COVID-19 IN GASTROINTESTINAL AND HEPATOBILLIARY SYSTEM

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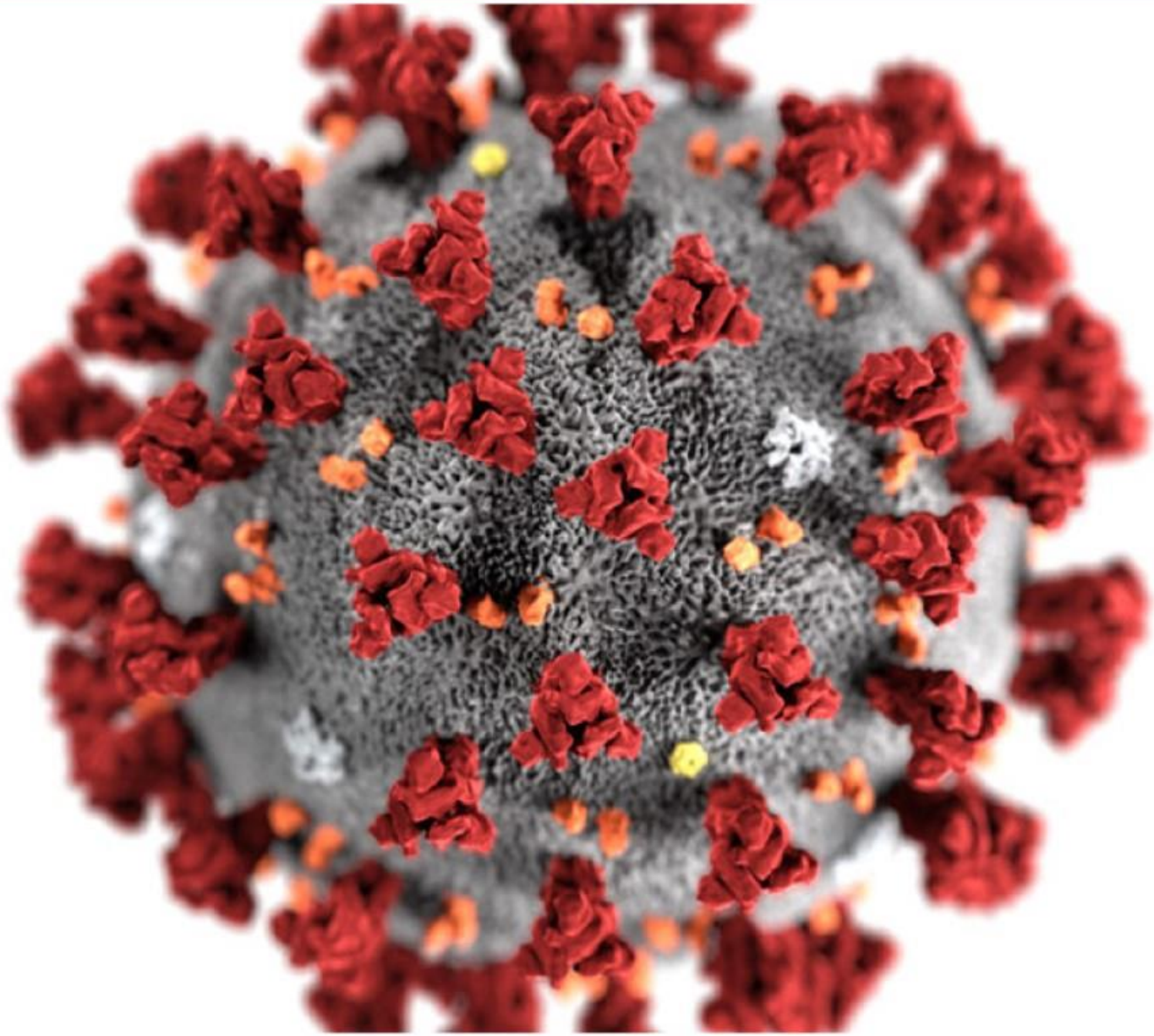
SARS-COV-2

- Genus ß 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?



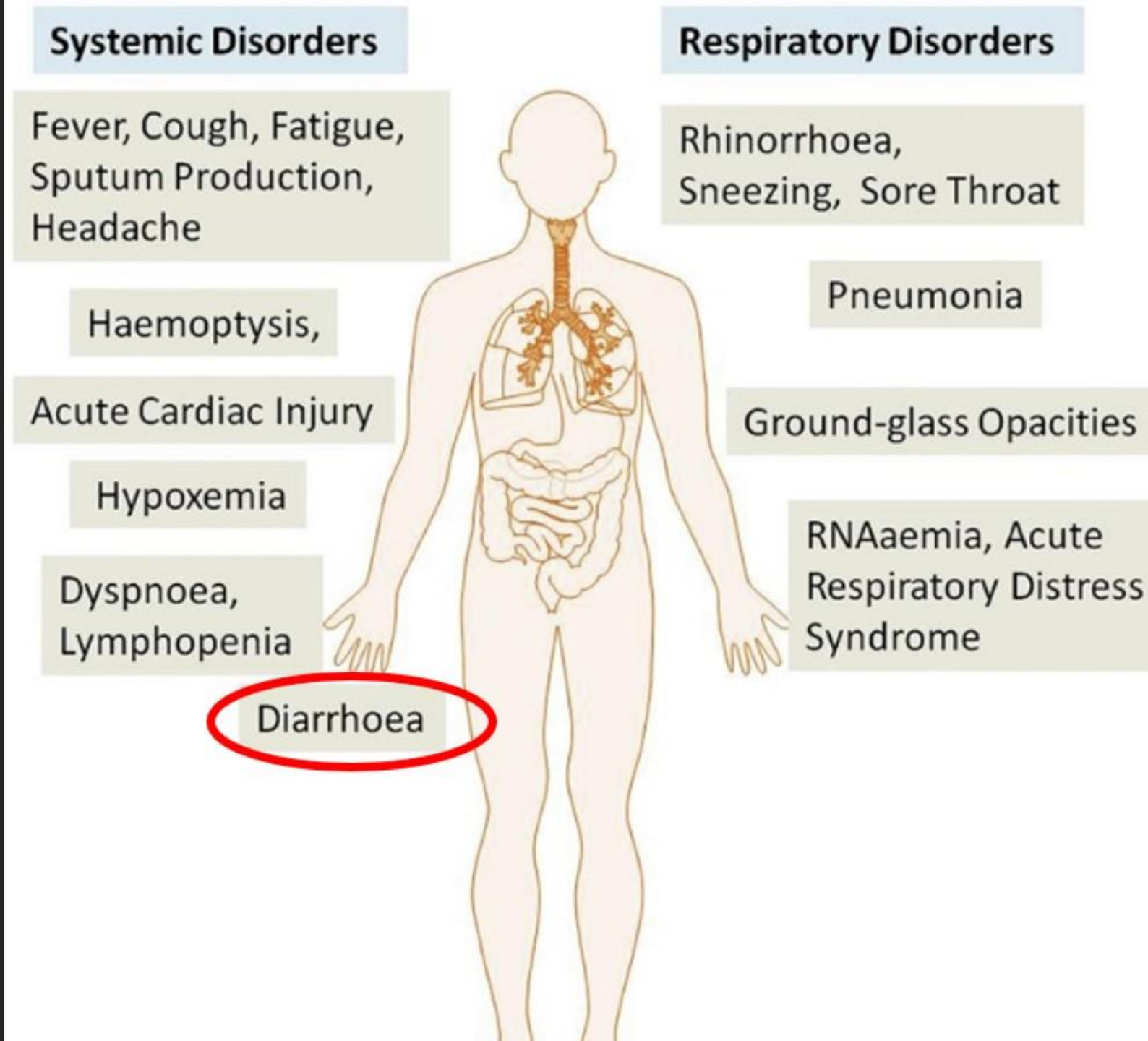
Kishan PP, et al. Journal of Clinical Virology. 2020

