بسم الله الرحمن الرحيم

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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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Mesenteric Thrombosis as a Complication of COVID-19 Infection: A systematic review with meta-analysis

Systematic Review & Meta-analysis

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General Surgery

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List of Abbreviations

Abb.	Full term

ACC ..... *American college of cardiology*

ACE2 ..... *Angiotensin-converting enzyme 2*

AGI ..... *Acute gastrointestinal injury*

AHA ..... *American heart association*

AMI..... *Acute mesenteric ischemia*

CAD ..... *Coronary artery disease;*

CFR..... *Case fatality rate*

CKD ..... *Chronic kidney Disease*

COVID-19..... *Coronavirus Disease 2019*

CRP ..... *C-reactive protein*

CT..... *Computed tomography*

CTA..... *Computed tomography angiography*

DM..... *Diabetes mellitus;*

DTA ..... *Descending thoracic aorta*

DVT ..... *Deep vein thrombosis*

ER..... *Endoplasmic reticulum;*

ERGIC..... *Endoplasmic reticulum-Golgi intermediate compartment*

HTN ..... *Hypertension;*

ICTV..... *International Committee on Taxonomy of Viruses*

IMV..... *Inferior mesenteric vein*

List of Abbreviations (Cont...)

Abb.	Full term
IVC	*Inferior vena cava*
MASP2	*Mannose-binding protein-associated serine protease 2*
MERS	*Middle East respiratory syndrome*
MERS–CoV	*Middle East respiratory syndrome coronavirus*
NIH	*National Institutes of Health*
NOMI	*Non-occlusive mesenteric ischemia*
NOS	*Newcastle-Ottawa Quality Scale*
NR	*Not reported*
OR	*Odds ratios*
PE	*Pulmonary embolism*
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta-analyses*
Protein S	*Spike protein*
PTA	*Percutaneous transluminal angioplasty*
PV	*Portal vein*
R_0	*Basic reproduction number*
RTPCR	*Reverse transcription-polymerase chain reaction*
S	*Envelope spike*
SARS	*severe acute respiratory syndrome*
SARS–CoV	*Severe acute respiratory syndrome coronavirus*
SARS-CoV-2	*Severe acute respiratory syndrome coronavirus 2*
SMA	*Superior mesenteric artery*
SMV	*Superior mesenteric vein*
TE	*thromboembolic*
TIPS	*Trans jugular intrahepatic portosystemic shunt*
WHO	*World Health Organization*

INTRODUCTION

On January 7, 2020, a novel coronavirus was isolated and named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) in the wake of an outbreak of pneumonia of unknown cause in Wuhan city, China. This pneumonia was called Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) on February 11, 2020.

It is well established that most patients with COVID-19 have fever along with respiratory signs and symptoms, such as cough and dyspnea. To date, there was some uncertainty about the prevalence of extra pulmonary symptoms, such as those arising from the gastrointestinal tract. However, with the evolution of the pandemic and the accumulation of case data, it is revealed that gastrointestinal symptoms are very common.

Although this disease affects mainly the respiratory system, other organs may be involved, usually due to coagulation disturbances that lead to a high rate of thrombotic complications. In this regard, deep vein thrombosis has been reported in up to 25–50% of COVID-19 patients requiring intensive care, with mortality rates being as high as 30–40%. Although less frequent, other thrombotic events such as intestinal, cerebral, and peripheral limb thrombosis have been reported, usually in critical patients ***(Abou-Ismail et al., 2020).***

The prothrombotic effects of the virus may be directly related to its structure. It is known that the membrane of SARS-CoV-2 contains a Spike protein (protein S) which binds to the angiotensin-converting enzyme 2 (ACE2) receptor located on the membrane of host cells. ACE2 is most abundant in the lungs, intestine, oral mucosa, liver, and endothelium ***(Cheung et al., 2020).***

The binding of SARS-CoV- 2 to ACE2 reduces the degradation of angiotensin II, which in turn stimulates the production of IL-6 and promotes a cytokine storm. Moreover, it has been shown that angiotensin II induces the expression of tissue factor and plasminogen activator inhibitor-1 by endothelial cells, leading to a hypercoagulable state ***(Görlinger et al., 2020).***

Finally, SARS-CoV-2 infection is associated with increases in levels of not only angiotensin but also other prothrombotic proteins such as tissue factor, factor VIII, von Willebrand factor, and plasminogen activation inhibitor-1 ***(Helms et al., 2020).***

