigations are required to identify patients suitable for a shorter treatment course.

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Homocysteine in nonalcoholic steatohepatitis: seemingly a paradox revisited

To the Editor,

Xu et al. [1] reported that lower homocysteine levels were independently associated with nonalcoholic steatohepatitis (NASH) and significant fibrosis (F≥2), and were correlated

with a higher grade of hepatocellular ballooning, albeit not with steatosis and lobular inflammation. Although being retrospective, this study is reportedly the largest to-date biopsy-proven study on the association between homocysteine and nonalcoholic fatty liver disease (NAFLD) [1].

We also previously reported that lower homocysteine levels were independently associated with NASH, despite being similar between NAFLD patients and controls matched for gender, age, body mass index and waist circumference with patients [2]. Likewise, homocysteine was lower by increasing the severity of fibrosis and portal inflammation, but not the steatosis grade, ballooning or lobular inflammation [2]. Subsequently, we incorporated homocysteine in a more integrated pilot analysis, leading to the introduction of a proposed term HSENSI (acronym of Homocysteine, Serum glutamic oxaloacetic transaminase [SGOT/AST], Erythrocyte sedimentation rate [ESR], Nonalcoholic Steatohepatitis Index), as a noninvasive marker differentiating NASH from simple steatosis (nonalcoholic fatty liver; NAFL) [3]; according to HSENSI, the lower the homocysteine and the higher the AST and ESR, the probability of NASH was higher [3]. In a post-hoc analysis of the same study, homocysteine was inversely associated with irisin levels in NAFLD patients, but not in the controls [4].

Our study [2] had a limited number of NAFLD patients compared with the Xu et al. study (31 vs. 289, respectively) [1]. It was a small sample being, however, sufficient to provide statistically significant similar associations, at least between homocysteine and NASH or fibrosis. However, our study was also specifically designed for the association between homocysteine and NASH and included 22 matched controls [2], contrary to the uncontrolled, retrospective study, acknowledged by Xu et al. [1]. Due to probable misconception, Xu et al. reported 39 rather than 31 NAFLD patients in our study and that homocysteine was “unrelated to NAFLD biopsy”, which is not the fact, as mentioned above [2, 4].

We have no mechanistic evidence of the lower homocysteine levels in NASH rather than simple steatosis (SS). However, because homocysteine levels provide substrate for glutathione repletion, we previously hypothesized that lower homocysteine in NASH may represent a counteracting effort of hepatocytes to increase glutathione through the transsulfuration pathway. Since NASH is a state of high oxidative stress, the intensification of synthesis of the antioxidant glutathione may mirror a self-defense mechanism of the hepatocytes, thus resulting in homocysteine depletion [2]. However, this remains to be demonstrated, since the observational design of our and Xu et al. studies does not allow cause-effect extractions [1, 2].

A meta-analysis of eight observational studies published in 2016, showed higher homocysteine levels in NAFLD patients than controls [5]. Nevertheless, there was high heterogeneity in this meta-analysis, which was not explained (e.g. by performing meta-regression). More importantly, a comparison between NAFL and NASH patients was not performed, possibly owing to the limited number of studies with histologically confirmed NAFLD. However, the main clinical question is the noninvasive diagnosis between NAFL and NASH, which currently requires liver histology. In this regard, the Xu et al. study adds to the literature and warrants mechanistic studies and specifically designed clinical studies with biopsy-proven NAFLD [1].

NAFLD is a multifactorial disease, thus diverse factors contribute to its development and progression on an individual basis. Insulin resistance is a prevailing contributing factor, so higher homocysteine levels might have been expected in NASH rather than NAFL, since homocysteine is associated with insulin resistance in other diseases. However, it seems that at least some NASH patients have lower than expected homocysteine levels, a seemingly paradox that is revisited following the Xu et al. [1] study and which gives birth to many scientific questions with possible clinical implication.