Symptoms near the time of presentation in various cohorts

	Guan et al. NEJM (largest cohort)	Shi et al Lancet	Yang et al. Lancet (critically ill pts)	Chen et al.	Huang et al.	Xu et al. BMJ
Constitutional						
Fever	473/1081 (43%)	18/21 (86%)	46/52 (88%)	82/99 (83%)	40/41 (98%)	48/62 (77%)
Myalgia	164/1081 (15%)		6/52 (12%)	11/99 (11%)		
Headache	150/1081 (14%)	2/21 (10%)	3/52 (6%)	8/99 (8%)	2/38 (8%)	21/62 (34%)
Upper respiratory						
Rhinorrhea	53/1081 (5%)	5/21 (24%)	3/52 (6%)	4/99 (4%)		
Sore throat	153/1081 (14%)			5/99 (5%)		
Lower respiratory						
Dyspnea	205/1081 (19%)	9/21 (43%)	33/52 (64%)	31/99 (31%)	22/40 (55%)	2/62 (3%)
Chest tightness		5/21 (24%)				
Cough	745/1081 (68%)	15/21 (71%)	40/52 (77%)	81/99 (82%)	31/41 (76%)	50/62 (81%)
Sputum	370/1081 (34%)	3/21 (14%)			11/39 (28%)	35/62 (56%)
Hemoptysis	10/1081 (1%)				2/39 (5%)	2/62 (3%)
Gastrointestinal						
Nausea/Vomiting	55/1081 (5%)	2/21 (10%)	2/52 (6%)	1/99 (1%)		
Diarrhea	42/1081 (4%)	1/21 (5%)		2/99 (2%)	1/38 (3%)	3/62 (8%)

Kishan PP, et al. Journal of Clinical Virology. 2020

CLINICAL MANIFESTATIONS



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

RECENTLY PUBLISHED REVIEW FROM AMERICAN GASTROENTEROLOGY ASSOCIATION (AGA)

RELEASED 4TH MAY 2020

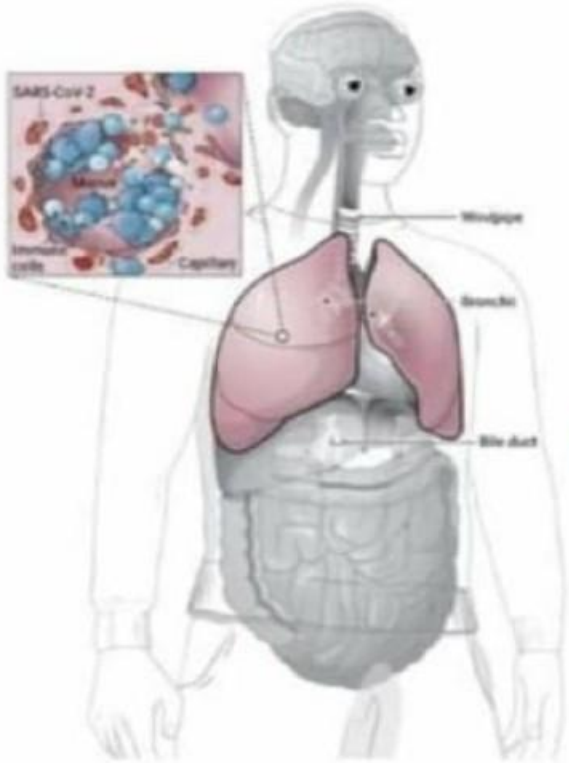
AGA Institute Rapid Review of the GI and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19

Authors: Shahnaz Sultan*[1], Osama Altayar*[2], Shazia M. Siddique[3], Perica Davitkov[4], Joseph D. Feuerstein[5], Joseph K. Lim[6], Yngve Falck-Ytter[4], Hashem B. El-Serag[7] 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.



