SARS-CoV-2 infection is associated with an increased risk of idiopathic acute pancreatitis but not pancreatic exocrine insufficiency or diabetes: long-term results of the COVIDPAN study

We recently published in GUT the outcomes of acute pancreatitis (AP) and coexisting SARS-CoV-2 infection. A number of patients who were SARS-CoV-2 positive had AP of unknown aetiology (23%) speculating SARS-CoV-2 as a cause for AP similar to other viruses. However, most patients did not complete investigations to exclude other causes of AP. In addition, SARS-CoV-2 infection may cause aberrant glycometabolic control, however it is unknown if this increases the risk of long-term diabetes mellitus (DM). The follow-up data were collected 12 months from the date of recruitment for 1476 patients (11 patients who were SARS-CoV-2 positive and 1358 patients who were negative) to establish an aetiology for AP and development of DM. Among the 118 patients who were SARS-CoV-2 positive, 35 patients had idiopathic or unknown aetiology AP. Sixteen patients underwent either MRCP (n=13) or EUS (n=4) and the remaining patients underwent biochemical investigations to exclude other causes of AP. The final aetiology of AP was available for 83 (70.3%) patients and included gallstones (56, 47.4%), alcohol (19, 16.1%), post ERCP (2, 1.7%) and other (6, 5.1%). Overall, 23 patients had a change of aetiology, and in 35 (29.7%) patients AP was considered idiopathic. Patients who were SARS-CoV-2 positive were more likely to have idiopathic AP (34.7% vs 13.9%, p<0.001) with over five times increased risk after adjusting for age, smoking status, body mass index and ethnicity (OR: 5.34, p<0.001) (table 1 and online supplemental table S1).

Thirteen (11.0%) patients in the SARS-CoV-2 positive group and 187 (13.8%) patients in the negative group were readmitted with AP (p=0.949). The aetiology and baseline characteristics are summarised in online supplemental table S2. The risk of readmission was higher in younger patients, and lower in those with gallstone and idiopathic aetiology (online supplemental table S3).

Two patients developed DM and nine patients developed pancreatic exocrine insufficiency (PEI) in the SARS-CoV-2 positive group. SARS-CoV-2 did not increase the risk of DM (2.3% vs 2.5%, OR: 0.61, p=0.541) or PEI (OR: 1.11, p=0.828) (p>0.05; table 2).

Mortality after discharge was 12.7% in the SARS-CoV-2 positive group and 5.4% in the negative group (log-rank, p<0.0001; online supplemental figure S1). However, this was not statistically significant in a multivariable Cox-regression model (HR: 1.89, p=0.078).

The higher number of patients with idiopathic AP in the present series raises speculation that SARS-CoV-2 may indeed cause AP. Recently autopsy evidence has identified SARS-CoV-2 virus in the pancreases of infected patients, with focal pancreatitis