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Inaction on IgA anti-tissue transglutaminase positivity

To the Editor,

We read with considerable interest an article recently published in the *Journal of Gastrointestinal and Liver Diseases* by Henry et al. [1] on the importance of endoscopic biopsy in certain patient cohorts in their manuscript entitled “Seronegative Coeliac Disease Masquerading as Irritable Bowel Syndrome type Symptoms”. They reported the case of a patient who was found to have coeliac disease on a duodenal biopsy despite serial negative serology. Henry et al. [1] concluded with the recommendation to perform duodenal biopsies in at risk patients despite normal serology owing to the 3-5% rate of false negatives [2]. We think this is an astute and appropriate

recommendation but would like to remind clinicians that duodenal biopsy is also important for the verification of a diagnosis of coeliac disease in the context of suggestive serology as per the British Society of Gastroenterology guidelines [3]. The positive predictive value of IgA anti-tissue transglutaminase (TTG) is in the region of only 54% [4]. We have found a low rate of endoscopic verification of diagnosis of coeliac disease in a cohort of adult patients cared for within the catchment area of our institution in the South-East of Ireland. On auditing positive IgA anti-TTG results over an 18 month period from January 2018 to June 2019 we found that only 42% of patients had proceeded to endoscopic biopsy by April 1st 2020. This is a worrying outcome with possible adverse effects for the unverified patients with coeliac disease and the potentially presumptively diagnosed patients who have been committed to a needless lifelong insistence on avoidance of gluten containing foods. Reaching the correct diagnosis by the appropriate means is central to the practice of medicine. In the context of positive coeliac serology and that described by Henry et al., endoscopy is of fundamental importance in achieving a definitive diagnosis of coeliac disease. Our audit suggests this is being somewhat neglected by the clinician community at large within our catchment and should alert others to the potential for such practice within their surroundings.

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Reply,

To the Editor,

We agree with the authors of the letter entitled “Inaction on IgA anti-tissue transglutaminase positivity” [1] on the

importance of performing a duodenal biopsy for the diagnosis of adult coeliac disease (CD) and we thank them for offering us the possibility to address some methodological issues relevant for the diagnosis of CD.

Firstly, Shanahan et al. [1] reported that, over an 18-month period, only 42% of their patients who had previously tested positive to IgA tissue transglutaminase antibodies (anti-tTG) proceeded to a confirmatory duodenal biopsy. Despite this disappointing result, it would be interesting to have more details regarding the clinical phenotype of these patients such as presenting symptoms, levels of IgA anti-tTG, and results of endomysial antibodies (EmA), if performed as a confirmatory testing. Anyway, we have to acknowledge that failure to recognize CD at this step of the diagnostic process is still common. Endoscopy-related diagnostic errors in CD can be due either to the lack of performing a gastroscopy despite a highly suggestive clinical picture for CD, or to inaccurate duodenal sampling during gastroscopy (which also includes not taking duodenal biopsies when CD is clinically suspected) [2-4]. Although ESPGHAN guidelines allow a biopsy-avoidance diagnostic strategy in selected children [5], for the time being, in adults this approach is simply not applicable, and duodenal biopsy is still the mainstay for the diagnosis of adult CD [6].

We are not surprised by the unsatisfactory positive predictive value (PPV) of IgA anti-tTG (54%) [7]. We previously reported a PPV for IgA anti-tTG of only 28.6% [2]. There may be several reasons for this. Firstly, positive anti-tTG have been found also in patients with liver disease, diabetes, end-stage heart failure and in non-coeliac children suffering from febrile infections [8-11]. Secondly, a reduced sensitivity for anti-tTG and EmA in patients with lesser degree of villous atrophy was reported [2, 12, 13]. Conversely, by using a higher cut-off value for anti-tTG, this leads to a higher PPV (75%) in the same population under investigation [2]. Thirdly, assuming that sensitivity and specificity of a test are stable, the PPV is largely dependent on the pre-test probability for a certain disease in the population under examination. Therefore, we believe that in real life clinical practice the correct interpretation of a serological test for CD strictly depends on the expected prevalence (pre-test probability) of CD in a specific clinical population [2, 14, 15]. We previously showed that pre-endoscopy serological testing based on IgA anti-tTG in combination with duodenal biopsy of patients at high-risk of having CD (ie. patients with severe malabsorption or haematinic deficiencies) had a 100% sensitivity for the final diagnosis of CD. Similarly, this approach confidently identifies also those patients who likely do not require a duodenal biopsy, because they belong to a low-risk group and have a negative antibody testing for CD [14]. Interestingly, a recent prospective study has shown that measurement of deamidated gliadin peptide antibody before endoscopy can increase the detection of CD in an endoscopy setting with high pre-test probability for CD [15].

