

COVID-19:
Gastrointestinal / Liver manifestations
&
Procedure Recommendation

整理：胃腸肝膽科系 馬德齡醫師

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GI manifestation in COVID-19

- An outbreak of coronavirus disease 2019 (**COVID-19**) has rapidly spread from China to almost all over the world affecting over 800,000 people across 199 countries.
 - Typical presentations of infection such as fever, cough, myalgia, fatigue and pneumonia are well recognized, while extrapulmonary symptoms may occur early in the disease course.
- Single cell analysis revealed the **digestive system as a potential route for the virus infection**, it is theoretically plausible that a portion of patients may present with GI tract symptoms

*- Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. **Gut.** 2020*

GI manifestation in COVID-19

- **ACE2** was not only highly expressed in the lung AT2 cells, but also in esophagus upper and stratified epithelial cells and absorptive enterocytes from ileum and colon

➤ **digestive system might be vulnerable** to COVID-19 infection

- Hao Zhang et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. *bioRxiv* 2020.01.30.927806

- **SARS-CoV-2 could be detected at various GI locations** in biopsies taken during endoscopy, even in patients **without GI symptoms**.

- Including **esophagus, stomach, duodenum and rectum**
- highlighting the **potential of faecal-oral transmission**

- Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA*. 2020

- **Not clear correlation of GI symptoms and detectable virus** in the stool

- outpatient centres of GI endoscopy may become **high-risk places**

- Ng SC, Tilg H. COVID-19 and the gastrointestinal tract: more than meets the eye. *Gut*. 2020

GI manifestation in COVID-19

- **>20%** of infected patients had **positive virus in faeces even after clearance of virus in the respiratory tract**
 - In over half of the patients, faecal samples remained positive for SARS-CoV2 RNA for a mean of **11 days after clearance of respiratory tract samples**

- Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology*. 2020

- **Digestive system** other than respiratory system may serve as an **alternative route** of infection when people are in contact with infected wild animals or sufferers
 - Clinicians should be **careful to promptly identify the patients with initial gastrointestinal symptoms**

- Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. *Gastroenterology*. 2020

GI manifestation in COVID-19

- Gastrointestinal (GI) symptoms, including **anorexia, nausea, vomiting, abdominal pain**, and/or **diarrhea** may occur early, but are **rarely the sole presenting feature**
- Based on a recent meta-analysis of 4243 patients from China. Approximately **17.6%** of patients had any gastrointestinal symptom, including 9.2% with pain, 12.5% with diarrhea, 10.2% with nausea/vomiting
- Up to **28%** of those with GI symptoms did **not** have respiratory symptoms

- Cheung KS, Hung IF, Chan PP, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis. *Gastroenterology*. 2020

- Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020

GI manifestation in COVID-19

- **Diarrhea** is the **most common (~71.6%)** GI symptom.
 - The median duration period was 4 days (**IQR: 3–6 days**). The shortest duration of 1 day and longest of 9 days.
 - Most diarrhoea was **self-limiting**
- 31.1% patients with **GI symptoms had family clustering**, which was prominently higher than that in patients without GI symptoms (20.45%, $p=0.037$)
 - May be related to **faecal shedding in shared toilets** in households
- The rate of **chronic liver disease** was 10.81% in patients with COVID-19 with **GI symptoms, which was significantly higher** than that of 2.95% in those without GI symptoms ($p=0.004$)

- Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020

GI manifestation in COVID-19

- Patients with COVID-19 with **GI symptoms had higher prevalence** in symptoms of **fever >38.5°C, fatigue, shortness of breath and headache**, respectively
- The rate of **increased AST**, but **not ALT**, was significantly higher in patients with COVID-19 with GI symptoms than in those without GI symptoms (29.35 vs 24.4, p=0.02)
- The rate of **unilateral pneumonia** was **12.16%** in patients with GI symptoms, **much lower** than 23.22% in those without GI symptoms (p=0.030)

- Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020

GI manifestation in COVID-19

- The rate of the **severe/critical type** was also markedly **increased in patients with COVID-19 with GI symptoms** than in those without GI symptoms (22.97% vs 8.14%, $p < 0.001$).
 - Especially in **ARDS** and **liver injury** ($p = 0.034$; $p = 0.035$)
 - **Sputum production**, increased **LDH/glucose** levels were the **independent risk factors for severe/ critical COVID-19 in patients with GI symptoms**
- **6.76%** patients with COVID-19 with GI symptoms were treated with mechanical **ventilation and transferred to the ICU**
 - significantly higher rate than that of 2.08% in the patients with COVID-19 without GI symptoms ($p = 0.034$)
 - **GI symptoms** may cause patients with COVID-19 to be more **prone to electrolyte disturbance**, such as significantly **decreased serum sodium levels** ($p = 0.016$), and hence they **trend towards the severe/critical type of the disease**

Liver manifestation in COVID-19

- Liver injury is estimated to occur in up to **20-30%** of patients at the time of diagnosis with SARS-CoV-2 infection
 - **more prevalent in severe cases** than in mild cases of COVID-19.

*- Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. **Gastroenterology**. 2020*

- Mild to moderate liver injury including **elevated aminotransferases, hypoproteinemia** and **prothrombin time prolongation** has been reported in the existing clinical investigations of COVID-19
 - **Severe hepatitis** has been reported but **liver failure appears to be rare**
 - The pattern of **liver injury appears to be predominantly hepatocellular.**
 - **not** appear to be a **major predictor of clinical outcomes**

*- Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. **Lancet Gastroenterol Hepatol**. 2020;5(5):428-430*

Liver manifestation in COVID-19

- Liver biopsy specimens obtained from a patient with COVID-19 disease revealed **microvesicular steatosis** and **mild lobular and portal activity**

- Suggestive of either **SARSCoV-2 infection** or **drug-induced liver injury**

- Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med.* 2020;8(4):420-422

- Recent single cell RNA sequencing data from independent cohorts revealed a significant enrichment of **ACE2 expression in cholangiocytes** (59.7% of cells) instead of hepatocytes (2.6% of cells)

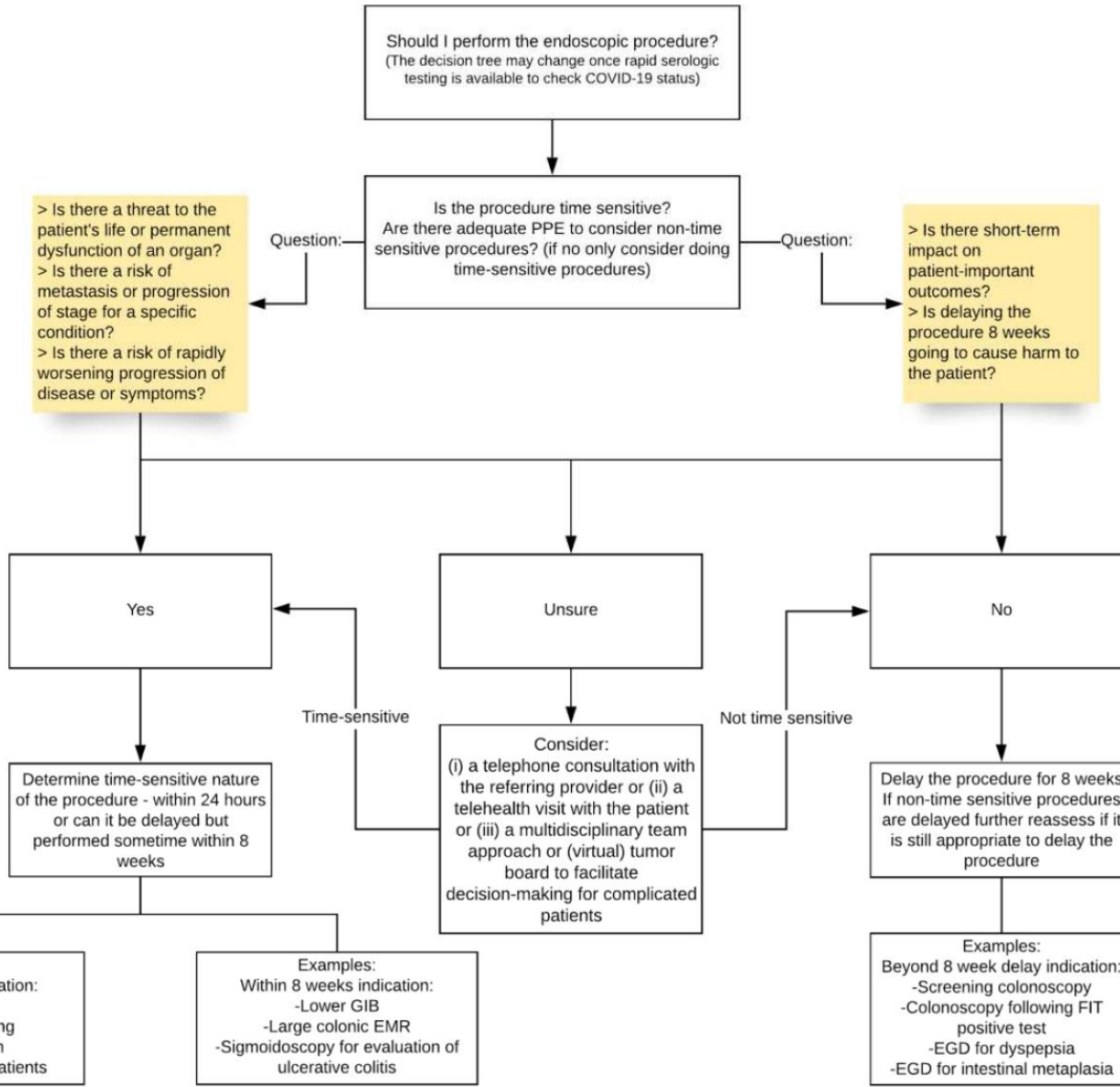
- suggesting that **2019-nCoV might lead to direct damage of intrahepatic bile ducts**

