Coronavirus Disease and Abdominal Pain: Mechanism, Diagnostic, and Treatment

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Abstract

BACKGROUND: On March 11, 2020, the General Director of the World Health Organization has announced that according to the organization, the level of spread and severity of symptoms of coronavirus disease (COVID-19) is becoming alarming and because of that, it can be characterized as a pandemic. The assessment of the World Health Organization stimulated more urgent and belligerent actions from the governments as the number of case reports and studies on COVID-19 symptoms and treatment increased dramatically.

AIM: In this paper, the aim is to make a review of the studies and case reports/series that indicate that abdominal pain is one of the manifestations of COVID-19.

METHODS: A search was performed on two electronic databases: PubMed Central and Google Scholar, using the key words “COVID-19 and abdominal pain.” Case reports and case series in adults and children were included regardless of the language, region, or the publication date. The methods of synthesis and comparison were also used.

RESULTS: In general, it can be noted that the manifestation of the COVID-19 infection on the digestive tract and the consequences on the same are not fully examined.

CONCLUSION: The conclusion of the analyzed papers is that clinical practitioners in COVID-19 pandemic should carefully distinguish abdominal pain and other GI symptoms from COVID-19 manifestations and should exclude acute surgical condition.

Introduction

Severe and acute abdominal pain is almost always a symptom for intra-abdominal disease that requires a surgical treatment (condition termed as acute abdomen). From a pathophysiological perspective, abdominal pain is divided as visceral, somatic, and referred pain.

Recent studies indicate that coronavirus disease (COVID-19) can also be a possible cause of abdominal pain. According to Widyadharma et al. [1], the mechanism of pain in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive patients “is associated with two-way communication between the gut microbiota and the brain, namely, between the endocrine (cortisol), the immune system (cytokines), and nerves (vagus nerve and enteric nervous system).” Namely, ACE2 receptors which are the target of SARS-CoV-2, in humans, are found on the luminal surface of the redifferentiated small intestinal epithelial cells and in crypt and colon cells [1], [2]. It is implied that the described mechanism is the reason for presentation of abdominal pain without respiratory symptoms in some, atypical, SARS-CoV-2-positive patients.

In this era of SARS-CoV-2 pandemic, it is important to rule out the acute surgical condition which needs emergency operation, having in mind that SARS-CoV-2 infection may be presented with abdominal pain and other GI symptoms. To do so, for clinical practitioners, it is important to have sufficient information about the scope of gastrointestinal (GI) symptoms manifested in COVID-19-positive patients. Therefore, in the following parts of the paper, the available case reports regarding this topic are presented.

Abdominal Pain in Adults with COVID-19

At the beginning of the COVID-19 pandemic, the clinical features of the novel coronavirus were mainly described as respiratory. However, as the time passed, the understanding of the COVID-19 evolved and it was concluded that COVID-19 can cause multiple organ dysfunction. Namely, the variety of the symptoms of the novel COVID-19 has rapidly increased. According to Liu et al. [3], the typical initial symptoms of COVID-19 include fever, cough, and muscle pain or fatigue, while the less typical symptoms of the infection reported are heart palpitations, diarrhea, and headache.

Besides the manifestations on the respiratory system, the smell and taste disorders (anosmia and dysgeusia, respectively), GI symptoms of COVID-19, and abdominal pain are also reported as less typical symptoms. The chronic respiratory disease report as of...
May 30, 2020, in the USA, among 373,883 confirmed COVID-19 cases with data on individual symptoms, 28,443 have reported abdominal pain, which is 7.6% [4]. In addition, in this report, it is noted that nausea/vomiting was reported in 42,813 cases (or 11.5%), while diarrhea was present in 72,039 cases (or 19.3%) [4].

However, various authors suggest that GI symptoms may be underestimated and indicate that abdominal pain, diarrhea, nausea, vomiting, and lack of appetite, in some cases are presented before [5] or together with mild respiratory symptoms. Zang et al. [6] suggested that patients with GI symptoms had longer duration between symptom onset and viral clearance.

In the following table (Table 1), the reported cases of SARS-CoV-2-positive patients with abdominal pain are summarized. It is important to note that some of them had also other GI symptoms, while others were without other GI symptoms. In addition, in regard to the localization of the abdominal pain, it can be concluded that most of the patients in the presented case reports experienced epigastric pain or diffused abdominal pain. Furthermore, significant number of patients has described pain in the right iliac fossa.