Finally, the diagnostic strategy of performing a gastroscopy with duodenal biopsy in patients with severe features of malabsorption, haematinic deficiencies and alarm symptoms despite negative coeliac antibodies is crucial in the diagnostic workup of seronegative CD and non-coeliac enteropathies

[16-18]. In fact, despite being rare, these conditions are characterized by peculiar clinical phenotypes and a higher mortality than conventional seropositive CD [17, 18]. Therefore, in the absence of specific biomarkers for these enteropathies, a duodenal biopsy still remains the gold standard for their diagnosis and for a prognostic evaluation by performing molecular testing, such as clonality for gamma T-cell receptor or flow cytometry analysis of intraepithelial lymphocytes [18].

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Challenges of pancreatic cancer chemotherapy in the COVID-19 era

To the Editor,

The recent pandemic of coronavirus disease 2019 (COVID-19) has challenged the oncology medical community, regarding the treatment for these patients. China reported that the rate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was higher in oncological patients (1%) compared to the general population (0.29%), with higher rates of respiratory complications [1]. The risk factors for severe respiratory complications were: recent past medical history of chemotherapy or surgery (OR=5.34, p=0.0026).

Pancreatic cancer (PC) is a malignancy with a high mortality, being the fourth leading cause of cancer related deaths in the United States and the sixth leading cause of cancer related deaths in Romania [2]. In locally advanced and metastatic pancreatic cancer (LAMPC) chemotherapy might determine conversion to resectable stages and prolong the overall survival (OS) [3]. Recent guidelines recommend oncologists to maintain optimal but safe cancer care and avoid the distraction effect [4].

Our experience consisted of eleven patients with LAMPC, enrolled at the Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania, at the time of the COVID 19 outbreak in Romania. The demographic data are summarized in Table I. The patients were with good performance status

(ECOG=0-1), with a median age of 62 years. Nine patients had at least one comorbidity at diagnosis (high blood pressure, diabetes mellitus, chronic ischemic heart disease). At the onset of the COVID-19 pandemic, nine patients were on chemotherapy and two patients were on the initial work-up.

In order to minimize the exposure, we switched the chemotherapy regimen from FOLFIRINOX protocol (oxaliplatin, calcium leucovorin, irinotecan, 5-fluorouracil (5-FU)) to gemcitabine-based chemotherapy: five patients were switched from FOLFIRINOX to GEMCAP regimen (gemcitabine, capecitabine) and one patient to Gemcitabine monotherapy. Two patients that were on GEMOX regimen (gemcitabine, oxaliplatin) were switched to gemcitabine monotherapy. The patient with leucovorin and 5-FU maintenance therapy was switched to capecitabine maintenance monotherapy. The two chemo-naïve patients started directly with the GEMCAP regimen. All patients tolerated the treatment well. The number of hospital admission and continuous hospital days decreased. During the new chemotherapy regimen none of the patients was infected with COVID-19.

In the COVID-19 era, the assessment risk/benefits of chemotherapy in LAMPC patients is stressed by the risk factors for severe infection. Chemotherapy might determine a weaker immune system. Other risk factors for severe infections are older age and the presence of comorbidities as in our cohort.

The European Society for Medical Oncology (ESMO) recommends initiation and continuation of first line chemotherapy in patients fit for a combined regimen, the goal being the improvement of quality of life and OS [5]. For patients with good performance status the standard chemotherapy is represented by combined regimens based on gemcitabine or 5-FU and for patients with poor performance status by gemcitabine alone [6, 7].