Brain

Eyes

Nose

Lungs

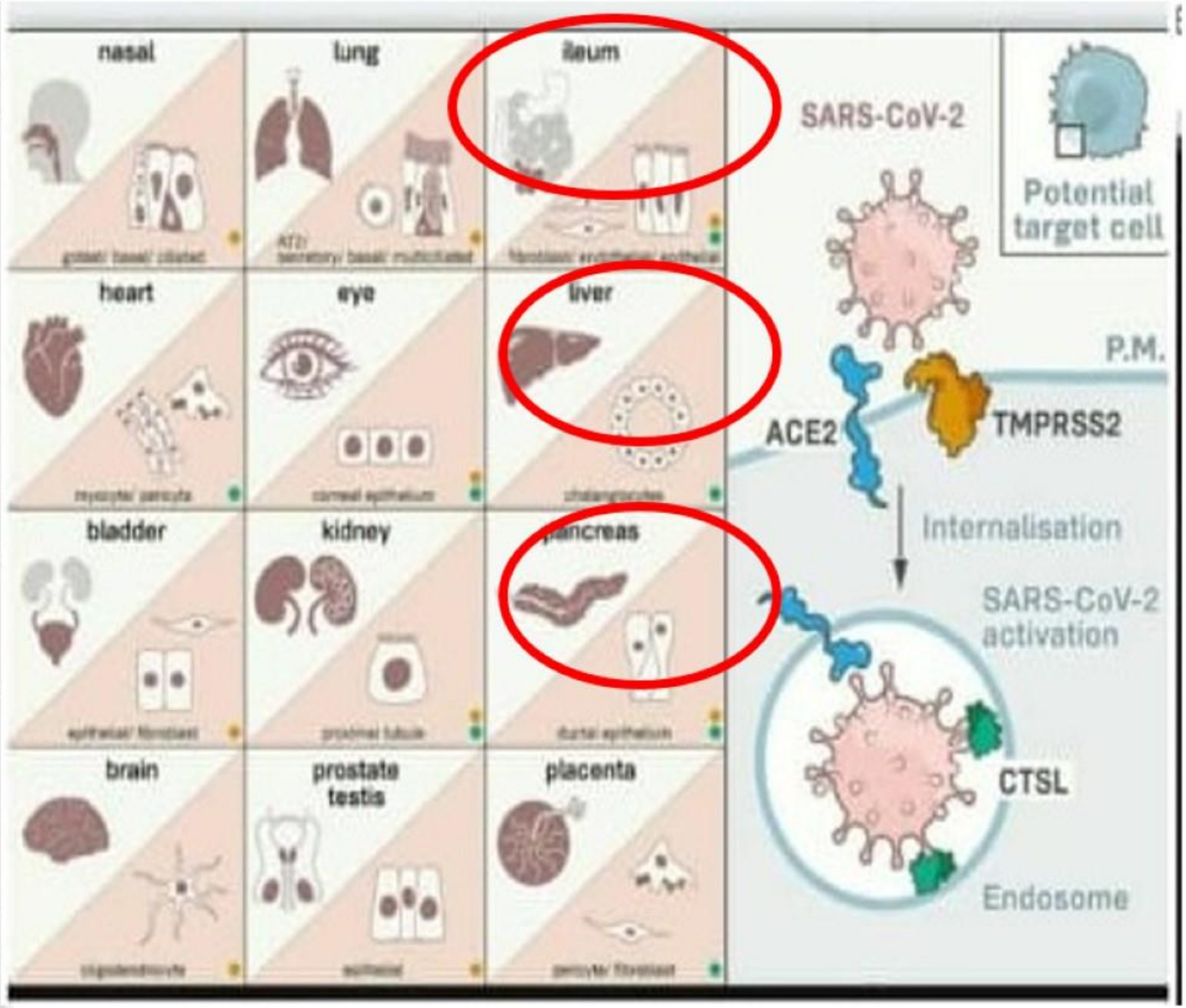
A cross section shows immune cells crowding an inflamed alveolus, or air sac, whose walls break down during attack by the virus, diminishing oxygen uptake. Patients cough, fevers rise, and breathing becomes labored.

Heart and blood vessels

Liver

Kidneys

Intestines



Sherief M. Journal of Gastroenterology. 2020

Incidence of Gastrointestinal (GI) Manifestations exhibited in COVID-19 Patients

Study	Number of Patients N	GI symptoms N (%)	No GI symptoms N (%)
Pan L, et al.[11]	203	103 (50.7%)	100 (49.3%)
Jin X., et al.[7]	651	74 (11.3%)	577 (88%)
Fang D, et al.[16]	201	159 (79.1%)	42 (20.8%)
Zhang JJ, et al[17]	139	55 (39.6%)	84 (60.4%)

COVID-19-coronavirus disease 2019, N- Number

Kishan PP, et al. Journal of Clinical Virology. 2020

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

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

COVID-19-coronavirus disease 2019, NA- not applicable

Kishan PP, et al. Journal of Clinical Virology. 2020

GI and Liver Symptoms	All Studies % (95% CI)	Studies from China % (95% CI)	Studies from countries other than China % (95% CI)
Diarrhea in all Patients*	7.7% (7.2 to 8.2) N/n = 43/10,676	5.8% (5.3 to 6.4) N/n = 32/8,612	18.3% (16.6 to 20.1) N/n = 11/2,064
Nausea/Vomiting in all Patients*	7.8% (7.1 to 8.5) N/n = 26/5,955	5.2% (4.4 to 5.9) N/n = 19/4,054	14.9% (13.3 -16.6) N/n = 7/1,901
Abdominal Pain*	3.6% (3.0 to 4.3) N/n = 15/4,031	2.7% (2.0 to 3.4) N/n = 10/2,447	5.3% (4.2 to 6.6) N/n = 5/1,584
Patients with Elevated AST	15.0% (13.6 to 16.5) N/n = 16/2,514	14.9% (13.5 to 16.4) N/n = 14/2,398	20.0% (12.8 to 28.1) N/n = 2/116
Patients with Elevated ALT	15.0% (13.6 to 16.4) N/n = 17/2,711	14.9% (13.5 to 16.3) N/n = 15/2,595	19.0% (12.0 to 27.1) N/n = 2/116
Patients with Elevated T. Bilirubin	16.7% (15.0 to 18.5) N/n = 10/1841	16.7% (15.0 to 18.5) N/n = 10/1841	-

*Regardless of Hospitalization and Timing of Symptoms.
Abbreviations: T. Bilirubin=total bilirubin; CI=confidence interval; N=number of studies; n=number of patients.

