COVID-19 IN
GASTROINTESTINAL AND
HEPATOBILLIARY SYSTEM

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BAGIAN/KSM ILMU PENYAKIT DALAM FK UNSRAT/RSUP PROF DR. R.D. KANDOU
MANADO
SARS-COV-2

- Genus β Coronavirus
- RNA positive
- Incubation range from 2-14 days
- Respiratory sign and symptom → dyspnea, fever, cough
- New Study→GI sign and symptom? Viral RNA in Stool sample?
### Symptoms near the time of presentation in various cohorts

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Constitutional</strong></td>
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</tr>
<tr>
<td>Fever</td>
<td>473/1081 (43%)</td>
<td>18/21 (86%)</td>
<td>46/52 (88%)</td>
<td>82/99 (83%)</td>
<td>40/41 (98%)</td>
<td>48/62 (77%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>164/1081 (15%)</td>
<td>6/52 (12%)</td>
<td>11/99 (11%)</td>
<td>8/99 (8%)</td>
<td>2/38 (8%)</td>
<td>21/62 (34%)</td>
</tr>
<tr>
<td>Headache</td>
<td>150/1081 (14%)</td>
<td>2/21 (10%)</td>
<td>3/52 (6%)</td>
<td>8/99 (8%)</td>
<td>2/38 (8%)</td>
<td>21/62 (34%)</td>
</tr>
<tr>
<td><strong>Upper respiratory</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>53/1081 (5%)</td>
<td>5/21 (24%)</td>
<td>3/52 (6%)</td>
<td>4/99 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>153/1081 (14%)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lower respiratory</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>205/1081 (19%)</td>
<td>9/21 (43%)</td>
<td>33/52 (64%)</td>
<td>31/99 (31%)</td>
<td>22/40 (55%)</td>
<td>2/62 (3%)</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>5/21 (24%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>745/1081 (68%)</td>
<td>15/21 (71%)</td>
<td>40/52 (77%)</td>
<td>81/99 (82%)</td>
<td>31/41 (76%)</td>
<td>50/62 (81%)</td>
</tr>
<tr>
<td>Sputum</td>
<td>370/1081 (34%)</td>
<td>3/21 (14%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>10/1081 (1%)</td>
<td></td>
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</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>55/1081 (5%)</td>
<td>2/21 (10%)</td>
<td>2/52 (6%)</td>
<td>1/99 (1%)</td>
<td>1/38 (3%)</td>
<td>3/62 (8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42/1081 (4%)</td>
<td>1/21 (5%)</td>
<td></td>
<td>2/99 (2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CLINICAL MANIFESTATIONS

Systemic Disorders
- Fever
- Cough
- Fatigue
- Headache
- Sputum Production

Respiratory Disorders
- Rhinorrhea
- Sneezing
- Sore Throat
- Pneumonia
- Ground-glass Opacities
- RNAemia
- Acute Respiratory Distress Syndrome

Diarrhoea

XIAOWEI LI, ET AL. JOURNAL OF PHARMACEUTICAL ANALYSIS. 2020

Authors: Shahnaz Sultan*, Osama Altayar*, Shazia M. Siddique, Perica Davitkov, Joseph D. Feuerstein, Joseph K. Lim, Yngve Falck-Ytter, Hashem B. El-Serag on behalf of the AGA

*co-first authors
An invader’s impact

In serious cases, SARS-CoV-2 lands in the lungs and can do deep damage there. But the virus, or the body's response to it, can injure many other organs. Scientists are just beginning to probe the scope and nature of that harm. Click on organ name for more.

Sherief M. Journal of Gastroenterology. 2020
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>GI symptoms</th>
<th>No GI symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan L, et al.</td>
<td>203</td>
<td>103 (50.7%)</td>
<td>100 (49.3%)</td>
</tr>
<tr>
<td>Jin X., et al.</td>
<td>651</td>
<td>74 (11.3%)</td>
<td>577 (88%)</td>
</tr>
<tr>
<td>Fang D, et al.</td>
<td>201</td>
<td>159 (79.1%)</td>
<td>42 (20.8%)</td>
</tr>
<tr>
<td>Zhang JJ, et al.</td>
<td>139</td>
<td>55 (39.6%)</td>
<td>84 (60.4%)</td>
</tr>
</tbody>
</table>