Gemcitabine alone has been the standard treatment in LAMPC since 1997, considering the overall survival benefit and the clinical benefit compared to 5-FU [3]. Several

trials investigated the association of gemcitabine with other chemotherapeutic agents (irinotecan, 5-FU, cisplatin, oxaliplatin or capecitabine) and reported contradictory results. The association of gemcitabine with capecitabine or cisplatin showed the biggest benefits [4]. Gemcitabine and capecitabine showed a trend towards the improvement of OS when compared to gemcitabine [8]. A recent meta-analysis that included 8 trials with gemcitabine and capecitabine versus gemcitabine monotherapy showed improved OS for combined regimen (HR=0.87, p=0.03) [9]. The preferred chemotherapy regimen for first line treatment is gemcitabine and nab-paclitaxel based on the results of the phase III trial MPACT in which OS was significantly improved with this association compared to gemcitabine alone (OS 8.7 months vs 6.6 months, HR=0.72, p<0.001) [10]. In patients with good performance status, the recommended chemotherapy for first line treatment is represented by the triplet FOLFIRINOX. The PRODIGE trial randomized between FOLFIRINOX and gemcitabine monotherapy and reported better OS overall in the FOLFIRINOX arm (11 months vs 6.8 months, p<0.001), but with more toxicities [11].

Based on guidelines, and on our experience regarding the benefits and risk of chemotherapy treatment in LAMPC patients in COVID-19 pandemic we propose the switch from FOLFIRINOX regimen to gemcitabine-based regimens or to initiate gemcitabine based first line chemotherapy.

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Table I.

Patient	Gender	Age at diagnostic	Histology grade	TNM	Sites of metastatic disease	Stage	Prior Therapies	No. of cycles	ECOG status	New Therapy
1	male	53	2	cT3N1M1	liver, peritoneum	IV	FOLFIRINOX	2	1	GEMCAP
2	male	62	3	cT4N2M1	liver	IV	LV5FU2*	4	1	Capecitabine
3	male	64	3	cT4N1M1	peritoneum	IV	FOLFIRINOX	2	1	GEMCAP
4	male	65	3	cT3N1M1	liver, peritoneum	IV	FOLFIRINOX	1	1	GEMCAP
5	female	54	3	cT4N1M0	none	III	FOLFIRINOX	3	1	GEMCAP
6	male	71	2	pT2N2cMo	lymph nodes relapse	III	FOLFIRINOX	6	1	GEMCAP
7	male	58	3	pT2N1cM0	lymph nodes relapse	IIB	FOLFIRINOX	12	1	Gem
8	male	61	3	cT4N1M1	liver	IV	none**	n/a	1	GEMCAP
9	female	67	3	cT4N1M1	lung	IV	none**	n/a	1	GEMCAP
10	male	56	3	cT4N1M0	none	III	GEMOX	8	1	Gem
11	female	66	3	cT3N1M0	none	III	GEMOX	15	1	Gem

FOLFIRINOX protocol: oxaliplatin, calcium leucovorin, irinotecan, 5-fluorouracil (5-FU); Gem: gemcitabine; GEMCAP regimen: gemcitabine, capecitabine; GEMOX regimen: gemcitabine, oxaliplatin; LV5FU2: leucovorin and 5-FU; n/a=not assessed. *LV5FU2 maintenance therapy after 12 cycles of FOLFIRINOX **chemonaïve new patients

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Pancreatic involvement in SARS-CoV-2: case report and living review

To the Editor,

Since the novel coronavirus outbreak started, as of May, 22, 2020, 5,067,579 individuals have been confirmed with COVID-19 and 332,711 of them have died from the disease [1]. Besides respiratory involvement, a meta-analysis of 60 studies reporting on 42,443 coronavirus disease 2019 patients proved that 18% of them had gastrointestinal symptoms [2]. Recently, it has been suggested that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, similar to other viral infections, might induce pancreatic injury or even worse, acute pancreatitis.

We report the case of a 47-year-old male patient with COVID-19, without significant medical history or home medication, who only complained of a dry cough for a week. Initial physical examination and chest x-ray did not show any abnormal changes. Admission laboratory work-up revealed mild lymphopenia (1,420/mm³), increased inflammatory marker levels [C reactive protein (CRP) 31 mg/l, erythrocytes sedimentation rate (ESR) 64 mm/h, ferritin 583 ng/ml], procalcitonin and D-dimers within normal range, minimal elevation in gamma glutamyl transpeptidase (GGT) (2.4 x ULN) and alanine aminotransferase (ALT) (1.3 x ULN) in the absence of viral hepatitis B or C.

