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# PRESENCE OF SARS-COV-2 IN PERITONEAL FLUID AND ITS SIGNIFICANCE IN CLINICAL COURSE: A REVIEW ANALYSIS

# PERİTON SIVISINDA SARS-COV-2'NİN VARLIĞI VE BUNUN KLİNİK AÇIDAN ÖNEMİ: BİR DERLEME ANALİZİ

Recep Erçin SÖNMEZ[1], Feride İrem ŞİMŞEK[2], Orhan ALİMOĞLU[1]

**ABSTRACT**
COVID-19 disease may become clinically apparent with some of the features such as fever, pneumonia, or diarrhea. This diversity of symptoms brings up to mind the possibility of its presence in different parts of the body. On this aspect, examination of peritoneal fluid draws particular attention for surgeons who perform abdominal surgery for COVID-19 patients. We aimed to review literature beginning from its first outbreak (December 2019, Wuhan, China) till September 2020 to put forward relevant data specifically investigating the presence of novel coronavirus (SARS-CoV-2) in peritoneal fluid. Seven relevant articles were identified of which five of them were single-patient case reports, one report of case series, and one ongoing clinical trial. All patients presented in those studies were undertaken surgeries due to different emergent abdominal conditions. RT-PCR (Reverse transcriptase-polymerase chain reaction) analysis of peritoneal fluids was found positive for SARS-CoV-2 considering four of the case reports. The documentation of SARS-CoV-2 in peritoneal fluid specifically is based upon a few case series. Thus, further clinical researches are needed to strengthen this claim based on scientific evidence, and also to clarify the significance of this if any in the era of surgical practice.

**Key Words:** COVID-19, SARS-CoV-2, peritoneal fluid

**ÖZET**
COVID-19 hastalığı; ateş, pnömoni veya ishal gibi farklı bulgularla klinik olarak belirgin hale gelebilir. Semptomların bu çeşitliliği, virüsün vücudun farklı bölgelerinde yerleşme olasılığını akla getirmektedir. Bu yönüyle COVID-19 hastalarına abdominal cerrahi uygulayan cerrahlar için de periton sıvısının incelenmesi büyük önem arz etmektedir. Periton sıvısında yeni korona virüsün (SARS-CoV-2) varlığını spesifik olarak araştıran çalışmaları ortaya koymak için COVID-19 pandemisinin ilk başladığı tarihten (Aralık 2019, Wuhan, Çin) Eylül 2020'ye kadar geçen süreyi kapsayan ilgili literatürü gözden geçirmeyi amaçladık. Beş adet tek hastalık vaka sunumları, bir vaka serisi ve bir de devam eden klinik araştırma olmak üzere toplamda yedi adet çalışma belirlendi. Bu çalışmalarda sunulan tüm hastalar, farklı sebeplere sekonder gelişen akut karın kliniği sebebiyle ameliyat edilmiştir. Vaka sunumlarından perioperatif olarak alınan periton sıvılarının RT-PCR (Ters transkriptaz-polimeraz zincir reaksiyonu) analizinde, dört hastada SARS-CoV-2 pozitif saptanmıştır. Bugüne kadar SARS-CoV-2'nin periton sıvısında varlığını dökümente eden çalışmalar sadece birkaç vaka serisi düzeyindedir. Dolayısıyla bu iddiayı bilimsel kanıtlara dayalı olarak güçlendirmek ve cerrahi uygulamada bunun önemini netleştirmek için daha fazla klinik araştırmaya ihtiyaç vardır.

