



# Efficacy of systematic coronavirus screening by PCR and viral cultures in addition to triage in limiting the spread of SARS-CoV-2 within a hemodialysis unit

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## Abstract

**Background** Patients with end-stage-renal-disease (ESRD) undergoing hemodialysis (HD) represent a vulnerable population for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, due to their intrinsic fragility and increased exposure to the virus. Therefore, applying effective screening strategies and infection control measures is essential to control the spread of the epidemic within hemodialysis centers.

**Objective** Description and evaluation of the efficacy of systematic screening by rt-PCR and viral cultures, in addition to triage to limit the spread of the epidemic. Evaluation of the performance of these tests using “post-hoc” SARS-CoV-2 serology as a surrogate marker of infection.

**Methods** One hundred and forty-four patients undergoing hemodialysis in the Nephrology-Hemodialysis center of CHU Brugmann, Brussels, benefited from systematic virological screening using viral cultures in asymptomatic patients, or molecular tests (rt-PCR) for symptomatic ones, in addition to general prevention measures. Post-hoc serology was performed in all patients.

**Results** Thirty-eight (26.3%) individuals were infected with SARS-CoV-2. Seventeen infected patients (44.7%) were asymptomatic and thus detected by viral culture. Our strategy allowed us to detect and isolate 97.4% of the infected patients, as proven by post-hoc serology. Only one patient, missed by clinical screening and sequential viral cultures, had a positive serology.

**Conclusion** The implementation of a control and prevention strategy based on a systematic clinical and virological screening showed its effectiveness in limiting (and shortening) the spread of the SARS-CoV-2 epidemic within our hemodialysis unit.

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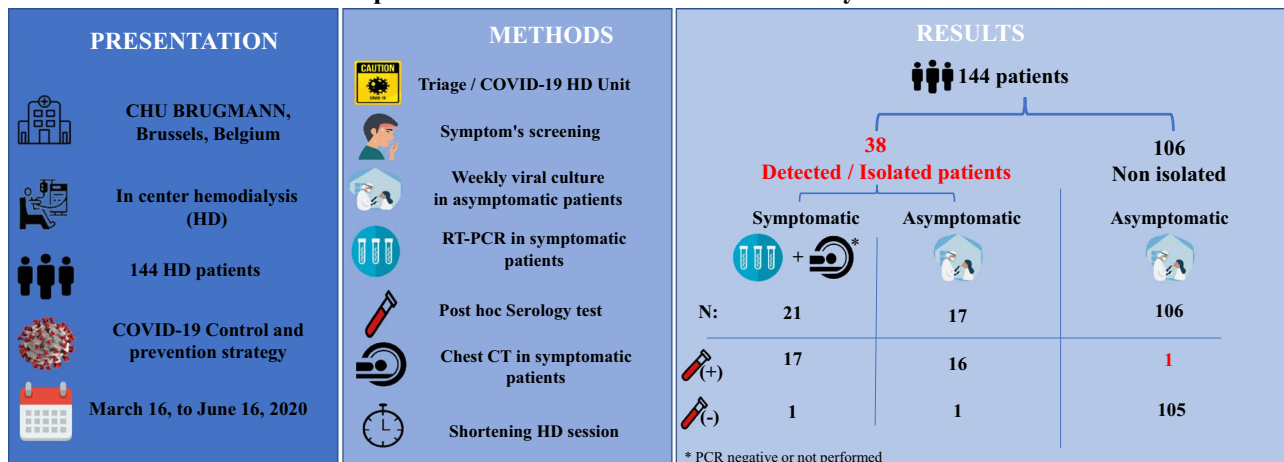
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## Graphic abstract

### Efficacy of systematic coronavirus screening by PCR and viral cultures in addition to triage in limiting the spread of SARS-CoV-2 within a hemodialysis unit.



**CONCLUSION:** We detected and isolated 97,4% of the infected patients, thank to our strategy based on a systematic screening of asymptomatic patients using viral culture and rt-PCR as a diagnostic test for symptomatic patients. The implementation of a control and prevention strategy based on a systematic clinical and virological screening showed its effectiveness in limiting and shortening the spread of SARS-COV-2 epidemic within our hemodialysis unit.

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**Keywords** SARS-CoV-2 · Chronic hemodialysis · Control and prevention · Viral culture · Screening

