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Keywords:
COVID-19 risk, esophageal manometry, anorectal manometry, 24-hour esophageal impedance-pH monitoring, functional tests of digestive motility.

Abbreviation list
esophageal manometry (EM)
anorectal manometry (ARM)
esophageal pH/impedance-pH monitoring (pH/I-pH)
functional tests (FT)
healthcare workers (HW)

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Abstract

Background
The impact of the COVID-19 pandemic has led to the interruption of most manometry or impedance-pH monitoring studies. The risk to restarting activities is unknown.

Objective
Assess the risk of SARS-Cov-2 virus contagion, both to patients and healthcare workers in relation to esophageal and anorectal functional tests during the pandemic without protective measures.

Method
A questionnaire was designed to find out whether patients and healthcare workers had COVID-19, confirmed either by a test or only compatible symptoms, after functional studies were performed from January until March 2020.

Results
263 (92.9%) patients answered the survey. In the two weeks after functional test, four (1.52%) patients had confirmed COVID-19 (adjusted rate 8.34 cases per 1,000 (95% CI -0.06-16.74), OR 0.84 (95% CI: 0.83-0.85), p<0.001), no one after anorectal manometry. Other five had only compatible symptoms, total 9 (3.42%) (adjusted rate 27.50 cases / 1,000 (95% CI: 7.27-47.74), OR 2.84 (95% CI: 2.81-2.87). In the total study period 18.25% had COVID-19 confirmed or with compatible symptoms.

The average of days between the procedure and the first day of symptoms was progressively shortened: January 56 days, February 33 days, March 10.5 days. Two out of 10 healthcare workers (20%) were confirmed with COVID-19.

Conclusions
The risk of COVID-19 contagion when performing functional tests is low and more related to the evolution of the pandemic than to the procedures themselves. The small number of healthcare workers included in the study does not allow a definitive conclusion to be drawn on their risk of contagion.

Introduction
Since the first descriptions in December 2019 of SARS-CoV-2 virus infection, which was the cause of COVID-19 in China, the disease has spread almost universally and was declared a pandemic by the World Health Organization (1).

In Spain, through May 14, 2020, 229,450 total cases of COVID-19 have been reported (66,262 cases in the Community of Madrid), with 27,321 deaths (11.9%). The number of healthcare workers (HW) affected was 39,349 (16.63%) (2, 3). In this period, the availability of diagnostic tests for COVID-19 was practically limited to hospitalization.

The impact of the pandemic caused an overflow in the health system, profoundly modifying its operation to focus attention on the treatment of the disease and controlling of infections. Like non-urgent endoscopy, most functional tests (FT) of digestive motility have been abruptly discontinued with the onset of the pandemic (4).

Transmission of the virus occurs primarily by airway, through the expulsion of microdroplets and aerosols when speaking, coughing or sneezing, or by direct contact with contaminated surfaces. The chances of contagion increase during the performance at a short physical distance of certain procedures such as nasal or oropharyngeal intubation, among others. SARS-Cov-2 has also been detected in feces (5-8), although there is no data that have demonstrated fecal-oral transmission and it is unclear whether the viral concentration in the stool is sufficient for transmission (9).

At present we are not aware of publications that establish the risk of transmission of SARS-CoV-2 during esophageal manometry (EM), anorectal manometry (ARM), or esophageal pH/impedance-pH monitoring (pH/I-pH) studies. The publication of protocols to avoid the risk of transmission in these situations has been mainly devoted to endoscopic procedures and has been after the limitation of endoscopies to emergency situations (10, 11). It has been speculated a higher risk than endoscopy procedures due to the insertion of the catheter through the nasopharynx (area with high viral load in patients with COVID-19) (12) and by the possibility of the patient coughing, sneezing or vomiting more frequently, by not using sedation. Although the risk of transmission decreases when appropriate personal protective equipment and the rest of the recommended measures are used (13), references to FT are scarce and targeted at protective measures, assuming empirically, these as high-risk examinations (4, 14-17). So, it is important to try to know the risk for both patients and the HW who perform them, and thus be able to make recommendations for restarting the activity.
The objective of the study is to know the risk of SARS-Cov-2 virus contagion, both in patients and in HW, in relation to esophageal and anorectal FT in the pandemic period in which additional protective measures had not yet been implemented.

