Prospective observational study evaluating the increased risk of SARS-CoV-2 infection associated with performing endoscopic procedures (DECORE Study)

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1.- Background and current status of the topic:

Following the recommendations of scientific societies, non-urgent endoscopic and ultrasound examinations in our center were suspended due to the SARS-CoV-2 pandemic in March 2020.

Given the decrease in the number of hospital admissions and deaths, scientific societies are planning to restart scheduled outpatient activity in a gradual and staggered manner, prioritizing by indication (1). Multiple proposals have been developed to try to minimize the risk of contagion associated with hospital care for both healthcare workers and patients (2–4). However, most of these recommendations have a mainly theoretical basis and, given their recent implementation, their effectiveness has not yet been assessed. Most of the recommendations are based on two premises. First, identify symptomatic patients / workers through clinical interviews or screening tests to limit their access to the system as much as possible. Second, establish barrier / cleaning methods (use of masks, hand hygiene and contact surfaces ...) to minimize the risk of transmission by potential asymptomatic carriers.

Knowing the effectiveness of these measures is especially important for both patients and healthcare workers. Healthcare workers are known to have high rates of infection, up to 14% in the UK, in workers with any symptom compatible with the infection (5). In Spain it is estimated that 15% of the total infected are health workers (6) A high percentage will not be diagnosed, including on the one hand the asymptomatic and on the other the subjects with atypical symptoms that can account for 15-20% (7) . Estimating the prevalence of asymptomatic cases in the population is difficult due to the lack of availability of a universal screening test. The best evidence so far comes from the Diamond Princess cruise ship, which was quarantined with all passengers and crew members repeatedly tested and closely monitored, identifying 18% of asymptomatic infections (8). However, a Japanese study of evacuated citizens from Wuhan City estimates the rate to be close to 31% (9) The first data from an isolated village of 3,000 people in (VO 'EUGANE) estimate the figure to be higher, 50% to 75% (10)

If activity is resumed, asymptomatic infected workers and patients could become a vector of disease transmission, especially in examinations that are performed without being able to maintain a safe distance between the worker and the patient.

The virus also supports more than 4 hours on copper, 24 hours on metal and 72 hours on plastic (11), so given the scheduling of a preferred endoscopy or ultrasound schedule in the de-escalation period, a potentially contagious patient could put 10 other patients scheduled during the day are at risk, since despite the disinfection carried out between one and the other patient, it is not possible to ensure the complete eradication of all viral particles.

2.- Working hypothesis:

Carrying out endoscopic or ultrasound examinations under controlled conditions does not imply an increased risk compared to the general population.

Operational hypothesis:

Patients undergoing endoscopic procedures have a suspected SARS-CoV-2 infection rate of 1%, after examination, an incidence not lower than other patients undergoing ultrasound examinations or patients without scheduled hospital visits.

3.- Objectives:

Main objective: to compare the proportion of patients who develop SARS-CoV-2 disease in 3 groups: patients who underwent abdominal ultrasound examination in a Specialty Center, patients who underwent endoscopic examination in a third-level hospital with hospitalization facilities COVID-19 and patients who make a non-face-to-face consultation (do not go to the hospital) in the digestive system service

Secondary objectives:

• Identify risk factors associated with the development of SARS-CoV-2 infection.

• Assess whether the type of procedure (endoscopic vs. ultrasound) implies an increased risk of SARS-CoV-2 infection.

• Evaluate the proportion of workers in the digestive system service who have developed disease

4.- Design:

Prospective observational study

We propose to compare the cohort of patients undergoing endoscopic examination first with a cohort of patients undergoing ultrasound. With these groups, we will evaluate the effect of endoscopic examination per se on the risk of infection, given that both patients have to travel outside their home to a health center, with the differences between a Specialty Center and a tertiary Hospital with plants dedicated to treating COVID-19 patients and coming into direct or indirect contact with healthcare workers and other patients. Second, it will be compared with a cohort of patients who have had a telephone consultation. With this group, we will evaluate the effect that not only endoscopy has, but also travel to a health center.

5.- Methods:

Patients:

All patients who are evaluated in the digestive system service in any of these scenarios will be included prospectively and consecutively:

Performing an ambulatory endoscopy (endoscopic cohort)

Performing an ambulatory abdominal ultrasound (ultrasound cohort)

Conducting a non-face-to-face telephone consultation (telephone cohort)

Inclusion criteria:

Patients scheduled to undergo an ambulatory endoscopy, an ambulatory abdominal ultrasound, or a face-to-face telephone consultation

Age ≥18 years.