To sum up, although at the early stages of the pandemic, the papers focused on the clinical characteristics of COVID-19, classified the GI symptoms as uncommon [7], the authors of the presented case reports have shown that manifestation of the disease on the digestive tract can be challenging for diagnostics. Besides, it is noted that in these cases, a computed tomography (CT) on the abdomen is the most commonly used diagnostic technique, while the ultrasound tomography (ultrasound scan) of the abdomen can also give good information regarding diagnostics. However, on the abdominal CT, in most of the cases, the lower parts of the lungs without guarding or non-guarding noticed.

Table 1: Summary of the case reports analyzed in adults

| S. No. | Case/author | Abdominal pain region | Other GI symptoms | Fever | CT abdomen | CT chest (at presentation), (or chest X-ray done instead) |
|-------|-------------|-----------------------|-------------------|-------|------------|-------------------------------------------------------|
| 1     | Widyadharma et al. [1] | Persistent stabbing pain that originates in the groin and migrates to the abdomen, pelvis, back, and chest | None | Yes | Pulmonary ground-glass opacification, pneumonia type of consolidation, potential sigmoid colitis, and distal descending colon | NA |
| 2     | Saeed et al. [2] | Epigastric | Nausea, vomiting | No | Normal | Bilateral ground-glass opacities |
| 3     | Saeed et al. [2] | Epigastric | Nausea, vomiting | Yes | Normal | Bilateral ground-glass opacities |
| 4     | Saeed et al. [2] | Global | Nausea | Yes | Normal | Bilateral ground-glass opacities |
| 5     | Saeed et al. [2] | Left iliac fossa | Nausea, vomiting | Yes | Normal | Bilateral ground-glass opacities |
| 6     | Saeed et al. [2] | Right iliac fossa | Nausea | Yes | Normal | Bilateral ground-glass opacities |
| 7     | Saeed et al. [2] | Global | Nausea, vomiting | No | Normal | Bilateral ground-glass opacities |
| 8     | Saeed et al. [2] | Right iliac fossa | Nausea, vomiting | No | Normal | Cholecystitis |
| 9     | Saeed et al. [2] | Right iliac fossa | Diarrhea | Yes | Appendicitis | Normal |
| 10    | Saeed et al. [2] | Umbilical | Nausea | No | Ileus | Normal |
| 11    | Walijope et al. [14] | Severe abdominal pain (renal colic susp.) | Vomiting, diarrhea | Yes | Normal | Multifocal peripheral patches of consolidation running through the periphery of the right lower lobe |
| 12    | Ahmed et al. [15] | At first diffused, later localized to the right lower quadrant | Diarrhea, vomiting | Yes | Diffuse paracolic gutters fat stranding, mild free fluid, bilateral mild pleural effusion with consolidations, and filling defect at superior mesenteric vein that is attributed to streaming artifact or thrombosis | NA |
| 13    | Ahmed et al. [16] | Right iliac fossa | Nausea, vomiting | Yes | Normal | Upper cut bilateral basal lung consolidation |
| 14    | Ahmed et al. [16] | Right upper quadrant | None | No | Right hypochondria epipic | Normal |
| 15    | Ahmed et al. [16] | Right iliac fossa | Nausea, vomiting | Yes | Normal | NA |
| 16    | Abdalhafad et al. [17] | Right iliac fossa | Nausea, vomiting | No | Normal | Bilateral patchy peripheral lung basal consolidation and ground-glass attenuations |
| 17    | Pazgan-Simon et al. [18] | Global | None | No | Normal | Intestinal consolidations in the lower lobes of both lungs |
| 18    | Voutsinas et al. [19] | Right lower quadrant | None | No | Normal | Hazy ground-glass opacities in the dependent portions of both lung bases |
| 19    | Voutsinas et al. [19] | Flank pain | Nausea, vomiting | Yes | Normal | Peripheral ground-glass opacities with associated increased interstitial markings in both lung bases |
| 20    | Voutsinas et al. [19] | Abdominal pain | Diarrhea, blood stool | No | Mild sigmoid colitis | Ground-glass opacification with a rounded morphology in the periphery of the right lung base |
| 21    | Voutsinas et al. [19] | Epigastric and flank pain | Nausea | No | Pyelonephritis | Rounded ground-glass opacities in the periphery of the imaged right lower lobe |
| 22    | Mahan et al. [20] | Periumbilical pain | None | No | None | Abdominal aorta showed thromboembolus, diffuse bilateral ground-glass opacities in the lungs |
| 23    | Gérald et al. [21] | Epigastric pain and RUQ sensitivity | Nausea | No | Bilateral subpleural irregular lines and scattered peribronchial ground-glass opacities at both lung bases | NA |
| 24    | Gérald et al. [21] | Epigastric pain | Nausea | No | No abdominal abnormal finding but demonstrated bilateral subpleural ground-glass opacities with intralobular reticulations at the lung bases | NA |
| 25    | Gérald et al. [21] | Diffuse abdominal pain without guarding | Nausea and diarre | No | Demonstrating predominantly right lower lobe crazy-paving associating ground-glass opacities and interlobular reticulations | NA |
| 26    | Purayil et al. [22] | Epigastric pain | Vomiting | Yes | Ultrasound scan* of the abdomen was normal | Chest X-ray** revealed bilateral infiltrates |
| 27    | Altermanini et al. [23] | Epigastric pain | None | No | None | Normal |