Shahnaz S , et al. America Gastroenterological Association. 2020

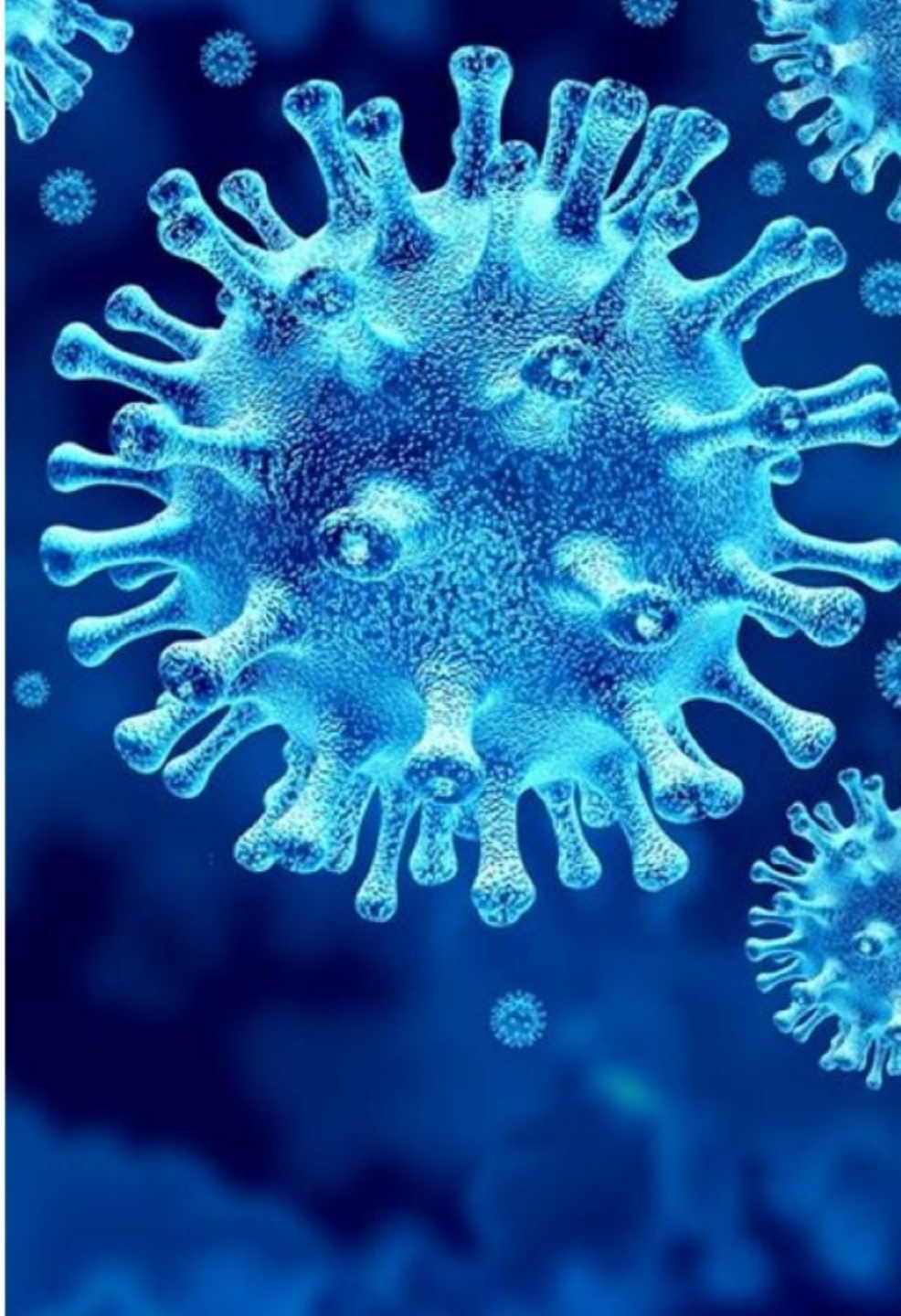
GI MANIFESTATIONS

- 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

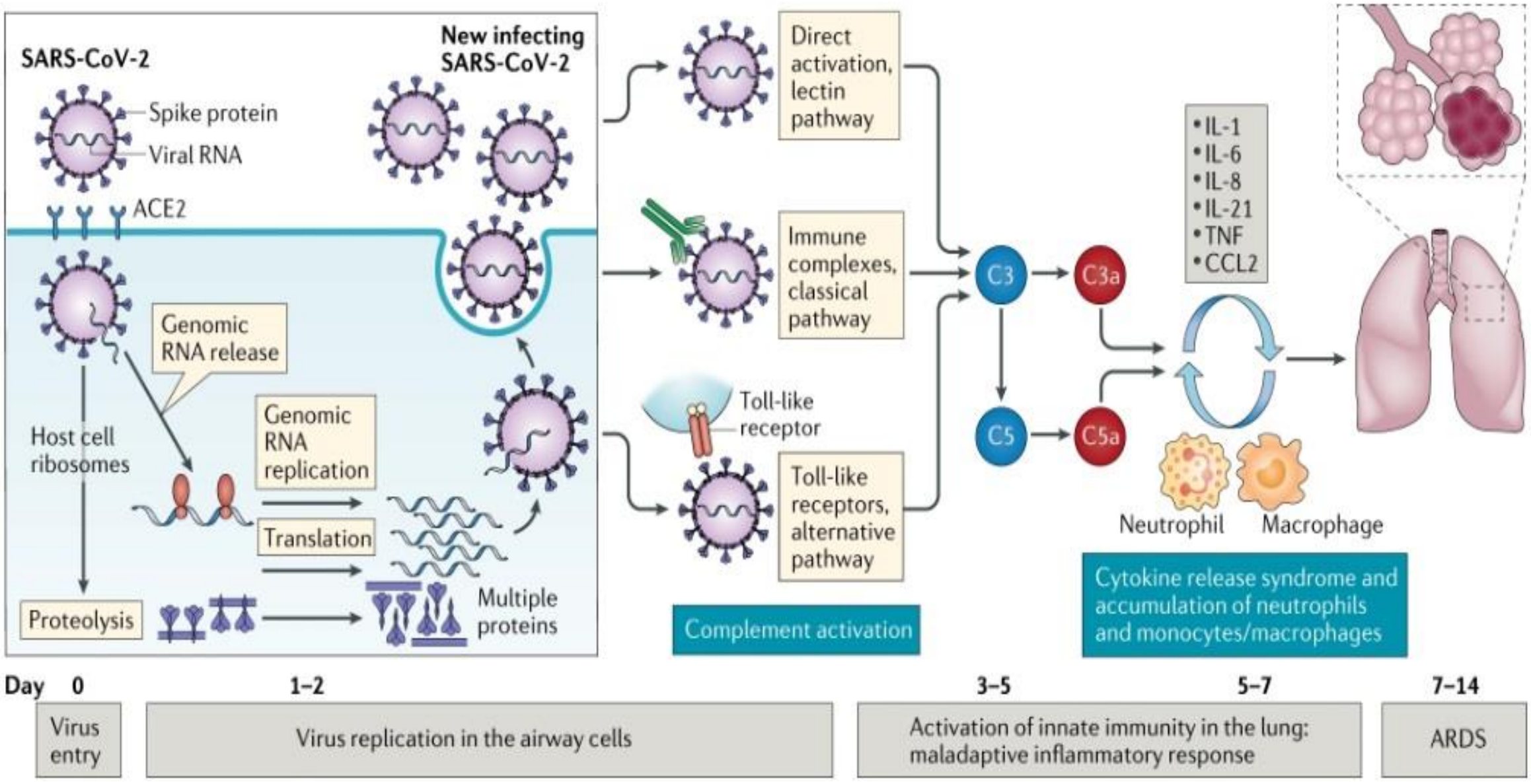
Shahnaz S , et al. America Gastroenterological Association. 2020