Material and Method

Patients
All patients who underwent EM, pH/I-pH or ARM in the Motility Unit of the Digestive Diseases Service of the Hospital Clínico San Carlos from January 2, 2020 until the suspension of these examinations on March 14, 2020 were included in the study. Demographic data were collected and clinical history available in hospital records was reviewed.

Medical staff of the Motility Unit who intervened in the testing, contacted patients by telephone. The telephone monitoring of the data was carried out until May 24, 2020, when phase zero was completed in Madrid and in which a month was completed without any new case in our series. The end of phase zero allowed mobility again based on hospital availability and low incidence of disease. A systematized questionnaire agreed by the members of the Unit (Table 1) was used to identify patients who had had symptoms considered by medical personnel as a possible COVID infection or were diagnosed by serology or PCR as COVID-19 positive in the 2 weeks following any of the procedures described.

Patients with specific tests (PCR and/or positive serology) and/or with COVID-19-compatible chest symptoms and radiology (criteria used at that time by the Ministry of Health as diagnostics) were considered to have confirmed COVID-19, and as a possible infection if they only had compatible symptoms.

The purpose of the survey was explained to all the patients and they were asked for their oral consent of acceptance to participate in the study. Once acceptance was obtained, they were asked whether they had had COVID-19 before or after the study, date of onset of symptoms if they had had it or symptoms suspected of being COVID-19, whether they underwent any diagnostic determination (PCR or serology) and their results.

Healthcare staff
We investigated whether HW involved in the tests performance during the study period developed COVID-19 or presented compatible symptoms (same criteria as for patients), the temporal relationship between patients and affected HW, as well as their participation in other hospital areas with possible risk of COVID-19 contagion.
All tests were carried out following the protocol and the usual protective measures (hospital uniform and nitrile gloves). A sheet was used to cover the patients. The usual cleaning and disinfection protocols were followed.

The study was approved by the Ethics and Clinical Trials Committee of the Hospital Clínico San Carlos (CI 20/413-E_COVID).

**Statistical analysis**

Study variables were summarized descriptively using numbers and percentages for discrete variables and the mean and standard deviation (SD) for continuous variables. Cumulative incidence of COVID-19 in our population was obtained by dividing cases by the overall population in the database. For the same time period, the cumulative incidence of confirmed SARS-CoV-2 infection in the general population of Madrid was extracted [Coordination Centre for Sanitary Alerts and Emergencies from Spain. Update 105. Coronavirus disease (COVID-19), May 14, 2020 (https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Actualizacion_105_COVID-19.pdf)]. Age and gender standardized incidence of COVID-19 in our population were obtained with the direct method using the general population of Madrid as standard. Results were presented as odds ratios (OR) and 95% confidence intervals (CI).

Multivariable analysis (binary logistic regression) adjusted for confounding factors was performed to estimate predictive factors and risk of COVID-19. A p-value < 0.05 was considered statistically significant. Statistical analyses were done using the Epidat 3.1 and SPSS 22.0.

Demographics characteristics were tested for differences using the χ² test for qualitative variables and the Student’s t-test for quantitative variables.

**Results**

**Patients**

During the study period, 357 studies were performed (137 EM, 115 I-pH/pH and 105 ARM) to a total of 283 patients (189 women, average age: 54.4 years (range 1-92 years)). The survey was completed by 263 patients (92.9%) (Table 2) for a total of 333 tests (126 EM, 106 pH/I-pH, 101 ARM). The age distribution is shown in Figure 1.
Two hundred and fifteen patients (81.75%) did not present with SARS-Cov-2 infection or compatible symptoms. Diagnostic tests were performed only in 15 patients in this group (9 serologies and 9 PCR, 3 with the 2 tests performed).

