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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 of restarting activities is unknown.

Objective: assess the risk of SARS-CoV-2 virus infection, 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 determine whether patients and healthcare workers had COVID-19, confirmed by either a test or compatible symptoms, after functional studies were performed from January until March 2020.

Results: the survey was answered by 263 (92.9 %) patients. Four (1.52 %) patients had confirmed COVID-19 in the two weeks after the functional test (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) and no patient after anorectal manometry. Another five had only compatible symptoms, for a total of nine patients (3.42 %) (adjusted rate 27.50 cases/1,000 [95 % CI: 7.27-47.74], OR 2.84 [95 % CI: 2.68-3.02]).
In the total study period, 18.25% had confirmed COVID-19 or compatible symptoms. The average number 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 of ten healthcare workers (20%) had confirmed COVID-19.

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

**Keywords:** COVID-19 risk, Esophageal manometry, Anorectal manometry, 24-hour esophageal impedance-pH monitoring, Functional tests of digestive motility.

**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). From May 14th, 2020 in Spain, 229,450 total cases of COVID-19 were 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 infections. Like non-urgent endoscopy, most functional tests (FT) of digestive motility were abruptly discontinued with the onset of the pandemic (4).

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

At present, there are no publications establishing 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 after the limitation of endoscopies for emergency situations (10,11). It has been speculated that there is a higher risk than in endoscopy procedures due to the insertion of the catheter through the nasopharynx (area with high viral load in patients with COVID-19) (12) and the possibility of the patient coughing, sneezing or vomiting more frequently when not using sedation. Although the risk of transmission decreases when appropriate personal protective equipment and other recommended measures are used (13), references to FT are scarce and targeted at protective measures, assuming empirically that these are high-risk examinations (4,14-17). Thus, it is important to determine the risk, both for patients and the HW who perform them, and therefore, make recommendations for restarting the activity.

The objective of the study was to determine the risk of SARS-CoV-2 virus infection, both in patients and in HW, in relation to esophageal and anorectal FT during the pandemic period, in which additional protective measures had not yet been implemented.

MATERIAL AND METHODS

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 2nd, 2020 until the suspension of these examinations on March 14th, 2020 were included in the study. Demographic data were collected and the clinical history 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 performed until May 24th, 2020, when phase zero ended in Madrid and in which a month passed without any new cases in our series. The end of phase zero allowed mobility again, based on hospital availability and a 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 two weeks following any of the described procedures.

Patients with specific tests (PCR and/or positive serology) and/or 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 patients and they were asked for their oral consent of acceptance to participate in the study. Once accepted, they were asked whether they had had COVID-19 before or after the study, the date of symptom onset if they had the infection 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 infection. All tests were performed 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. The 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 a 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 the risk of COVID-19. A p-value < 0.05 was considered as statistically significant. Statistical analyses were performed using the Epidat 3.1 and SPSS 22.0. Demographic 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) in a total of 283 patients (189 females, 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 a SARS-CoV-2 infection or compatible symptoms. Diagnostic tests were performed in only 15 patients in this group (nine serology tests and nine PCRs, three cases with the two tests performed).

Forty-eight patients (18.25%) were either confirmed COVID-19 positive (22, 8.36%) or possible during the period studied. There was a progressive distribution over time, practically zero in January and a maximum in March (Fig. 2). In the two weeks after the tests were performed, four patients (1.52%) had confirmed COVID-19 (all of them with EM or pH/I-pH) and five patients had a possible COVID-19 infection (1.90%), for a total of nine patients (3.42%) (Table 3). The distribution of confirmed or possible COVID-19 cases in the study population by decades and gender is shown in figure 3.

The interval between the tests performed and the first day of symptom onset in the two weeks following the test was shortened throughout the study (Table 3). There were no patients in January, three patients in February without serological confirmation and four confirmed and two possible cases in March. One patient had symptoms three days before an EM and pH/I-pH were performed, and another patient had compatible symptoms the day after ARM but no diagnostic tests were performed.