*It was described by an ultrasound scan on the abdomen. **It was done by chest X-ray, not CT on the chest. CT: Computed tomography.

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or the lungs bases are visible, which is important for detecting any abnormalities in these organs, too.

According to Ye *et al.* [8], the mechanisms that cause GI symptoms in COVID-19-positive patients can be different:

1. **Direct infection of GI cells** – the expression and distribution of ACE2 in humans is a potential infection pathway for SARS-CoV-2. ACE2 is widely found in human small intestinal epithelial cells, especially in type II epithelial cells. In addition, high expression of ACE2 has been detected in the intestinal epithelial cells, the esophagus, and the lungs. Ye *et al.* suggested that the presence of GI symptoms in COVID-19 patients indicates that SARS-CoV-2 may invade target organs of the digestive tract through ACE2 receptors and cause primary damage. In addition, several authors indicate that SARS-CoV-2 is 10–20 times more transmissible than SARS-CoV. Furthermore, Ye *et al.* hypothesized that ACE2 expressing cells in humans, secretes large number of cytokines which induces cytokines’ storm that can cause damage to multiple organs and may also cause immune cell death;

2. **GI damage caused by lung infection** – which mainly refers to the effect called “gut-lung axis” which means that disorders of the GI flora affect the respiratory tract and vice versa, respiratory tract changes impact the digestive tract through immune regulation;

3. **GI symptoms caused by drug’s side effects** – use of large amount of antibiotics (especially macrolides, cephalosporins, and β-lactam antibiotics), is the most common cause for diarrhea as a side effect in COVID-19-positive patients.

Furthermore, Perisetti *et al.* [9] suggested a classification of four pathogenic mechanisms that cause GI manifestations in COVID-19 patients:

1. **Cytopathic effects** – SARS-CoV-2 binds on ACE 2 receptors and enters the stomach and small intestine;

2. **Gut inflammation** – induced pro-inflammatory pathways with increased cytokine release and fecal calprotectin;

3. **Altered gut microbiota** – increased mTor activity, hypochlorhydria, altered gut-lungs axis;

4. **Others** – include drug-induced changes, pre-existing condition worsening, and secondary infection.

In general, “after the entry into GI tract, SARS-CoV-2 can exert its cytopathic/inflammatory changes, which can potentially lead to visceral pain. If this is a somatic due to the involvement of the peritoneum or a referred pain is unknown” [9]. However, the exact mechanism of appearance of abdominal pain in COVID-19-positive patients is unclear.

Several case reports also indicate a correlation between COVID-19 and cholecystitis. Authors have presented case of COVID-19 that was associated with acalculous cholecystitis [10], [11], [12]. All patients in reported cases with this condition are aged over 60 years. This condition may lead to gallbladder ischemia, necrosis, and perforation that require emergency surgical operation. They suggested that pathophysiological mechanism is that SARS-CoV-2 binds to ACE-2 receptor in the liver, gallbladder, and bile ducts [13]. Systemic endotheliitis, hypercoagulability, antiphospholipid antibodies, and thrombotic microangiopathy are the other contributors to the occurrence of cholecystitis in COVID-19-positive patients. Furthermore, some reports describe patients with SARS-CoV-2 acute calculus cholecystitis [13] that has had no clinical manifestation of gallstones before this viral infection. The abdominal pain caused by cholecystitis is usually not the first manifestation of SARS-CoV-2 infection (for acalculous cholecystitis).

**Abdominal Pain and COVID-19 in Children**

Before the COVID-19 pandemic, few studies have focused on the correlation between viral infections (cytomegalovirus, Epstein–Barr virus, hepatitis A virus, and human herpes virus) and acalculous cholecystitis in children [24], [25], [26], [27]. According to these studies, diagnosis of acute cholecystitis may be challenging. Supposed pathogenic mechanism in these cases is direct invasion or inflammation triggered by bile stasis [26].