The histology of the small intestine secondary to a mesenteric thrombosis revealed a prominent endothelitis of the submucosa with an evidence of direct viral infection of the endothelial cells as well as diffuse endothelial swelling with mononuclear cell infiltrate. It is believed that there is an activation of alternate and lectin complement pathways (C5b-9

(membrane attack complex), C4d, and mannose-binding protein-associated serine protease 2 (MASP2)), which injures the endothelial cells ***(Ignat et al., 2020).*** Hence, it is believed that micro vascular changes, rather than major embolic events, play a central role in intestinal damage. It is important to note that venous thromboembolic complications are generally more common than arterial thrombosis ***(Karna et al., 2020).***

Apart from deep venous thrombosis and pulmonary embolism (PE), acute mesenteric ischemia (AMI) has been reported in severe COVID-19 patients ***(Keshavarz et al., 2021).*** The effects of the virus rise the incidence of mesenteric ischemia from a mere 0.09–0.2% in the general population to 1.9–3.8% in patients with COVID-19 ***(Azouz et al., 2020).***

AMI is a devastating complication with high mortality rate, so high suspicion, early recognition is needed to avoid morbidity and mortality associated with this disorder, also In Mesenteric ischemia, the time lag between onset of symptom to treatment is crucial for good outcome. The optimal time for intervention is initial 12 hours from symptom onset, when it is possible to perform vascular surgery effectively without requiring intestinal resection. However, patients with COVID-19 often present late and treatment of respiratory symptoms is given precedence over abdominal symptoms ***(Ignat et al., 2020).***

Mucosal ischemia may further induce massive spread of virus from bowel epithelium leading to vasoplegic shock after surgery ***(Keshavarz et al., 2021).***

The exact pathological mechanism explaining the complication of AMI in COVID-19 is not known at present. Putatively, more than one mechanism, in isolation or in varying combinations could account for this fulminant complication in severe COVID-19. First, a coagulation disorder (hypercoagulability) induced by systemic inflammatory state, endothelial activation, hypoxia and immobilization may lead to mesenteric vascular thrombosis. The evidence available at present has not conclusively demonstrated large mesenteric vessel (arterial or venous) thrombosis. Preliminary pathological evidence has shown bowel necrosis with small vessel thrombosis involving the submucosal arterioles, thereby pointing to an in-situ thrombosis of small mesenteric vessels rather than an embolic event ***(Singhania et al., 2020).***

Second, elevated levels of von Willebrand Factor have been reported in severe COVID-19, von Willebrand Factor is released from Weibel-Palade bodies in response to endothelial damage, Vascular endothelium expresses angiotensin converting enzyme 2, the target receptor for severe acute respiratory syndrome 2 (SARS-CoV-2), which possibly explains the endothelial cell tropism of SARS-CoV-2 and subsequent endothelial dysfunction or damage with resultant vascular thrombosis.

Third, expression of angiotensin converting enzyme 2 on enterocytes of small bowel, the target receptor for SAR-Cov-2, may result in intestinal tropism and direct bowel damage.

Lastly, shock or hemodynamic compromise which is commonly associated with severe COVID-19 pneumonia may lead to a nonocclusive mesenteric ischemia ***(Singhania et al., 2020).***

Patients with severe COVID-19 complicated by AMI may present with abdominal pain, nausea/vomiting, diarrhea, abdominal distention or worsening systemic status (sepsis), blood tests may reveal elevated lactate levels and fibrin degradation products (D-dimer). However, both these tests are nonspecific and may be elevated in severe COVID-19 without AMI ***(Singhania et al., 2020).***

Imaging has a vital role to play in timely detection of AMI and is the mainstay of diagnosis. Although readily available, abdominal radiographs lack sensitivity and specificity. Ultrasound avoids the use of ionizing radiation but is also nonspecific. Computed tomography angiography (CTA) is the imaging study of choice to diagnose AMI. CTA is usually performed to detect PE in severe COVID-19 patients. CTA done for detection of PE may need to be extended to cover the abdomen so that both the chest and abdomen are scanned in the same examination. This might come at the cost of higher radiation dose but given the seriousness of AMI the trade-off is worth it ***(Nepogodiev et al., 2020).***

Finally, patients with severe COVID-19 and hemodynamic instability or shock are at risk of suffering non-occlusive mesenteric ischemia ***(Seeliger et al., 2020).***

Aim of the Work

To investigate the prevalence and outcomes of COVID-19 patients with digestive thrombo- embolic events and outline the preventive measures which can avoid this complication.