Exclusion criteria:

Refusal to sign the informed consent

Immunosuppression (steroid treatment with a dose of 20 mg or more of prednisone daily, azathioprine, cyclosporine, mercaptopurine, methotrexate, mycophenolate, tacrolimus, everolimus, chemotherapeutic agents, anti-TNF-α drugs or other biological treatments for inflammatory bowel disease)

Immunodeficiency due to a non-pharmacological cause (HIV, hematological dyscrasias, primary immunodeficiencies ...)

Previous confirmed diagnosis (by PCR or serology) of SARS-CoV-2 disease.

Diagnosis of previous suspicion (documented in the medical history by a physician) of SARS-CoV-2 disease.

Previous clinical picture compatible with SARS-CoV-2 in the previous 2 months (defined as any positive response to the check-list questionnaire contained in Annex III)

Cognitive impairment or hearing impairment preventing the phone visit

Habitual residence outside the province of Valladolid

Ultrasound interventionism (liver biopsy, ultrasound-guided paracentesis, biliary drainage ...)

Procedures

Patients will undergo 48-96h before the procedure to a clinical telephone interview in which they will be asked about the presence of symptoms suggestive of SARS-CoV-2 infection. Optionally, a scan (PCR) will also be performed to detect infection 48-96h before the procedure, and patients with positive PCR or infection suspected by clinical data will be withdrawn from the study according to the questionnaire included in Annex III, after evaluating the questionnaire responses. by one of the members of the research team. The variables of the data collection notebook

(Annex I) will be collected between the recruitment visit (procedure visit) and the follow-up visit

Endoscopic examinations: They will be performed according to the recommendations of the Spanish society for digestive endoscopy (SEED) (1). In summary, the patient will perform a hand wash with hydroalcoholic solution before entering the endoscopy room, and will put on a surgical mask and gloves. Personnel close to the patient will wear an FFP2 mask, exceptionally a surgical mask, a gown (waterproof in high-risk examinations as established in the SEED guidelines), a cap, nitrile gloves and face shield or safety glasses (reusable) and shoe covers. The examinations will be performed by endoscopist-guided sedation in accordance with current clinical guidelines.

Ultrasonographic examinations: They will be carried out according to international clinical guidelines (12). The explorer will wear an FFP2 mask, exceptionally a surgical mask, a gown, a hat, nitrile gloves, and a face shield or safety glasses (reusable) and shoe covers. The gel bottle, transducer, and stretcher will be washed prior to each scan with low-level disinfectant.

Tracing

Patients who meet the inclusion criteria and do not meet any exclusion criteria will be invited to participate in the study. The patients who agree to participate will complete the informed consent (see annex II) according to the law 41/2002 of patient autonomy

without thereby altering the relationship with their doctor or causing any harm in their treatment. The monitoring period will have a maximum duration of 17 days. It will consist of a telephone control through a pre-established check-list (see annex III). In case of any positive answer to the questionnaire, the study will be completed through the consultation of the digestive system using a polymerase chain reaction (PCR) test of the nasal exudate.

Evaluation of service workers

Once the study period is completed, after two weeks of the study, a serological test will be performed on all workers in the endoscopy and ultrasound unit who have not developed symptoms compatible with SARS-CoV-2 infection and who have been in Contact with patients to assess whether they have present or past SARS-CoV-2 infection.

Data will be collected from workers who have developed symptomatic SARS-CoV-2 infection during the study period and in the two subsequent weeks (see CRD, Annex II)

Sample size

In a recently published study by Repici et al (13), an incidence of SARS-CoV-2 infection of 1% was estimated in patients undergoing endoscopy in Italy between January and March 2020 throughout the 2 weeks following the process.

Assuming that the proportion of infections is the same in the groups, to demonstrate the non-inferiority of each of the control groups with respect to the group undergoing endoscopy with a limit of 3%, 137 patients per group would be necessary. Assuming 10% losses (patients who cannot be contacted), 151 patients per group would be necessary.

Bias control

2 control groups are established. The group of patients who come to perform an ultrasound will allow evaluating the effect of performing an endoscopic examination compared to other non-invasive examinations performed in a health center. The group of patients in which a telephone review is carried out will make it possible to compare the group of patients who underwent digestive endoscopy with respect to the subjects who have not attended health centers in the same time interval.

6. Data management.

The CRD data will be entered anonymously by the principal investigator or collaborating investigators, encrypted and dissociated from the clinical information using a patient identification code (ID), in a database generated in Access®. The responsible doctor, who is also a researcher, will define an ID for each patient, whose relationship with the medical history will only be accessible by him, with its custody in a file protected by personal password. The data entered in the database will be encrypted and the database will be protected with a password that only researchers will have access to.