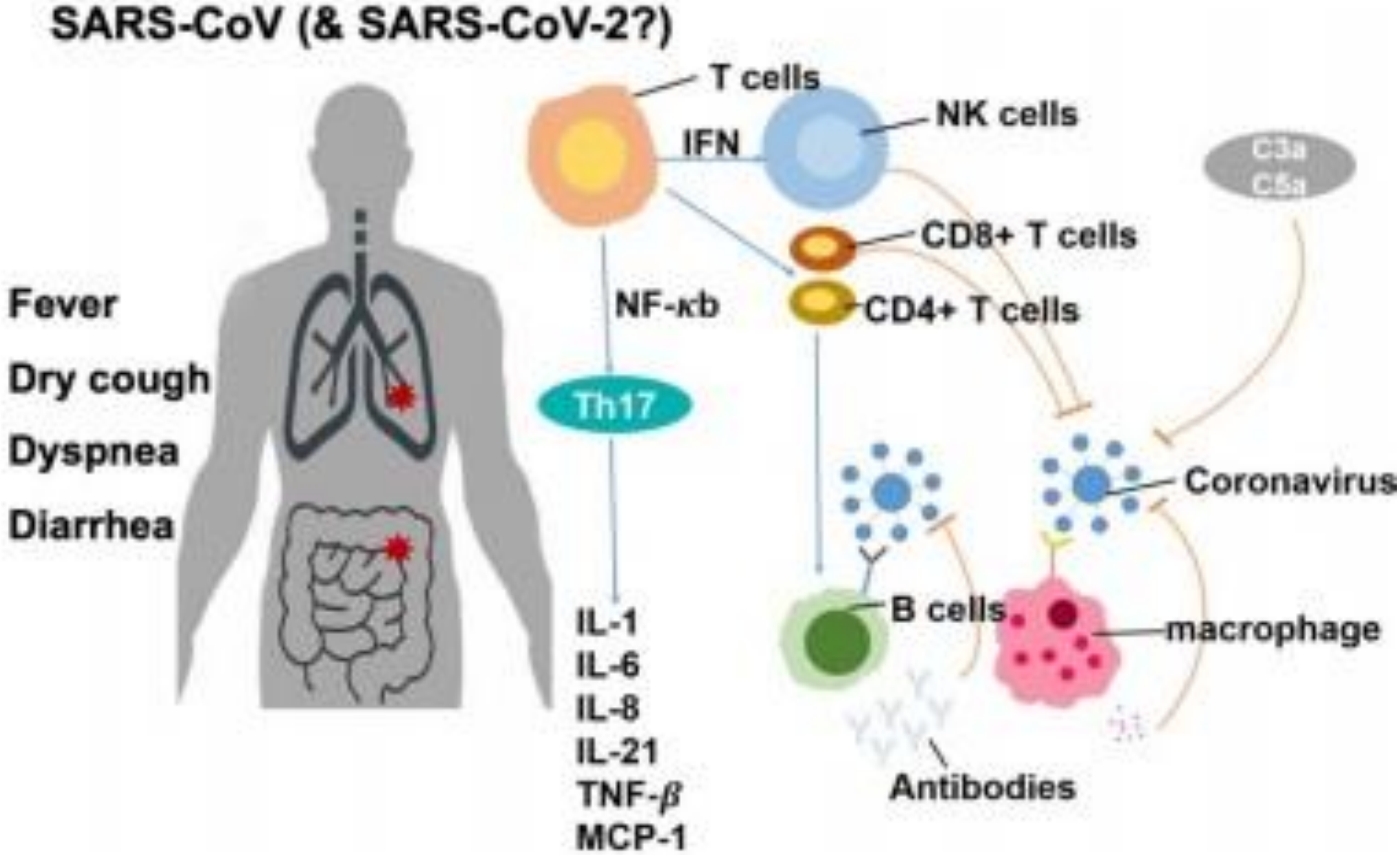
PATHOPHYSIOLOGY

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

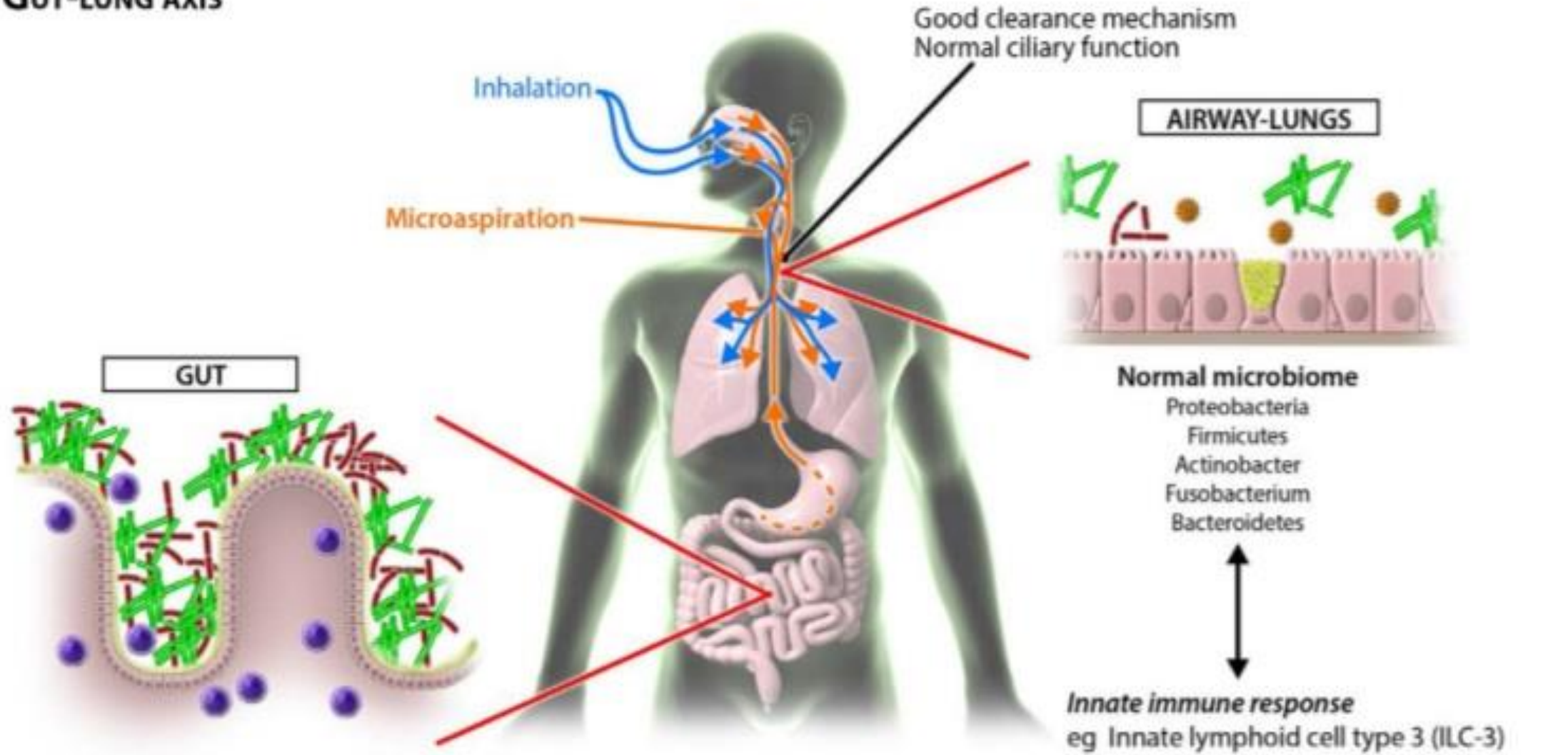


Azwar MK, et al. J Intern Med. 2020


SARS-CoV-2
New infecting SARS-CoV-2
Spike protein
Viral RNA
ACE2
Genomic RNA release
Host cell ribosomes
Genomic RNA replication
Translation
Proteolysis
Multiple proteins
Direct activation, lectin pathway
Immune complexes, classical pathway
Toll-like receptor
Toll-like receptors, alternative pathway
Complement activation
C3
C3a
C5
C5a
•IL-1
•IL-6
•IL-8
•IL-21
•TNF
•CCL2
Neutrophil
Macrophage
Cytokine release syndrome and accumulation of neutrophils and monocytes/macrophages
Day 0
1–2
3–5
5–7
7–14
Virus entry
Virus replication in the airway cells
Activation of innate immunity in the lung: maladaptive inflammatory response
ARDS