From May 24th, 2020, the 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 1,000 (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 had confirmed COVID-19 two weeks after the procedure, the studied patients had a significantly lower standardized risk of COVID-19 compared with the general population (OR 0.84 [95% CI: 0.83-0.85], p < 0.001). However, if the total of nine patients (confirmed and possible) are considered, the adjusted rate was 27.50 cases/1,000 subjects (95% CI: 7.27-47.74) and the adjusted OR was 2.84 (95% CI: 2.81-2.87). Thus, there was a slight increase in the risk of infection in our population (p < 0.001). There was no mortality in our series.

Healthcare staff
Two of ten (20%) members of the unit were affected by COVID-19, with symptom onset on 03-14-2020 and 03-16-2020, respectively. Although they were also performing other tasks during this period besides FT, a HW developed bilateral pneumonia and required hospitalization after she had performed a pH monitoring on a patient who presented symptoms and a positive PCR a day later. We have no evidence of infection in patients from HW. In addition, the infection of the HW were related to the period of highest rate of the pandemic, with a possible five infected patients.

DISCUSSION AND CONCLUSIONS
Digestive functional examinations are susceptible to the transmission of SARS-CoV-2, and there are no studies that allow a real risk approximation. In this study, this risk was assessed 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 this period, HW did not use protective equipment. Our findings suggest a low risk of COVID-19 after these procedures with an OR of 0.84. However, it may be a little higher (OR 2.87) if we consider the possible infection cases. Nevertheless, it must be taken into account that the patients could have been contaminated due to other circumstances, as there was a parallel increase of cases as the pandemic grew in the Madrid population and the early appearance of symptoms after FT in two patients, one of them living with COVID-19 positive family members. In addition, it is important to note that none of the patients who underwent ARM had a COVID-19 infection in the following two weeks.
Although the population included in our study is not homogeneous, neither was the population with COVID-19. In both series, there was a small number of cases in the first two decades of life. In the group studied, the percentage of females was higher than in the general population affected by COVID-19 (68.1% vs 56.3%), with a clear predominance of females aged between 40 and 80 years (Fig. 1). Likewise, the mean age of the group was lower (55 vs 60 years), which is explained by the advanced mean age of the Spanish population exposed to the infection, unlike the population with gastrointestinal pathology, which is usually younger. Both factors justify the lower morbidity and mortality in our cases, with a single hospitalized patient and no mortality. However, the study has the advantage of having been carried out in the community with the highest incidence in Spain, during the highest growth of the pandemic and when additional protection measures had not yet been implemented. The time in which the study was performed included 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 with confirmed COVID-19 during the study was 22 (8.36%), with an increasing trend depending on the evolution of the pandemic. The incidence of infection in our series followed a clear parallel with the evolution of the pandemic, with a possible impact of performing tests for patients and with a progressive risk to HW from February 20th and reaching its peak in March (Fig. 2). Specifically, on the last day of testing on March 14th, the circulating virus level was remarkably high. In Spain, 5,100 active cases (1,519 new) were declared, with a total of 5,753 registered cases. In the Community of Madrid, the total cases detected reached 2,940. These data are undervalued, considering the low number of tests performed on those dates. The predominance of females 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, which requires this type of FT.

The absence of similar studies prevents us from 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 was similar in both studies. The study indicated an estimate of the risk of infection in HW as 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 highlight, as in our case, the limitations caused by the ignorance of infected subjects who were tested due to the lack of diagnostic tests in the early stages of the pandemic. In our center, 10/67 (14.92%) HW from the Endoscopy Unit were infected by COVID-19 with a total of 4,680 examinations during the same period and without taking protective measures (non-published data).