| Table 1 | Comparison of baseline characteristics of all patients in the follow-up cohort by aetiology |
|---------|---------------------------------------------------------------------------------------------|
| Levels  | Known aetiology | Idiopathic | P | Total N | Missing N |
| SARS-CoV-2 status | SARS-CoV-2 negative | 1107 (94.4) | 178 (83.6) | <0.001 | 1386 (100.0) | 0 |
|          | SARS-CoV-2 positive | 66 (5.6) | 35 (16.4) | | |
| Age     | Mean (SD) | 54.5 (18.1) | 56.5 (17.8) | 0.14 | 1376 (99.5) | 10 |
| Sex     | Female | 557 (47.7) | 103 (48.6) | 0.877 | 1379 (99.5) | 7 |
|         | Male | 610 (52.3) | 109 (51.4) | | |
| Ethnicity | Asian | 56 (5.6) | 17 (9.6) | 0.129 | 1170 (84.4) | 216 |
|         | Black | 8 (0.8) | 3 (1.7) | | |
|         | Other | 147 (12.8) | 22 (12.4) | | |
|         | White | 781 (78.7) | 136 (76.4) | | |
| Premorbid ECOG status | 0 | 690 (62.2) | 129 (64.8) | 0.462 | 1309 (94.4) | 77 |
|         | 1 | 268 (24.1) | 45 (22.6) | | |
|         | 2 | 103 (9.3) | 17 (8.5) | | |
|         | 3 | 43 (3.9) | 5 (2.5) | | |
|         | 4 | 6 (0.5) | 3 (1.5) | | |
| Smoking | No | 749 (68.5) | 147 (76.2) | 0.041 | 1286 (92.8) | 100 |
|         | Yes | 344 (31.5) | 46 (23.8) | | |
| Follow-up ferritin | Median (IQR) | 234.5 (186.5 to 385.2) | 496.0 (343.0 to 649.0) | 0.667 | 12 (0.9) | 1374 |
| Follow-up LDH | Median (IQR) | 250.0 (187.5 to 455.5) | 416.0 (299.0 to 426.0) | 0.605 | 44 (3.2) | 1342 |
| Follow-up revised Atlanta Classification | Mild | 107 (71.3) | 13 (72.2) | 0.256 | 168 (12.1) | 1218 |
|         | Mod-severe | 27 (18.0) | 5 (27.8) | | |
|         | Severe | 16 (10.7) | | | |
| Follow-up ARDS | Yes | 146 (10.5) | | | |
|         | No | 124 (96.9) | 18 (100.0) | 1 | | |
| Follow-up liver steatosis | No | 37 (28.7) | 7 (38.9) | 0.389 | 147 (10.6) | 1239 |
|         | Not reported | 70 (54.3) | 10 (55.6) | | |
|         | Yes | 22 (17.1) | 1 (5.6) | | |
| Admission BMI | Median (IQR) | 27.4 (23.8 to 32.0) | 25.6 (22.8 to 29.2) | 0.012 | 774 (55.8) | 612 |
| Follow-up necrosectomy | Both | 2 (1.2) | 0.85 | 177 (12.8) | 1209 |
|         | Neither | 157 (98.1) | 17 (100.0) | | |
| Percutaneous/MIRP | 1 (0.6) | | | | | |

ARDS, acute respiratory distress syndrome; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MIRP, minimally invasive retroperitoneal pancreatic necrosectomy;
seen in autopsy specimens higher than that is diagnosed clinically. Laboratory evidence further suggests there is expression of ACE 2, TMPRSS and NeureoP1 receptors in exocrine and endocrine cells of pancreas which enables SARS-CoV-2 entry and replication, resulting in elevated cytokine levels causing ribosomal dysfunction and pancreatic injury. Recent series have further shown that AP during SARS-CoV-2 infection is frequent in intensive care unit with a third of critically ill patients developing AP.

Hyperglycaemia frequently noted in SARS-CoV-2 infection is likely from viral replication in beta cells causing impaired glucose-stimulated insulin secretion, with glycemic abnormalities detected for up to 2 months after recovery. In the present series, two patients in the positive group developed DM during follow-up and both had severe AP with necrosis which is likely the cause of DM rather than SARS-CoV-2-induced damage.

We have shown that SARS-CoV-2 infection increases the risk of idiopathic AP but not long-term diabetes. Further laboratory studies that can prove replication of SARS-CoV-2 virus in human pancreas cells with resultant cell injury are warranted to establish SARS-CoV-2 virus as an aetiology for AP. Epidemiological studies are needed that can show an increase in the incidence of AP during the current pandemic to further implicate SARS-CoV-2 infection as a cause for AP and will add indirect evidence. Similarly, larger cohort of patients with SARS-CoV-2 with temporal trends to support or refute the long-term risk of developing DM are warranted.

Table 2 Impact of SARS-CoV-2 on mortality, PEI and DM

| SARS-CoV-2 negative | SARS-CoV-2 positive* |
|---------------------|----------------------|
| 12-Month mortality after discharge | Ref |
| DM | Ref |
| PEI | Ref |

*HR for mortality, and OR for DM and PEI, 95% CI, and p value from adjusted logistic regression models. Mortality adjusted for premorbid ECOG performance status and revised Atlanta classification. DM adjusted for sex and revised Atlanta classification. PEI adjusted for age, sex, premorbid ECOG performance status and revised Atlanta classification.

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