COVID-19 - coronavirus disease 2019, N - Number

### Incidence of Type of Gastrointestinal Symptoms exhibited in COVID-19 Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Anorexia N (%)</th>
<th>Nausea N (%)</th>
<th>Vomiting N (%)</th>
<th>Diarrhea N (%)</th>
<th>Abdominal Pain N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan L, et al.11</td>
<td>103</td>
<td>81 (78.6%)</td>
<td>NA</td>
<td>4 (3.9%)</td>
<td>35 (34%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Jin X., et al.7</td>
<td>74</td>
<td>NA</td>
<td>13 (17.5%)</td>
<td>14 (18.6%)</td>
<td>56 (75%)</td>
<td>NA</td>
</tr>
<tr>
<td>Fang D, et al.16</td>
<td>201</td>
<td>NA</td>
<td>59 (29.4%)</td>
<td>32 (16%)</td>
<td>44 (22%)</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Guan W, et al.18</td>
<td>1095</td>
<td>NA</td>
<td>55 (5%)</td>
<td>55 (5%)</td>
<td>42 (3.8%)</td>
<td>NA</td>
</tr>
<tr>
<td>Zhang JJ, et al.17</td>
<td>139</td>
<td>17 (12.2%)</td>
<td>24 (17.3%)</td>
<td>7 (5%)</td>
<td>18 (13%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Wang D, et al.19</td>
<td>138</td>
<td>55 (40%)</td>
<td>14 (10%)</td>
<td>5 (3.6%)</td>
<td>14 (10%)</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Shi H, et al.20</td>
<td>81</td>
<td>1 (1%)</td>
<td>NA</td>
<td>4 (5%)</td>
<td>3 (4%)</td>
<td>NA</td>
</tr>
<tr>
<td>Zhou F, et al.21</td>
<td>191</td>
<td>NA</td>
<td>7 (4%)</td>
<td>7 (4%)</td>
<td>9 (5%)</td>
<td>NA</td>
</tr>
<tr>
<td>Mo P, et al.22</td>
<td>155</td>
<td>NA</td>
<td>3 (3.7%)</td>
<td>3 (4%)</td>
<td>7 (4.5%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Chen N, et al.23</td>
<td>99</td>
<td>NA</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>NA</td>
</tr>
<tr>
<td>Yang X. et al.24</td>
<td>52</td>
<td>NA</td>
<td>NA</td>
<td>2 (4%)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

COVID-19-coronavirus disease 2019, NA- not applicable
<table>
<thead>
<tr>
<th>GI and Liver Symptoms</th>
<th>All Studies % (95% CI)</th>
<th>Studies from China % (95% CI)</th>
<th>Studies from countries other than China % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea in all Patients*</td>
<td>7.7% (7.2 to 8.2)</td>
<td>5.8% (5.3 to 6.4)</td>
<td>18.3% (16.6 to 20.1)</td>
</tr>
<tr>
<td></td>
<td>N/n = 43/10,676</td>
<td>N/n = 32/8,612</td>
<td>N/n = 11/2,064</td>
</tr>
<tr>
<td>Nausea/Vomiting in all Patients*</td>
<td>7.8% (7.1 to 8.5)</td>
<td>5.2% (4.4 to 5.9)</td>
<td>14.9% (13.3 -16.6)</td>
</tr>
<tr>
<td></td>
<td>N/n = 26/5,955</td>
<td>N/n = 19/4,054</td>
<td>N/n = 7/1,901</td>
</tr>
<tr>
<td>Abdominal Pain*</td>
<td>3.6% (3.0 to 4.3)</td>
<td>2.7% (2.0 to 3.4)</td>
<td>5.3% (4.2 to 6.6)</td>
</tr>
<tr>
<td></td>
<td>N/n = 15/4,031</td>
<td>N/n = 10/2,447</td>
<td>N/n = 5/1,584</td>
</tr>
<tr>
<td>Patients with Elevated AST</td>
<td>15.0% (13.6 to 16.5)</td>
<td>14.9% (13.5 to 16.4)</td>
<td>20.0% (12.8 to 28.1)</td>
</tr>
<tr>
<td></td>
<td>N/n = 16/2,514</td>
<td>N/n = 14/2,398</td>
<td>N/n = 2/116</td>
</tr>
<tr>
<td>Patients with Elevated ALT</td>
<td>15.0% (13.6 to 16.4)</td>
<td>14.9% (13.5 to 16.3)</td>
<td>19.0% (12.0 to 27.1)</td>
</tr>
<tr>
<td></td>
<td>N/n = 17/2,711</td>
<td>N/n = 15/2,595</td>
<td>N/n = 2/116</td>
</tr>
<tr>
<td>Patients with Elevated T. Bilirubin</td>
<td>16.7% (15.0 to 18.5)</td>
<td>16.7% (15.0 to 18.5)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>N/n = 10/1841</td>
<td>N/n = 10/1841</td>
<td></td>
</tr>
</tbody>
</table>

*Regardless of Hospitalization and Timing of Symptoms.

Abbreviations: T. Bilirubin=total bilirubin; CI=confidence interval; N=number of studies; n=number of patients.