During the following days regular blood tests came back normal and the cough faded. On day 12 he complained of severe epigastric pain with radiation to the back, nausea, constipation and lack of flatus. Abdominal examination revealed epigastric tenderness and bloating, while blood tests showed mild leukocytosis with lymphopenia, increased pancreatic enzymes (lipase 22 x upper normal limits (ULN), amylase 6 x ULN) and CRP (63.24 mg/l). Procalcitonin along with liver and kidney function tests were within the normal range. Chest and abdomen computed tomography scans revealed the presence of scattered bilateral subpleural ground-glass opacities, edematous changes in the caudal region of the pancreas (Fig. 1a) and bowel distention without evidence of obstruction (Fig. 1b). According to the modified Atlanta criteria the patient was diagnosed with acute pancreatitis complicated by ileus.

Other causes of acute pancreatitis, such as gallstones/biliary obstruction, alcoholism, smoking, drugs, trauma, hypertriglyceridemia and hypercalcemia were excluded. Since no other plausible cause was found for both acute pancreatitis and ileus, and sustained by the evolution, we concluded that SARS-CoV-2 infection might be responsible. He was managed conservatively with bowel rest, intravenous crystalloid fluid resuscitation, prokinetic medication and analgesia. After 2 days colonic transit normalized, and pancreatic enzymes gradually decreased.

There is evidence that the virus remains in the gastrointestinal tract, perhaps in the pancreas as well, even after negative nasopharyngeal swabs had become negative [2, 3], possibly explaining the delayed onset of pancreatitis in our patient.

Since there is hardly any data on pancreatic involvement in SARS-CoV-2 infection, an extensive literature search was performed on 21 May 2020 in six major databases: PubMed, Web of Science, Springer, Ovid, Scopus, Wiley, using the terms: "pancreatitis", "pancreatic injury", "lipase", "amylase", "COVID-19" and "SARS-CoV-2". The initial search yielded 160 articles. After title and abstract screening, removing duplicates and assessment for eligibility, we identified a total of 4 articles [4-7], comprising thirteen COVID-19 patients, labeled either as pancreatic injury (9/13) or acute pancreatitis (4/13). Since some of the reported cases lacked in details regarding diagnostic criteria, only two (2/13) of the cases might be interpreted as acute pancreatitis based on the revised Atlanta classification. In a retrospective study, 13/121 patients with COVID-19 had increased pancreatic enzymes, but none had values above 3 x ULN [3].

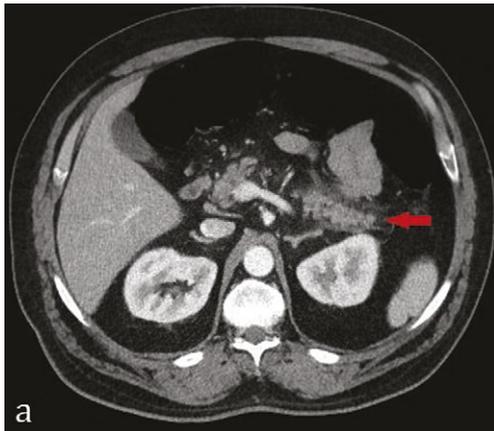


Fig. 1a. Blurring of the pancreatic contours due to the edema of the surrounding adipose tissue.



Fig. 1b. Cecum and ascending colon distension due to ileus.

Whereas some authors support the theory that increased pancreatic enzymes in COVID-19 patients might not suggest pancreatic injury at all, and due to the clinical context additional causes should be considered, we suggest that some patients might indeed have at least a mild pancreatic injury.

However, since there is still limited evidence of pancreatic involvement in SARS-CoV-2 infection, no definite conclusions can be made. We mitigate that the potential for pancreatic injury still remains, and all patients with features suggestive of acute pancreatitis should be properly investigated. Nevertheless, abnormal pancreatic enzymes should only be interpreted as acute pancreatitis based on the revised Atlanta classification.

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