Forty-eight patients (18.25%) were either COVID-19 confirmed positive (22, 8.36 %) or possible during the period studied. There was a progressive distribution over time, practically zero in January and maximum in March (Figure 2). In the two weeks after the tests were carried out 4 patients (1.52%) presented confirmed COVID-19 (all of them with EM or pH/I-pH) and 5 patients possibly COVID-19 (1.90%), total 9 patients (3.42%) (Table 3). Distribution of confirmed or possible COVID-19 patients in the study population by decades and gender is shown in Figure 3.

The interval between the tests performed and the first day of onset of symptoms in the 2 weeks following the test was shortened throughout the study (Table 3): no patient in January, 3 patients in February without serological confirmation, and 4 confirmed and 2 possible in March (one patient started with symptoms 3 days before an EM and pH/I-pH were performed, and another patient started with compatible symptoms the day after ARM was made, but no diagnostic tests were performed on him.

Through May 24, 2020, cumulative incidence of laboratory-confirmed COVID-19 in the general population of Madrid was 9.86 cases per 1,000 (95% CI: 9.78-9.93) (65,693 reported cases among an overall population of 6,663 million), with a mortality rate of 1.33 deaths per 1000 (8,779 deaths). In the same period, the crude incidence rate of COVID-19 positive patients in our study population was 15.21 cases per 1,000 patients, and the age and sex adjusted rate was 8.34 cases per 1,000 (95% CI -0.06-16.74). Since only four patients were confirmed COVID-19 after two weeks of the procedure, studied patients had a significantly lower standardized risk of COVID-19 compared with the general population (OR 0.84 (95% IC: 0.83-0.85), p<0.001). However, if the total of 9 patients (confirmed and possible) are considered, adjusted rate was 27.50 cases/1,000 subjects (95% CI: 7.27-47.74) and the adjusted OR 2.84 (95% CI: 2.81-2.87), that is, a slight increase in the risk of infection in our population (p <0.001).

There was no mortality in our series.

Healthcare staff

Two out of ten (20%) members of the Unit were affected by COVID-19, with onset of symptoms on 03-14-2020 and 03-16-2020, respectively. Although during this period they were
also performing other tasks besides FT, a HW developed bilateral pneumonia and required hospitalization after she had performed a pH monitoring on a patient who presented symptoms and positive PCR a day later.

We have no evidence of infection to patients from HW. In addition, the infection of the HW were related to the period of highest rate of the pandemic, with possibly five patients infected.

Discussion and conclusions

Digestive functional examinations are susceptible to transmission of SARS-Cov-2 without our knowledge of any study that allows at least one real risk approximation. In this study, we have tried to assess this risk by investigating the incidence of confirmed or possible COVID-19 infection in patients who underwent esophageal or anorectal functional tests within the onset period of the pandemic, during which HW did not use protective equipment’s. Our findings suggest a low risk of COVID-19 after these procedures with an OR 0.84 although it may be a little higher (OR 2.87) if we consider the possible infection cases. Nevertheless, it must be taken into mind that the patients could have been contaminated because other circumstances as it can be seen with the parallel increase of cases as the pandemic grew in the population in Madrid and the early appearance of symptoms after FT in two patients, one of them living with family members COVID-19. In addition, it is important to note that none of the patients who underwent ARM had COVID-19 infection in the following two weeks.