- Chai XQ, Hu LF, Zhang Y, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. *bioRxiv* 2020.02.03.931766

How should medical staff triage GI procedures?

- In evidence of **upper GI bleeding** likely should have an **EGD performed within 24 hours**
- **lower GI bleeding**, might **consider opting to delay** the procedure (especially while awaiting COVID-19 testing)
 - following a **positive FIT test**, a **colonoscopy can be delayed up to 6 months** without negatively impacting patient outcomes.
- Indirect evidence supports that **delays of weeks to a few months** in some **cancer diagnoses may not** lead to progression of stage or worse clinical outcomes even when symptoms are present in some GI cancers.

Framework for Triage



Time-Sensitive* (within 24 hours-8 weeks)			Non-Time Sensitive
Threat to the patient's life or permanent dysfunction of an organ	Risk of metastasis or progression of stage of disease	Risk of rapidly worsening progression of disease or severity of symptoms	No short-term impact on patient-important outcomes
e.g. diagnosis and treatment of GI bleeding or cholangitis	e.g. work up of symptoms suggestive of cancer	e.g. management decisions, such as treatment for IBD	e.g. screening or surveillance colonoscopy, follow up colonoscopy for +FIT

- Sultan S, Lim JK, Altayar O, et al. AGA Institute Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic. *Gastroenterology*. 2020

Summary

- Digestive system might be vulnerable to COVID-19 infection
- GI symptoms including **anorexia, nausea, vomiting, abdominal pain**, and/or **diarrhea**, but are rarely the sole presenting feature
 - **Diarrhea** is the most common GI symptom.
- Patients of COVID-19 with **GI symptoms** had prone to have **severe/critical disease** and **family clustering** history.
- The pattern of **liver injury** of COVID-19 appears to be predominantly **hepatocellular**.
 - Severe hepatitis has been reported but **liver failure appears to be rare**
- Current management of liver injury and GI symptoms are both **supportive therapy**.
- Medical staff should triage GI procedure carefully under COVID-19 pandemic.

Reference

- *Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. Gastroenterology. 2020*
- *Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020*
- *Ng SC, Tilg H. COVID-19 and the gastrointestinal tract: more than meets the eye. Gut. 2020*
- *Sultan S, Lim JK, Altayar O, et al. AGA Institute Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic. Gastroenterology. 2020*
- *Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5(5):428-430*