GI MANIFESTATIONS

- Diarrhea (7.2%-18.3%)
  - Duration 1-4 days, Stool culture -, Stool Leukocytes -
- Loss of appetite (39.9%-50.2%)
- Nausea (1%-29.4%)
- Vomiting (3.6%-66.7%)
- Abdominal pain(3.9%)
- GI symptoms may occur before COVID-19
- Respiratory symptom

PATHOPHYSIOLOGY

- Enterocyte invasion via ACE2 receptor → increase permeability and malabsorption
- Inflammatory reaction
- ACE2 receptor was found along the digestive tract lining

SARS-CoV-2
- Spike protein
- Viral RNA
- ACE2

New infecting SARS-CoV-2

- Direct activation, lectin pathway
- Immune complexes, classical pathway

Complement activation
- C3
- C3a
- C5
- C5a

Cytokine release syndrome and accumulation of neutrophils and monocytes/macrophages
- IL-1
- IL-5
- IL-8
- IL-21
- TNF
- CCL2

Host cell ribosomes
- Genomic RNA release
- Genomic RNA replication
- Translation
- Proteolysis
- Multiple proteins

Virus entry

Virus replication in the airway cells

Activation of innate immunity in the lung: maladaptive inflammatory response

ARDS

Day 0

Day 1-2

Day 3-5

Day 5-7

Day 7-14
SARS-CoV (& SARS-CoV-2?)

- Fever
- Dry cough
- Dyspnea
- Diarrhea

Potential immune responses:

- T cells
- NK cells
- CD8+ T cells
- CD4+ T cells
- IFN
- NF-κb
- Th17

Related cytokines:

- IL-1
- IL-6
- IL-8
- IL-21
- TNF-β
- MCP-1

Other cells and factors:

- B cells
- Macrophages
- Antibodies
- C3a
- C5a
**Gut-Lung Axis**

**GUT**
- Bacterial ligands (e.g., Lipopolysaccharide)
- Bacterial metabolites (e.g., Short chain fatty acids)
- Migratory cells (e.g., T cells)

**AIRWAY-LUNGS**
- Good clearance mechanism
- Normal ciliary function

**Normal microbiome**
- Proteobacteria
- Firmicutes
- Actinobacter
- Fusobacterium
- Bacteroidetes

**Innate immune response**
- E.g., Innate lymphoid cell type 3 (ILC-3)

**Acquired immune response**
- E.g., T helper cell-dendritic cell interaction to generate inhibitory T<sub>reg</sub> cells
EVIDENCE OF SARS COV-2 IN GI TRACT

- Some studies → viral RNA was found in saliva and stool
- Viral RNA in saliva → highest viral load on 1st week, and detectable until 29 days
- Study from Cai et al → RNA COVID-2 can be detected 2 weeks until 1 month
- Viral RNA in stool can remain even after viral RNA in the respiratory tract clears → Fecal-oral transmission and diagnostic are unclear
HEPATOBILIARY AND PANCREAS MANIFESTATION

- Increased transaminase serum (14.8%-53%)
- Increased bilirubin serum
- Increased Amilase and lipase (17%)
POST MORTEM PATHOLOGICAL FINDING

- Xu et al:
  - Moderate Microvesicular steatosis and mild lobular activity

- Liu et al
  - Lobular focal necrosis with infiltration of neutrophils, hepatic sinuses congestion with microthrombosis, and monocytes and lymphocytes in the portal area.
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients (N)</th>
<th>AST N (%)</th>
<th>ALT N (%)</th>
<th>Total Bilirubin N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan L, et al.</td>
<td>204</td>
<td>22 (11%)</td>
<td>27 (13%)</td>
<td>NA</td>
</tr>
<tr>
<td>Fang D, et al.</td>
<td>304</td>
<td>24 (8%)</td>
<td>19 (6%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Guan W, et al.</td>
<td>741</td>
<td>168 (22%)</td>
<td>158 (21%)</td>
<td>76 (10%)</td>
</tr>
<tr>
<td>Chen N, et al.</td>
<td>99</td>
<td>35 (35%)</td>
<td>28 (28%)</td>
<td>18 (18%)</td>
</tr>
<tr>
<td>Xu X, et al.</td>
<td>62</td>
<td>10 (16%)</td>
<td>26 (20-32)</td>
<td>NA</td>
</tr>
<tr>
<td>Huang C et al.</td>
<td>41</td>
<td>15 (37%)</td>
<td>32 (21-50)</td>
<td>11.7 (9.5-13.9)</td>
</tr>
<tr>
<td>Zhou F, et al.</td>
<td>189</td>
<td>NA</td>
<td>59 (31%)</td>
<td>NA</td>
</tr>
<tr>
<td>Mo P, et al.</td>
<td>155</td>
<td>32 (24-48)</td>
<td>23 (16-38)</td>
<td>NA</td>
</tr>
<tr>
<td>Shi H, et al.</td>
<td>81</td>
<td>43 (53%)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