SARS-CoV (& SARS-CoV-2?)
T cells
NK cells
IFN
C3a
C5a
CD8+ T cells
CD4+ T cells
NF-κb
Fever
Dry cough
Dyspnea
Diarrhea
Th17
Coronavirus
B cells
macrophage
IL-1
IL-6
IL-8
IL-21
TNF-β
MCP-1
Antibodies

GUT-LUNG AXIS



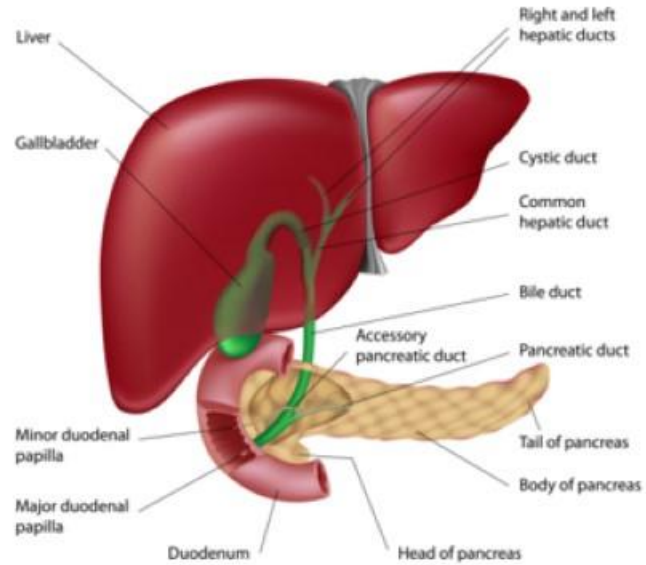
EVIDENCE OF SARS COV-2 IN GI TRACT

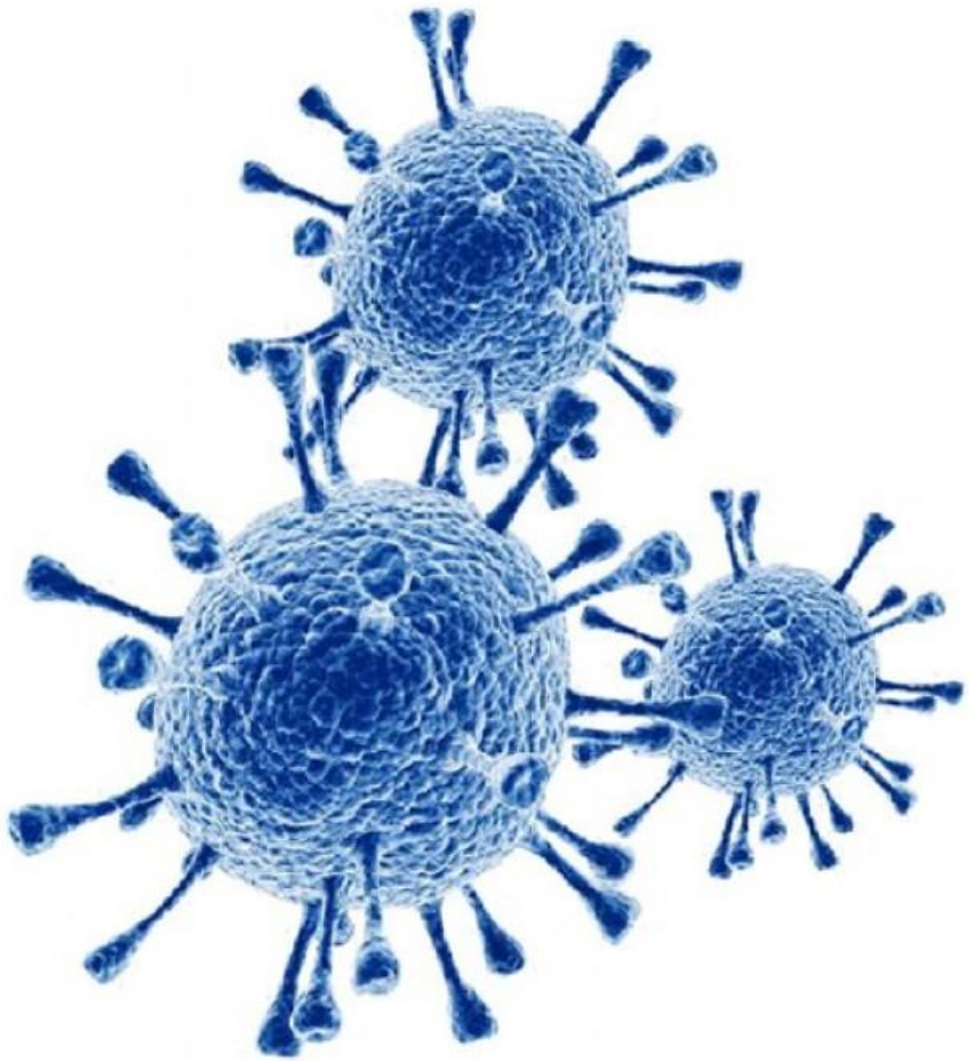
- Some studies→ viral RNA was found **in saliva and stool**
- Viral RNA in saliva→ highest viral load on 1st week, and detectable until 29 days
- Study from Cai et al → RNA COV-2 can be detected 2 weeks until 1 month
- Viral RNA in stool can remain even after viral RNA in the respiratory tract clears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

Shahnaz S , et al. America Gastroenterological Association. 20

HEPATOBILLIARY 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.