Although the population included in our study is not homogeneous, neither is the population with COVID-19. In both series there is a small number of cases in the first 2 decades of life. In the group studied, the percentage of women is higher than in the general population affected by COVID-19 (68.1% vs 56.3%), with clear predominance of women aged between 40 and 80 years of age (Figure 1). Likewise, the mean age of the group is lower (55 vs 60 years), which is explained by the advanced mean age of the Spanish population exposed to infection, unlike the population with gastrointestinal pathology, usually younger. Both factors justify the lower morbimortality in our cases, with a single hospitalized patient and no mortality. However, the study has the advantage, as far as the objective is concerned, of having been carried out in the Community with the highest incidence of Spain, during the highest growth of the pandemic and when additional protection measures had not yet been implemented. The time in which the study has been conducted includes from the beginning of
the epidemic to the absence of suspicious or positive cases among our patients. This moment coincides with the declaration of the end of the Phase 0 period in our community.

The total number of patients who had confirmed COVID-19 along the study was 22 (8.36%) with an increasing trend depending on the evolution of the pandemic.

The incidence of infection in our series follows clear parallel with the evolution of the pandemic, with a possible impact of carrying out tests for patients and with progressive risk to HW from February 20 and reaching its peak in March (Figure 2). Specifically, on March 14, the last day of testing, the circulating virus level was remarkably high. In Spain, 5,100 active cases (1,519 new) were declared, with a total of registered cases of 5,753. In the community of Madrid, the total cases detected reached 2,940. These data are undervalued considering the low number of tests carried out on those dates.

The predominance of women in our study population could be explained by the higher prevalence of gastroesophageal reflux disease (18) and anorectal pathology, such as fecal incontinence (19) and obstructive defecation-defecatory dysinergia (20, 21), in the female population that require this type of FT.

The absence of similar studies prevents drawing conclusions by comparison with the experience of other groups. In a recent study (13) assessing the relationship of the pandemic and the risk of contagion with endoscopy at different centers in Italy, the methodology followed, and the mean age of the patients is similar in this study and ours. The study indicates an estimate of the risk of contagion of HW in low endoscopic procedures (4.3%). However, it has a wide variability between the different participating centers, reaching 54.7% in some centers and in relation to the absence of additional protective measures. They also point out, as in our case, the limitations caused by the real ignorance of infected subjects who were tested for lack of diagnostic tests in the early stages of the pandemic. In our center, during the same period and without taking protective measures, 10/67 (14.92%) HW from the Endoscopy Unit were infected by COVID-19 with a total of 4,680 examinations (non-published data).

In our study, the risk of contagion to HW is low in relation to the number of examinations performed. The infection became apparent from 20-02-2020 with an increasing trend towards the end of the study period. However, since HW performed other functions that required contact with patients during the pandemic’s expansion phase, it is difficult to establish the relationship.
Our limited number of cases related to HW (20%) does not allow us to draw definitive conclusions about the risk of infection, but it seems to be in line with published data in our environment, with an impact on HW of 16.63% (22).

Regarding the procedures performed, there is a widespread opinion in considering EM and I-pH/pH monitoring high-risk techniques for HW due to the possibility of generating aerosols with contagious capacity by coughing, sneezing or vomiting. This perception of the risk of contagion is much lower in relation to ARM since, although the presence of the virus has been confirmed in the feces of infected patients (5-9) so far, the existence of fecal-oral transmission has not been confirmed. In our study, there was no confirmed COVID-19 infection in the following two weeks after anorectal manometry.

In any case, the use of protective measures in any health activity seems to be important, with the absence of contagion having been noted when they are implemented (23, 24).

Therefore, while the characteristics of the healthcare activity performed might have a different risk of contagion, our results and published data suggest that it is low, both in the performance of endoscopies and FT, and more related with the evolution of the pandemic and the application of appropriate protective measures than with the procedures practiced.

Our study has several limitations derived from the scarce performance of diagnostic tests for both symptomatic or asymptomatic patients and healthcare providers at the height of the epidemic (which occurred in all countries). For this reason, it is likely that the number of infected patients could be higher than reported. Other limiting aspects are the asymmetrical distribution of the population studied in relation to gender (clear predominance of women), age (although a statistical correction was made), and the conduct of studies in a hospital setting, at those times with common waiting rooms and circulation points for all patients. Although it would have been desirable to make a comparison with a group of patients that attended gastroenterology consultations at the same time, it was impossible to obtain an adequate number of patients with a similar age, gender, and pathology. Also, the consultation and waiting rooms are also completely different from those used in examinations. Therefore, even being aware of the inconveniences, it was decided to use the general population of Madrid as a reference.