**Anahtar Sözcükler:** COVID-19, SARS-CoV-2, periton sıvısı

[1]Department of General Surgery, İstanbul Medeniyet University, İstanbul, Turkey
[2]Faculty of Medicine, İstanbul Medeniyet University, İstanbul, Turkey

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**Sorumlu Yazar / Corresponding Author:**
Recep Erçin Sönmez
Address: Istanbul Medeniyet University, Department of General Surgery, Eğitim Mah. Dr. Erkin Cad. Istanbul, Turkey 34722
Tel: +90 541 445 4063
E-mail: sonmezercin@gmail.com *ORCID: 0000-0003-2740-126,*

**Yazar Bilgileri /Author Information:**
Feride İrem Şimşek: ORCID: 0000-0003-3696-690X, fisres77@gmail.com,
Orhan Alimoğlu: ORCID: 0000-0003-2130-2529, sonmezercin77@outlook.com,

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## INTRODUCTION

The SARS-CoV-2 virus which we commonly refer to as novel coronavirus, or as 'COVID-19' more commonly, is RNA based member of the coronoviridae family.1 This new type of virus was first discovered in Wuhan city, China in December 2019. Afterward, as the disease had spread all around the world, it was declared as pandemia by World Health Organisation (WHO) on 11 March 2020.2 It most commonly presents with clinical features such as fever, dry cough, dyspnea, pneumonia and even may show up with gastrointestinal symptoms like diarrhea and abdominal pain. Being a highly contagious disease, it spreads via air-borne droplets through close contact with individuals.3 RNA of SARS-CoV-2 can be identified in several body fluids like tracheal aspirate, feces, cerebrospinal fluid by use of RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction).4,5,6 Though, other sites of contamination had not been proven yet and are a subject of interest.[7]

Even though the virus mainly hosts in the respiratory tract, it's not known if it may host in the peritoneal fluid as well. This obscurity makes some of the surgeons uncomfortable dealing with COVID-19 patients to perform laparoscopic surgery considering the potential risk of transmission through aerosolization.8,9,10,11 In this regard, the examination of peritoneal fluid bears great importance in maintaining maximum security for health care workers helping to protect themselves, and also providing the most suitable environment for COVID-19 patients to be treated who especially may need emergent abdominal surgery.

Currently, there are only a few studies published in relevant literature investigating the presence of viruses in peritoneal fluid. Even though the early studies published were not able to document the presence of SARS-CoV-2 in peritoneal fluid, several proceeding pieces of research had become able to prove this with scientific facts. Since the available data up to now is mostly based upon evidence from only a few case reports, we don't have enough knowledge under what circumstances this may occur, and any impact of this on the clinical course and treatment of the patients.

Selection of patients for further analysis

Systematic research had been performed on 'Pubmed', 'Google Scholar' and 'Medline' search engines to look for relevant articles specifically investigating the presence of SARS-CoV-2 in peritoneal fluid from December 2019 up to September 2020. 'COVID-19 in peritoneal fluid', 'COVID-19 in abdomen', 'Transmission of COVID-19', 'SARS-CoV-2 in peritoneal fluid', 'COVID-19 and Surgery', 'SARS-CoV-2 and Surgery' were following terms that were typed in to look for related articles. Throughout the present study, the virus is defined as 'SARS-CoV-2', and when discussing the pandemia and disease itself generally refer to as 'COVID-19'.

Table: Demonstration of articles asesssing presence of SARS-CoV-2 in peritoneal fluid

| Author | Desig | Study populatio | Pulmona involvem | RTPCR analys of periton fluid | Center study | Numb of patien | Outcon |
|---|---|---|---|---|---|---|---|
| Ngaserin et a | Case repor | Acute appendicit | + | negativ | Singapo | 1 | Recove |
| Coccolini et (13) | Case repor | Intestinal volvulus | + | **positiv** | Italy | 1 | Recove |
| Barberis et al | Case repor | Emergenc subtotal colectomy | + | **positiv** | Italy | 1 | Deceas |
| Rimini et al. | Case repor | Acute abdominal | - | **positiv** | Italy | 1 | Recove |
| Flemming et | Case repor | Emergenc cholesystec | + | **positiv** | Germar | 1 | Recove |
| Seeliger et al | Case series | Multiple ac abdomina pathologic | + | negativ | France | 7 | All recover |
| (LAPTRANS ClinicalTrials NCT04361 (12) | Clinic trial | Multiple ac abdomina pathologic | NE (*) | NE (*) | France | NE (* | NE (* |