Hepatobiliary Laboratory Abnormalities seen in COVID-19 Patients

Study	Number of Patients (N)	AST N (%)	ALT N (%)	Total Bilirubin N (%)
Pan L, et al.[11]	204	22 (11%)	27 (13%)	NA
Fang D, et al.[16]	304	24 (8%)	19 (6%)	6 (2%)
Guan W, et al.[18]	741	168 (22%)	158 (21%)	76 (10%)
Chen N, et al.[23]	99	35 (35%)	28 (28%)	18 (18%)
Xu X, et al.[30]	62	10 (16%)	26 (20-32)+	NA
Huang C et al.[31]	41	15 (37%)	32 (21-50)+	11.7 (9.5-13.9)++
Zhou F, et al.[21]	189	NA	59 (31%)	NA
Mo P, et al.[22]	155	32 (24-48)++	23 (16-38)	NA
Shi H, et al.[20]	81	43 (53%)	NA	NA

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

Kishan PP, et al. Journal of Clinical Virology. 2020

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)

Kishan PP, et al. Journal of Clinical Virology. 2020

Medication Type	Medication Name	Gastrointestinal AEs	Hepatic AEs	Major drug-drug interactions
Anti-malarial	Chloroquine	Nausea, vomiting, abdominal pain, and diarrhea reported; frequency not defined	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	Substrate for CYP2D6 and CYP3A4 substrate
	Hydroxychloroquine			Same as above; also substrate for CYP3A5 and CYP2C8
Anti-viral	Remdesivir	Not reported (limited data available)	Likelihood score: Not scored Description: Hepatotoxicity reported; frequency not yet known	Not a significant inducer/inhibitor of CYP enzymes
	Lopinavir/ritonavir	Nausea and vomiting: 5-10% (higher in children: 20%) Abdominal pain: 1-10% Diarrhea: 10-30% + dose-dependent Other: dysguesia in adults <2%, children: 25%, increased serum amylase, lipase: 3-8%	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.	Substrate for: CYP3A4, CYP2D6 P-gp Inducer for: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A1 Inhibitor for: CYP3A4
	Favipiravir	Nausea/vomiting: 5-15% Diarrhea: 5% Limited data available	Likelihood score: Not scored Description: 3% prevalence, but little data available	Inhibitor for: CYP2C8 and aldehyde oxidase Metabolized by xanthine oxidase and aldehyde oxidase

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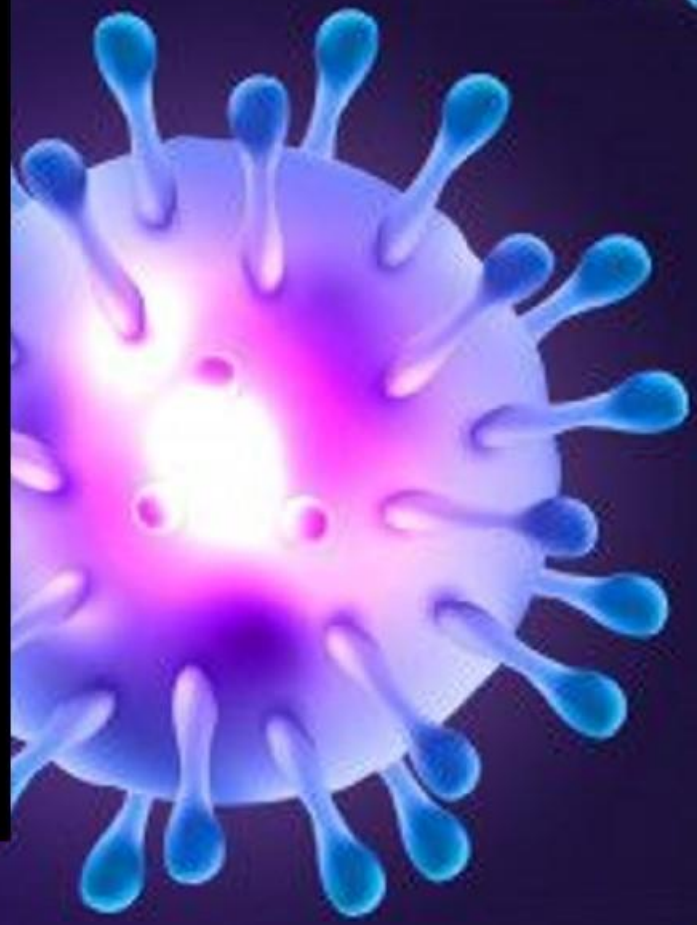
IMPLICATIONS OF GI-LIVER INVOLVEMENT RELATED TO COVID-19 PROGNOSIS

- 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 Gastroenteroogy & 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



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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