The unified file will be kept at the Río Hortega University Hospital and will be kept until the end of the study. The CRDs collected in the file will be kept at the Digestive Service to ensure their accessibility to researchers and their control.

Regarding the application of Law 3/2018 on the Protection of Personal Data and guarantee of digital rights and, additionally, the General Regulation (EU) 2016/679 on

Data Protection, it should be noted that the protocol defined in the project aimed at epidemiological analysis, determines that the files will record fully encoded information. The security, access and availability levels will be those defined in said document.

7. Statistical analysis.

Categorical variables will be described as percentages. The continuous ones with normal distribution as mean and standard deviation. Continuous variables with non-normal distributions will be described as medians and interquartile range (the range can also be offered).

For the main objective, the Z test will be used without Yates correction. The difference between both groups and the confidence interval of thesame. The analysis will be performed using Stata (StataCorp. 2013. College Station, Texas).

8. Ethical aspects.

8.1 Benefit-risk assessment for research subjects

The present study supposes the realization of a prospective observational study. The procedure to which the patients undergo will be carried out independently of the participation in the study. The only consequence of participating is that the data concerning the procedure will be collected, an epidemiological survey will be carried out prior to recruitment, and the patient will be contacted after 2 weeks of the procedure to carry out a predefined questionnaire. Therefore, the participation will not suppose any benefit for the participant. On the other hand, the prejudices derived from participation in the study are also minimal, since the patient will only be contacted by telephone. The benefit that we hope to obtain is to identify if the performance of endoscopic procedures or ultrasound examinations represent an increased risk of SARS-CoV-2 infection. This study will be carried out following the standards specified in the Declaration of Helsinki, the Standards of Good Clinical Practice and the ICH (International Conference on Harmonization) guidelines.

The patient will be identified in the study database by an identification code (ID), sex and date of birth. The databases and other documents of the study will be available to the Health Authorities if they consider it relevant, in no case will they be available to third parties.

This study will not require a civil liability insurance policy, which covers any possible damages or losses derived from it.

Patients recruited for telephone consultations will not be able to sign the informed consent at the time of recruitment. These patients will be informed of the content of the informed consent and, if accepted, their consent will be collected, which they will grant verbally. for participation in the clinical trial and a copy of the informed consent will be sent to them by post. Patients scheduled for endoscopy and ultrasound will receive informed consent on the day of the examination, giving written consent at that time.

8.2. Confidentiality of data

The study data will be initially dissociated from the medical history, by means of an ID, from the responsible physician. The relationship between the ID and the medical record will be kept by the investigating doctors in a file protected with a personal password. The data will be entered into the database anonymously with the patient's ID, to maintain anonymity. The database will be password protected, and only accessible by

researchers. During the study, strict compliance with Law 3/2018 on the Protection of Personal Data is guaranteed.

9. Timeline and plan for dissemination of the study.

May 2020: Inclusion of patients

June 2020: Data analysis

10. Definitions:

Suspected SARS-CoV-2 infection: including definitions of probable or possible case according to the Ministry of Health (14). Being the symptoms evaluated by one of the investigating doctors.

Probable case: case of severe acute respiratory infection with clinical and radiological criteria compatible with an unconfirmed diagnosis of COVID-19.

Possible case: case with mild acute respiratory infection that has not undergone a microbiological diagnostic test.

Confirmed SARS-CoV-2 infection: dichotomous variable. Defined by a positive direct (PCR) or indirect (serology) test.

Close contact of possible, probable or confirmed cases (14): Anyone who has provided care while the case had symptoms: healthcare workers who have not used adequate protection measures, family members or people who have another type of similar physical contact. Co-survivors, relatives and people who have been in the same place as a case while the case presented symptoms at a distance of less than 2 meters for a time of at least 15 minutes

Isolation type: categorical variable. Depending on the out-of-home outings from endoscopy to follow-up at 2 weeks. Includes strict categories (does not leave the home except for essential activities (<1 daily departure), very high risk worker, high, medium, or low according to the pyramid of the Occupational Safety and Health Administration (OSHA) (Annex IV).

Type of dwelling: categorical variable. It includes the categories private and institutionalized housing (in case of living in a residence, psychiatric center, penitentiary, etc.).

Active neoplasm: malignant tumor in treatment or one that has been less than 2 years from the end of a treatment with curative intention.

Chronic renal failure: Basal creatinine higher than 2mg / dl.

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