It needs similar studies with more cases and in different situations, such as with or without protective measures, to determine accurately the risk of infection implicit in each procedure and the impact of these on the transmission of the pandemic to patients and HW.
With the knowledge of the real risk of each technique, improved measures for protection and recovery of activity could be planned. In any case, knowledge of the level of virus circulating in each geographical area, through a good system of identification and monitoring of new cases is essential to establish an adequate level of protection and activity.
Acknowledgements

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References


Table 1. Questionnaire used in the telephone survey.

- Have you had Coronavirus infection (COVID-19)?
  - COVID-19 confirmed disease (positive PCR)
  - Clinical disease by COVID-19 (Clinical and radiological criteria. PCR not performed)
  - COVID-19 Possible (Meets only clinical criteria. No tests have been performed)
  - No COVID-19

- Did you have a serological study?
  - Positive
  - Negative
  - Not done

- Did they perform PCR?
  - Positive
  - Negative
  - Not done

- Date the test was performed

- Exploration performed

- Other tests performed (endoscopies), analytics, consultations in this period.

- Onset date of symptoms
  - Dry cough
  - Dyspnea
  - Fever
  - Pharyngeal Pain
  - Myalgias
  - Headache
  - Anosmia/Ageusia
  - Asthenia
  - Vomiting
  - Diarrhea

- Have you lived with someone with COVID-19, before or after the motility study?
Table 2. Total results and by gender of confirmed or possible COVID-19 cases in all patients who underwent functional tests.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean age</th>
<th>Range</th>
<th>COVID-19 NEGATIVE</th>
<th>COVID POSITIVE/POSSIBLE</th>
<th>COVID-19 POSITIVE</th>
<th>COVID-19 possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>84</td>
<td>48</td>
<td>6-84</td>
<td>69</td>
<td>15</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Women</td>
<td>179</td>
<td>58</td>
<td>14-92</td>
<td>146</td>
<td>33</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>263</td>
<td>55</td>
<td>6-92</td>
<td>215</td>
<td>48 (18.25%)</td>
<td>22 (8.36%)</td>
<td>26 (9.88%)</td>
</tr>
</tbody>
</table>
Table 3. Tests performed and COVID-19 cases positive per month in the first two weeks after them and thereafter, until 24/05/2020. Shortening of the period of onset of symptoms from January to March. Two weeks after the test only four patients were positive COVID-19.

<table>
<thead>
<tr>
<th></th>
<th>2 weeks after test</th>
<th>&gt; 2 weeks after test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COVID-19</td>
<td>COVID-19</td>
</tr>
<tr>
<td></td>
<td>No. Patients</td>
<td>Confirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impedance-pH monitoring</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>Esophageal manometry</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Anorectal manometry</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>333</td>
<td>106</td>
</tr>
</tbody>
</table>

† (until March 11)

‡1 patient started symptoms 3 days before, 1 patient started symptoms 1 day later along with other cohabiting relatives)

§ asymptomatic
**Figure 1.** Distribution of the study population by decades and gender. The highest incidence registered was between the ages of 40 and 80 years of age.
Figure 2. Number of daily positive COVID-19 cases in the Madrid population (blue/dark line) and confirmed or possible cases in the study population (red/light line) (different scale). There is a parallel increase in both series during the month of March 2020 that follows less marked on later dates after the healthcare activity is suspended.
Figure 3. Distribution of confirmed or possible COVID-19 patients in the study population by decades and gender. Positive cases in bold (men in blue bars, women in green bars). The highest incidence registered was between the ages of 40 and 80 years of age.