• RTPCR; Reverse Transcriptase-Polymerase Chain Reaction, NE; Not Enough Available
*Actively ongoing trial collecting data

### Eligibility criteria

All the publications that were mentioned specifically about the presence of SARS-CoV-2 in peritoneal fluid, whether open or laparoscopic surgery, and positive or negative according to RT-PCR analysis with study population older than 18 years of age were included in review analysis for further evaluation. Studies reporting the clinical outcomes of intra-abdominal surgeries for COVID-19 patients whether open or laparoscopic but without assessment of peritoneal fluid by RT-PCR had not been taken into consideration.

## RESULTS

Seven different studies had been included in review analysis of relevant literature of which five of them are the presentation of case reports separately assessing the presence of SARS-CoV-2 in the peritoneal fluid by RT-PCR during abdominal surgeries performed due to different causes of emergent intra-abdominal pathologies, one presentation of case series consisting of 7 patients with a preoperative diagnosis of COVID-19 infection who had undergone abdominal surgeries due to various conditions. Peritoneal fluid sampling had been performed perioperatively for all the patients in the study, and gene amplification was performed with RT-PCR to look for SARS-CoV-2.12 All of the patients in the study were found negative for SARS-Cov-2.

Flemming et al. had performed an RT-PCR test for detection of SARS-CoV-2 in peritoneal fluid, bile, liver, and gall bladder biopsy samples of a cholesystectomized patient who was COVID-19 positive and none of them had been found positive for SARS-CoV-2.7

Another 21-year-old COVID-19 positive patient without any symptoms of the respiratory tract had undergone emergent surgery due to acute appendicitis. The peritoneal fluid sample that was taken at the beginning of the operation was found negative for COVID-19 after analysis.[4]

Coccolini et al. had presented a 78-year-old COVID-19 positive male patient having bilateral pneumonia who was tested for SARS-CoV-2 in the peritoneal sample that was taken during surgery performed for intestinal volvulus. RT-PCR analysis of nasopharyngeal swap and peritoneal fluid samples had revealed a bigger amount of viral load for SARS-CoV-2 in peritoneal fluid. This result was also supported by the statement of the researchers that the relevant sample was not contaminated by feces or blood. Thus, the presence of SARS-CoV-2 in the peritoneal was proven for the first time.[13]

73-year-old female patient with immunoglobulin G and M antibodies positive for COVID-19 and without active pneumonia on CT scan was found to have SARS-CoV-2 in peritoneal fluid samples which were retrieved during surgery performed due to incarcerated hernia while there were no recorded findings of intestinal perforation or contamination in the abdomen.[14]

Another study had presented a 71-year-old woman who was hospitalized due to COVID-19 related pneumonia with typical findings of a chest CT scan and positive result for SARS-CoV-2 on the oropharyngeal swab. She had several episodes of gastrointestinal bleeding during her stay and had undergone subtotal colectomy as her clinical course had deteriorated. RT-PCR analysis of the peritoneal fluid sample that was taken peri-operatively was found positive for SARS-CoV-2. She had deceased on the seventh postoperative day due to respiratory failure.[15]

Lastly, there is one ongoing clinical trial (LAPTRANSCOV; ClinicalTrials.gov NCT04361396) based in France which was initiated on April 2020, intended to assess the SARS-CoV-2 virus in the peritoneum of COVID-19 patients who were performed laparoscopic exploration due to acute abdominal emergencies.[16]