The literature also provides papers and case reports that depict patients that had COVID-19 manifested with pediatric abdominal pain. These cases can be challenging for diagnostics, in the same way as with adults. The available cases are presented in Table 2.

In the analyzed case reports, it is outlined that in COVID-19 pediatric patients with GI symptoms, adequate imaging studies (ultrasound and CT) should be done to exclude the acute abdomen. The GI symptoms, including abdominal pain, may be only a presentation of the SARS-CoV-2 infection without the need for emergency surgical treatment. Furthermore, some studies prove that the surgical treatment in these patients may deteriorate the condition.

**Treatment**

The key point in treatment of COVID-19 patients with abdominal pain is to exclude acute surgical suffering. Besides physical examination, adequate imaging studies are necessary.

In adults, the reported cases show that abdominal pain may manifest before respiratory signs
of SARS-CoV-2 infection, and therefore, adequate imaging studies are required. It can be noted that in these cases, abdominal CT is the most commonly used diagnostic technique, while the ultrasound scan can also give good information regarding the diagnosis. However, on the abdominal CT, in most of the cases, the lower parts of the lungs or the lungs bases are visible, which is important for detecting any abnormalities in these organs, also. This is the advantage when using abdominal CT scan as a diagnostic tool.

### Table 2: Summary of the case reports analyzed in children

| S. No. | Case/author                          | Age and gender | Underlying medical conditions | Abdominal pain | Other GI symptoms | Fever | CT abdomen | CT chest | SARS-CoV-2 PCR |
|--------|--------------------------------------|----------------|-------------------------------|----------------|-----------------|-------|------------|----------|----------------|
| 1      | Hanwood et al. [28]                  | 14 years, Female | No medical conditions         | Abdominal pain which migrated to the right iliac fossa | None | Yes | Abdominal ultrasound scan demonstrated mesenteric adenitis without free fluid and chest X-ray was unremarkable | 12 h later, urgent computed tomography scan of the chest and abdomen revealed diffuse intra- and interstitial thickening consistent with SARS-CoV-2 infection and no intra-abdominal pathology | Negative |
| 2      | Hanwood et al. [28]                  | 3 years, Male   | Nil                           | Abdominal pain | Diarrhea and vomiting | Yes | Revealed perforated appendicitis with intra-abdominal collections | NA | Positive |
| 3      | Tullie et al. [29]                   | 4 years, Male   | Autism spectrum disorder      | Abdominal pain | Diarrhea and vomiting | Yes | US abdomen: Mesenteric lymphadenopathy, terminal ileitis, normal appendix | NA | Positive |
| 4      | Tullie et al. [29]                   | 5 years, Male   | Nil                           | Abdominal pain | Diarrhea and vomiting | Yes | US abdomen: Mesenteric lymphadenopathy and free fluid in right iliac fossa, no bowel wall thickening, normal appendix | NA | Negative |
| 5      | Tullie et al. [29]                   | 8 years, Male   | Nil                           | Abdominal pain | Diarrhea and vomiting | Yes | US abdomen: Echogenic fat and mild terminal ileal thickening, appendix not visualized, no significant lymphadenopathy | NA | Positive* |
| 6      | Tullie et al. [29]                   | 11 years, Female| Mild asthma                  | Abdominal pain | Diarrhea and vomiting | Yes | US abdomen: Bowel wall thickening involving ileocecal junction with mesenteric lymphadenopathy. Appendix not seen CT abdomen: Fluid-filled appendix with appendicolith but no inflammation. Thinned cecum and multiple enlarged mesenteric lymph nodes | NA | Positive |
| 7      | Tullie et al. [29]                   | 12 years, Female| Nil                           | Abdominal pain | Diarrhea and vomiting | Yes | US abdomen: Multiple enlarged lymph nodes in right lower quadrant. Appendix not seen CT abdomen: Non-inflamed retrocaecal appendix, terminal ileal thickening and mesenteric lymphadenopathy | NA | Positive |
| 8      | Tullie et al. [29]                   | 14 years, Male  | Nil                           | Abdominal pain | Diarrhea and vomiting | Yes | US abdomen: Inflammatory changes in ileocecal region associated with lymphadenopathy. No features of appendicitis. (No. This was performed after the CT to confirm findings) CT abdomen (non-contrast): Inflammatory change in the right iliac fossa with matted bowel loops. Focal collection and enlarged mesenteric lymph nodes. Collapsed bowel loops, no visible collection or evidence of appendicitis | NA | Positive |
| 9      | Tullie et al. [29]                   | 15 years, Male  | Nil                           | Abdominal pain | Diarrhea and vomiting | Yes | US abdomen: Inflammatory change and echogenic fat in right iliac fossa, mesenteric lymphadenopathy. Appendix not visualized. CT abdomen: Calcified appendicolith in non-inflamed appendix. Thinning of terminal ileum consistent with terminal ileitis | NA | Negative |
| 10     | Tullie et al. [29]                   | 16 years, Female| Nil                           | Abdominal pain | Diarrhea and vomiting | Yes | US abdomen: Terminal ileal inflammation with local lymphadenopathy | NA | Negative |
| 11     | Saleh et al. [30]                    | 4 months, Male  | Orthogenesia imperfecta      | Abdominal pain, tenderness, and guarding | Poor feeding, bilious vomiting | No | Coffee bean sign in the left upper quadrant viewed on abdominal X-ray | Typical lesions for SARS-CoV-2 on chest | Positive |
| 12     | Saleh et al. [30]                    | 10 years, Male  | Nil                           | Abdominal pain, tenderness, and guarding | Vomiting | Yes | US: Signs of appendicitis | Typical lesions for SARS-CoV-2 on chest | Positive |
| 13     | Saleh et al. [30]                    | 5 years, Female | Nil                           | Abdominal pain, tenderness, and guarding | Oral intolerance and irritability | No | Abdominal X-ray: Coffee bean sign | Typical lesions for SARS-CoV-2 on chest | Positive |
| 14     | Saleh et al. [30]                    | 45 days, Male   | Cerebral palsy, seizures      | Abdominal pain, tenderness, and guarding | | | | | |
In addition, in adults when acute abdomen is excluded, treatment is based on analgesia, and in some of the presented cases, opioid analgesics were needed for relieving pain. The additional treatment is based on the COVID-19 Protocols and Guidelines. Furthermore, the use of probiotics may improve GI symptoms in patients diagnosed with COVID-19. According to Falch et al. [31], most appropriate treatment of abdominal pain when the need for surgery is ruled out includes opioid or non-opioid analgesics. Opioid analgesics bind to opioid receptors both in the central nervous system and in peripheral tissues to provide pain relief. Non-opioid analgesic agents are divided into acidic which mainly accumulate in tissues with a low pH (such as tissue with active inflammatory processes, the kidneys, and the stomach) and non-acid anti-pyretic analgesics which distribute to all tissues. The intensity of pain is crucial for determining the type of analgesics that need to be used. The administration of the drugs largely depends on the estimated potential for enteric absorption of the delivered agent [31].