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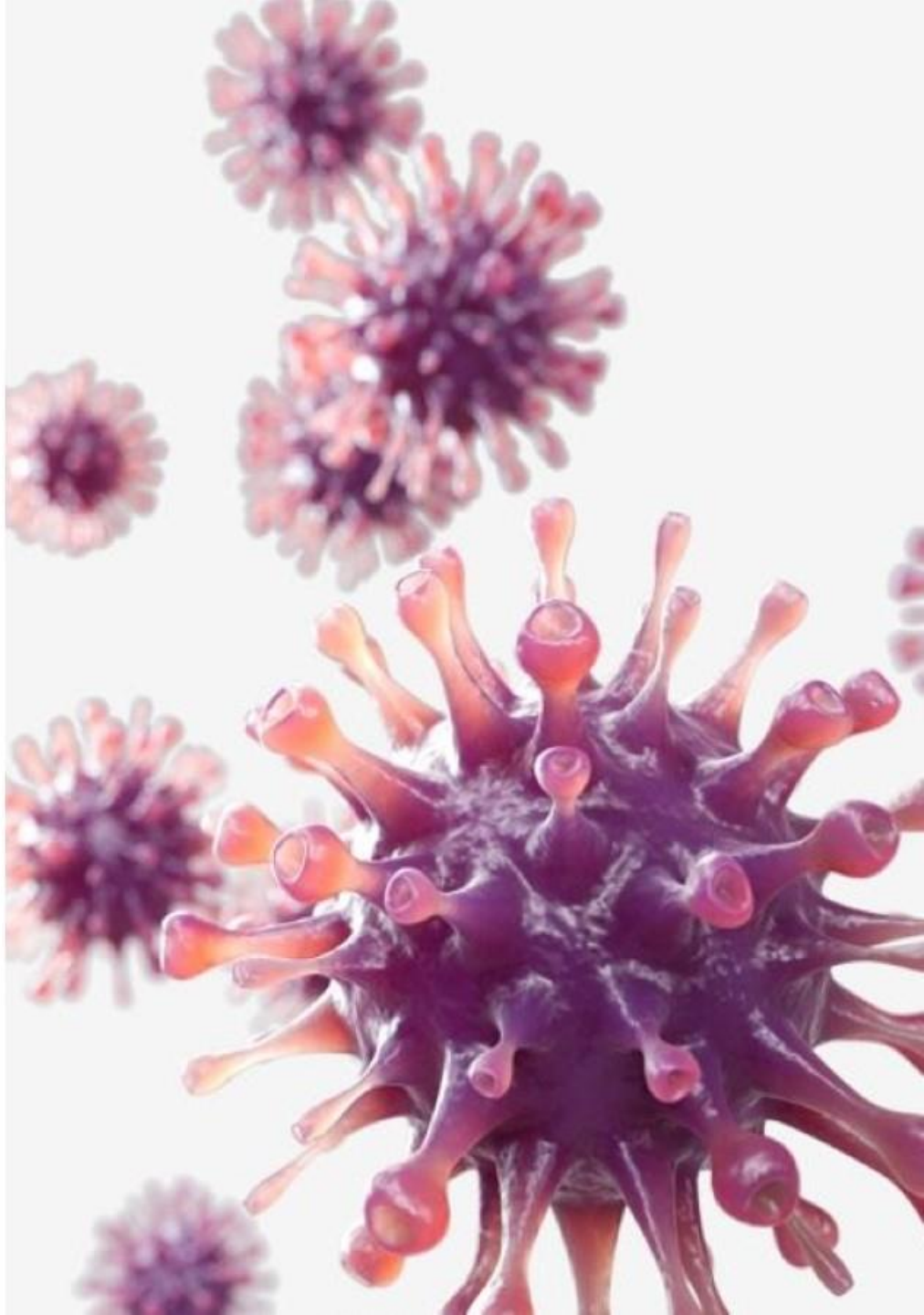
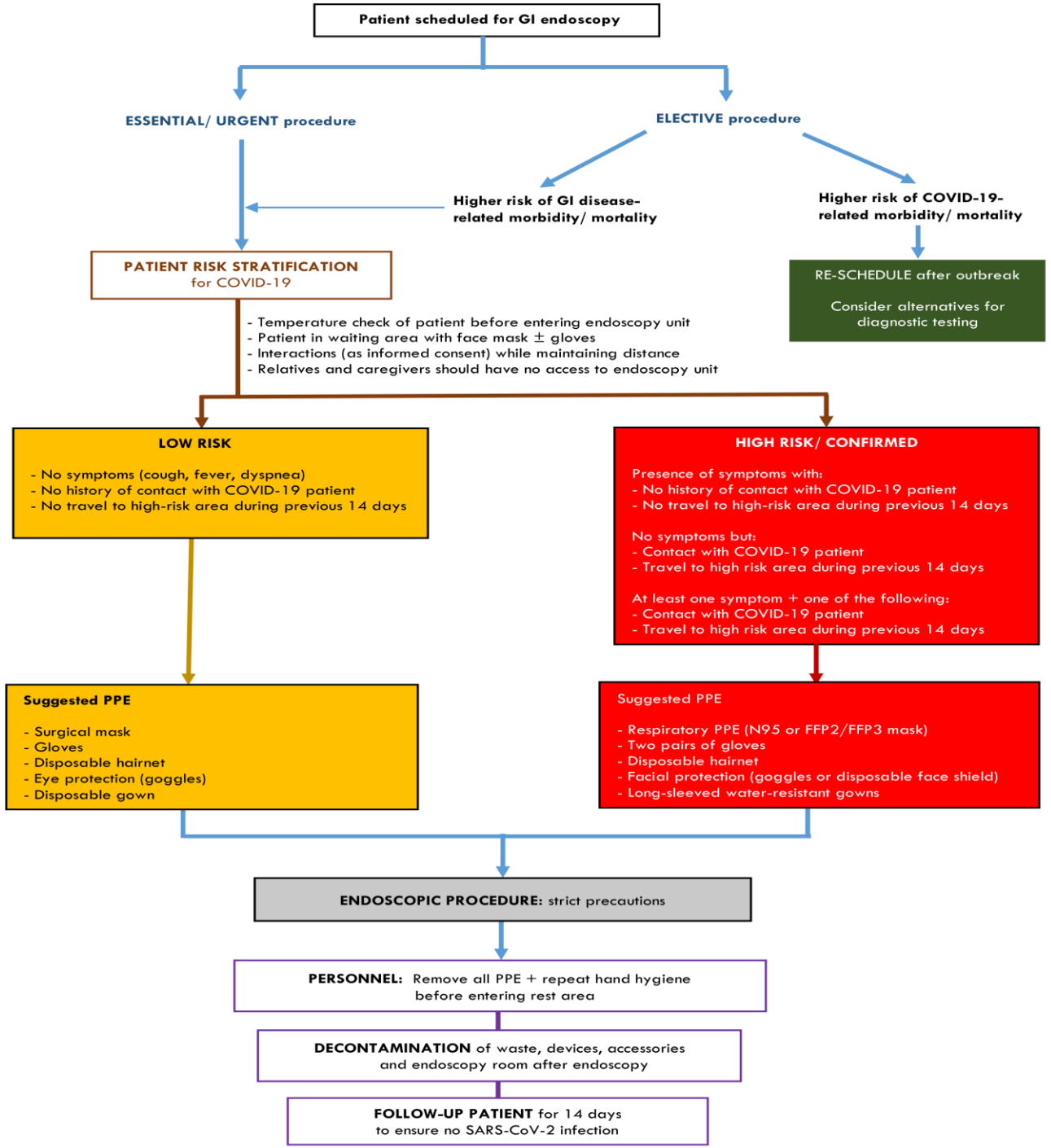


workflow in GI endoscopy units during SARS-CoV-2 outbreak



TERIMA KASIH