## DISCUSSION

Recent knowledge regarding the presence of SARS-CoV-2 in the peritoneal fluid is scant, still, there is a common fear and a major concern among most general surgeons that disease may act more in a trend of transmission during laparoscopic surgery with creation of intra-abdominal pneumoperitoneum and aerosolization especially due to heating of tissues with the use of energy devices like ultrasonic devices and harmonic scalpels.[17] There are some controversies

regarding this matter. Such as some stand for the safety of laparoscopic surgery claiming that it would be more regulated and a secure working environment in a closed abdominal cavity compared to the conventional approach. Depending on certain restrictions and following some technical regulations (like minimizing the size and count of port sites to prevent air leak, or maintaining intra-abdominal pressure at a lower level during insufflation, etc.) that would be defined before surgery, the risk of contamination would be much less according to some authors.18,19 Currently, there are only a few case reports published showing the presence of SARS-CoV-2 in peritoneal fluid, though there is no scientific evidence yet to demonstrate its spread via aerosols and gas particles that occur during surgical procedures. Based on recent knowledge; it would be radical to make such proposition that the safest approach for the surgeons to proceed with whether it is open or laparoscopic, mainly depends on how they feel most comfortable with, have adequate training with and what is fitting best for the good of the patient as well.

The most evident and presenting symptoms of COVID-19 are due to the involvement of the respiratory tract.20 In a recent systematic review and meta-analysis conducted by Mao R et al., the occurrence of gastrointestinal symptoms was found correlated with the severity of the clinical course.21 Even though no reasonable explanation can be maintained between gastrointestinal affliction and the clinical course of SARS-CoV-2 based on recent knowledge, there may be some unknown relation of its presence in peritoneal fluid with the existence of gastrointestinal symptoms. Considering our present findings, we can't build up any link between the presence of SARS-CoV-2 in peritoneal fluid and the severity of the disease. Only one patient in the literature review had been reported as deceased following subtotal colectomy performed for massive bleeding. Though the severity of the clinic was due to extensive involvement of the respiratory tract rather than gastrointestinal problems. All other patients had recovered uneventfully whether theirs' peritoneal fluid analysis was found negative or positive for SARS-CoV-2.

Another probable connection may be established also between the affinity of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE-2), and its presence in peritoneal fluid. ACE-2 is a transmembrane protein that is needed for receptor-mediated entry of SARS-CoV-2 into the cells. It has been proved that not only on pneumocytes (Type II alveolar cells) but also it is expressed on cells of the gastrointestinal (GI) tract.22 A similar explanation could be attributed to the presence of virus in peritoneal fluid as well, like in four of the case series presented above. Although it has been stated there was no recorded finding of intestinal contamination (perforation, leakage, etc.) considering those four cases, it would still be possible and should be kept in mind that there could be spread of the virus from other infected sites of the abdomen to the peritoneal fluid which couldn't be detected then by other means. In other words, contamination may still occur on a microscopic level during surgery that may be overlooked or not noticed. But all these assumptions are insignificant unless proved based on scientific evidence.

Until we discover the pathophysiology of this new organism entirely, we have to take all necessary measurements at first to protect ourselves from this uncertainty. All health care workers working in close contact with COVID-19 patients should be equipped with PPEs (Protective personal equipment) to lower the potential risk to a minimum level. Surgeons and other health workers dealing with acute abdominal surgeries should take extra precautions according to recent knowledge that there seems to be a tendency of the virus to be contained in peritoneal fluid as well.

This systematic review has some limitations. Relevant literature specifically focused on the presence of SARS-CoV-2 in the peritoneal fluid is lacking. There are only case report studies presented up till now, so it's not possible to draw a definite conclusion or to make directing suggestions in terms of disease management. Rather than that, current knowledge only allows us to make some assumptions about disease behavior based upon a few clinical findings. The results of the ongoing clinical trial,16 and other similar studies will help us to understand more about the nature of the disease.

## CONCLUSION

We need to understand in what circumstances COVID-19 is found in peritoneal fluid and what it means to us in surgical practice considering patient management and our self-protection as well. Currently, there is an ongoing clinical trial investigating the presence of SARS-CoV-2 in peritoneal fluid and hence aiming to discover the unknowns in this subject which has now become a fact in our lives. Through future studies in this era, new protocols may be established to direct surgeons and help them to take necessary precautions.

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