COVID-19-coronavirus disease 2019, AST-Aspartate aminotransferase, ALT- Alanine aminotransferase, ++ median in mmol/L, + median in U/L, N- number
PATOPHYSIOLOGY OF LIVER INVOLVEMENT

- Unclear mechanism
  - Viral invasion via ACE2 receptor
    - ACE2 receptor was found along the digestive lining (such as Cholangiocytes, and little found in hepatocytes)
  - Immune-mediated → cytokine storm
  - Hypoxemia → Ischemic hepatitis
  - Drug hepatotoxicity (Chloroquine; macrolides; quinolones; and lopinavir/ritonavir)

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Medication Name</th>
<th>Gastrointestinal AEs</th>
<th>Hepatic AEs</th>
<th>Major drug-drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-malarial</td>
<td>Chloroquine</td>
<td>Nausea, vomiting, abdominal pain, and diarrhea reported; frequency not defined</td>
<td>Likelihood score: D (possible rare cause of clinically apparent liver injury) Description: Rare elevations in aminotransferases. Most reactions are hypersensitivity with no known cross reactivity to hepatic injury. If this occurs, reasonable to switch between chloroquine therapies</td>
<td>Substrate for CYP2D6 and CYP3A4 substrate</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine</td>
<td></td>
<td></td>
<td>Same as above; also substrate for CYP3A5 and CYP2C8</td>
</tr>
<tr>
<td>Anti-viral</td>
<td>Remdesivir</td>
<td>Not reported (limited data available)</td>
<td>Likelihood score: Not scored Description: Hepatotoxicity reported; frequency not yet known</td>
<td>Not a significant inducer/inhibitor of CYP enzymes</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/ritonavir</td>
<td>Nausea and vomiting: 5-10% (higher in children: 20%) Abdominal pain: 1-10% Diarrhea: 10-30% + dose-dependent Other: dysgesia in adults &lt;2%, children: 25%, increased serum amylase, lipase: 3-8%</td>
<td>Likelihood score: D (possible, rare cause of clinically apparent liver injury) Description: Hepatotoxicity ranges from mild elevations in aminotransferases to acute liver failure. Recovery takes 1-2 months. Re-challenging may lead to recurrence and should be avoided if possible.</td>
<td>Substrate for: CYP3A4, CYP2D6</td>
</tr>
<tr>
<td></td>
<td>Favipiravir</td>
<td>Nausea/vomiting: 5-15% Diarrhea: 5% Limited data available</td>
<td>Likelihood score: Not scored Description: 3% prevalence, but little data available</td>
<td>Inhibitor for: CYP2C8 and aldehyde oxide Metabolized by xanthine oxidase and aldehyde oxidase</td>
</tr>
</tbody>
</table>

IMPLICATIONS OF GI-LIVER INVOLVEMENT RELATED TO COVID-19 PROGNOSIS

- No significant difference in Procalcitonin and CRP between patients with and without GI related symptoms
- ARDS occurs significantly more common in COVID-19 patient groups with GI symptom
- Liver injury more commonly occur among COVID-19 patients with GI symptom
- More likely to be transferred to ICU and need mechanical ventilation

Jin X et al. The Lancet Gastroenterology & Hepatology. 2020
DIAGNOSTIC APPROACH

- Patient with diarrhea → information about contact exposure, obtain a detailed history of symptoms associated with COVID-19, obtain a thorough history for other GI symptoms, including nausea, vomiting, and abdominal pain
- Patient with elevated transaminase serum → is there other etiology?
- Presently → Stool testing for COVID-19 diagnosis is not recommended
Management of COVID in GI & Liver

• Treat COVID-19 using available drug

• Supportive & Symptomatic therapy
  • Nausea and vomiting → anti-emetic
  • Diarrhea → anti-diarrhea

• Patient with eating problem → Consider enteral/parenteral nutrition
DIGESTIVE ENDOSCOPY IN COVID-19 PANDEMIC

- Prior to any procedure, COVID-19 screening is performed first
- If the initial screening is negative → secondary protection standards
- If COVID-19 is diagnosed or suspected → tertiary protection standards and in a negative pressure procedure room
- Patients who are unable to be screened for COVID-19 due to emergency are treated as suspected cases

Sherief M. Journal of Gastroenterology. 2020
DIGESTIVE ENDOSCOPY IN COVID-19 PANDEMIC

- American Society of Gastrointestinal Endoscopy: Endoscopy, ERCP are high-risk procedures → potential transmission of the virus via a fecal-oral route
- Colonoscopy: Intermediate-risk
- Suspend elective endoscopy procedures

Sherief M. Journal of Gastroenterology, 2020
workflow in GI endoscopy units during SARS-CoV-2 outbreak
TERIMA KASIH

STAY HOME
STAY SAFE

LET'S STOP
CORONAVIRUS