In our study, the risk of infection to HW was low in relation to the number of examinations performed. The infection became apparent from 02-20-2020 with an increasing trend towards the end of the study period. However, since HW performed other functions that required contact with patients during the expansion phase of the pandemic, 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 was a widespread opinion in considering EM and I-pH/pH monitoring as high-risk techniques for HW due to the possibility of generating aerosols with a contagious capacity by coughing, sneezing or vomiting. This perception of the risk of infection is much lower in relation to ARM, since, even though the presence of the virus has been confirmed in the feces of infected patients (5-9), 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 infection having been noted when they are implemented (23,24). Therefore, while the characteristics of the healthcare activity performed might have a different risk of infection, our results and published data suggest that it is low. Both in the performance of endoscopies and FT, and was 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 limited 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 studies in a hospital setting, when there were 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. Furthermore, 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. Similar studies with more cases and in different situations, such as with or without protective measures, are needed 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
3. Red Nacional de Vigilancia Epidemiológica (RENAVE), Centro Nacional de Epidemiología (CNE), Centro Nacional de Microbiología (CNM) (Instituto de Salud Carlos III,


<table>
<thead>
<tr>
<th>Questionnaire used in the telephone survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you had coronavirus infection (COVID-19)?</td>
</tr>
<tr>
<td>- COVID-19 confirmed disease (positive PCR)</td>
</tr>
<tr>
<td>- Clinical disease by COVID-19 (clinical and radiological criteria; PCR not performed)</td>
</tr>
<tr>
<td>- COVID-19 possible (meets only clinical criteria; no tests have been performed)</td>
</tr>
<tr>
<td>- No COVID-19</td>
</tr>
<tr>
<td>Did you have a serological study?</td>
</tr>
<tr>
<td>- Positive</td>
</tr>
<tr>
<td>- Negative</td>
</tr>
<tr>
<td>- Not done</td>
</tr>
<tr>
<td>Did they perform PCR?</td>
</tr>
<tr>
<td>- Positive</td>
</tr>
<tr>
<td>- Negative</td>
</tr>
<tr>
<td>- Not done</td>
</tr>
<tr>
<td>Date the test was performed</td>
</tr>
<tr>
<td>Exploration performed</td>
</tr>
<tr>
<td>Other tests performed (endoscopies), analytics, consultations in this period.</td>
</tr>
<tr>
<td>Onset date of symptoms</td>
</tr>
<tr>
<td>Dry cough</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Pharyngeal pain</td>
</tr>
<tr>
<td>Myalgias</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Anosmia/ageusia</td>
</tr>
<tr>
<td>Asthenia</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Have you lived with someone with COVID-19, before or after the motility study?</td>
</tr>
</tbody>
</table>
Table 2. All 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-19 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 positive cases per month in the first two weeks after the procedure and thereafter, until May 24th, 2020

<table>
<thead>
<tr>
<th>No. total tests</th>
<th>Impedance-pH monitoring</th>
<th>Esophageal manometry</th>
<th>Anorectal manometry</th>
<th>No. patients</th>
<th>Confirmed</th>
<th>Only symptoms</th>
<th>Confirmed</th>
<th>Only symptoms</th>
<th>Average days</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>128</td>
<td>42</td>
<td>46</td>
<td>40</td>
<td>101</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>February</td>
<td>153</td>
<td>48</td>
<td>57</td>
<td>48</td>
<td>122</td>
<td>0</td>
<td>3</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>March*</td>
<td>52</td>
<td>16</td>
<td>23</td>
<td>13</td>
<td>40</td>
<td>4'</td>
<td>2</td>
<td>1'</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>333</td>
<td>106</td>
<td>126</td>
<td>101</td>
<td>263</td>
<td>4</td>
<td>5</td>
<td>18</td>
<td>21</td>
</tr>
</tbody>
</table>

Shortening of the period of the onset of symptoms from January to March. Two weeks after the test, only four patients were positive COVID-19.

*Until March 11th. †One patient started symptoms three days before; one patient started symptoms one day later, along with other cohabiting relatives. ‡Asymptomatic.
Fig. 1. Distribution of the study population by decades and gender. The highest incidence registered was between the ages of 40 and 80 years.
Fig. 2. Number of daily COVID-19 positive 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 is less marked on later dates after the healthcare activity was suspended.
Fig. 3. Distribution of confirmed or possible COVID-19 patients in the study population by decade 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.