Mattone et al. suggested that in the cases of COVID-19-positive patients that developed acute cholecystitis, although laparoscopic cholecystectomy is considered the gold standard, Tokyo Guidelines advice to delay surgical operation and to perform the percutaneous gallbladder drainage for surgically high-risk patients with acute cholecystitis and comorbidities.

As presented in the case reports in the previous section, in children, the abdominal pain and other GI signs are usually presented later, during hospital stay of the patients, and often mimicking atypical appendicitis or volvulus. Therefore, in the case reports described above, when explorative laparotomy or laparoscopy was executed, the intraoperative finding was peritoneal lymphadenopathy and/or serous peritoneal effusion. According to Hijaz et al., "...pediatric patients in general are at risk for receiving less than optimal analgesia. In the setting of acute AP (author remark: Abdominal pain), providers are often concerned about the possibility that strong analgesia (e.g., opioids) may mask symptoms and result in complications and increased morbidity. Several prospective, randomized studies have shown that judicious use of analgesia may enhance diagnostic accuracy by permitting a more thorough physical examination. It appears that opioids may be used to treat acute AP in children without delaying the diagnosis" [32].

Conclusion

According to the literature review, abdominal pain may be the first sign of SARS-CoV-2 infection in adults, occasionally without any respiratory symptoms and fever. In the further development of the disease, the abdominal pain relievers and the other respiratory symptoms prevail. Acute acalculous cholecystitis may be present in SARS-CoV-2-positive patient with severe clinical manifestations.

In the described case reports of children, the situation is different. Namely, in the analyzed cases, the abdominal pain and GI symptoms worsened after the patients were diagnosed with SARS-CoV-2 infection and were hospitalized due to the severity of other symptoms.

Overriding conclusion of the analyzed papers is that clinical practitioners in COVID-19 pandemic should carefully distinguish abdominal pain and other GI symptoms from COVID-19 manifestations and should exclude acute surgical condition.

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