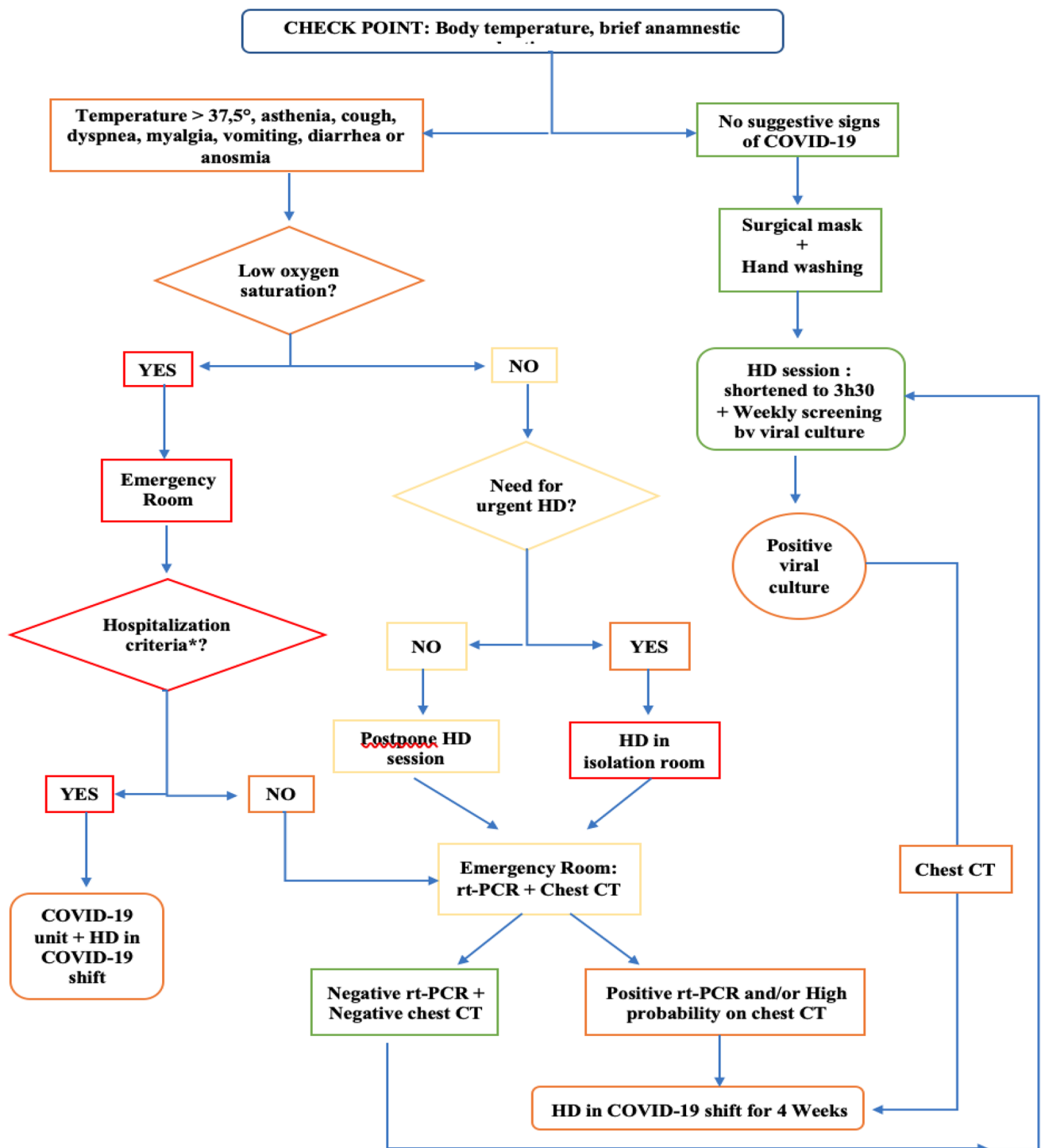
## Introduction

COVID-19 is significantly more severe in certain populations like the elderly and those with comorbidities [1, 2]. Patients with end-stage-renal-disease (ESRD) undergoing hemodialysis (HD) often present with multiple comorbidities, older age and intrinsic immune deficiency [3]. In addition to their household contacts, HD patients form a closed healthcare workers/other patients community pertaining to their HD shifts. They are at increased risk of bringing, acquiring and/or perpetuating the transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) inside their cluster. HD facilities have been recognized as a high-risk hub for disseminating SARS-CoV-2 among patients, to and from healthcare workers and to and from family members [4].

Several organizations have developed guidance for the prevention of SARS-CoV-2 infection in HD facilities. Clinical screening for COVID-19 symptoms, isolation of suspected and confirmed patients, hand hygiene and personal protective equipment for healthcare workers are recommended in the effort to control the SARS-CoV-2 epidemic in HD facilities. On February 26th, 2020, the American Society of Nephrology (ASN) published their first recommendations

for the prevention and control of COVID-19 in dialysis facilities [5], upon which we based our prevention strategy. However, screening limited to symptoms might not be reliable enough as up to 50% of HD patients suffering from COVID-19 are asymptomatic and would have been missed although they are potential transmitters [6]. A systematic seroprevalence study among HD patients found that more than 30% of them had been infected with SARS-CoV-2 and that 40% of them were missed by the symptoms screening/reverse transcriptase PCR (rt-PCR) test strategy [7]. Systematically and frequently carrying out virological testing, regardless of the presence of symptoms, was shown to be the optimal method to contain the epidemic among university students [8].

Since March 2020, we decided to perform systematic virological screening using viral cultures in asymptomatic patients, in addition to the general prevention measures. Symptomatic patients were tested by rt-PCR. All SARS-CoV-2 carriers were isolated irrespective of symptomatology.



**Fig. 1** Management of hemodialysis patients during the COVID-19 epidemic. \*Hospitalisation criteria: Patients at high risk, Oxygen saturation <94% (<90% in COPD patients), sepsis signs (hypotension,

tachycardia, tachypnea > 30 cycles/min), deterioration of general condition, extra-pulmonary damages, severe pulmonary damages on the chest CT

### Objective

Description and evaluation of the efficacy of systematic screening by rt-PCR and viral cultures, in addition to triage

to limit the spread of the epidemic in a HD unit. Evaluation of the performance of these tests using “post-hoc” SARS-CoV-2 serology as a surrogate marker of infection.

## Methods

### Triage and patient relocation

One hundred and forty-four patients undergo hemodialysis in the Nephrology-Hemodialysis center of CHU Brugmann, Brussels. A one-way forward patient circulation circuit was established to limit inter-patient contact. All patients had to perform hand hygiene and wear a surgical mask. They were symptom-screened at each HD shift. Patients were categorized as “suspect” based on symptoms while awaiting rt-PCR confirmation, “asymptomatic” undergoing weekly culture screening and “SARS-CoV-2 positive” by either PCR or culture screening. Patients were segregated in conventional HD shifts for “asymptomatic” patients, transit unit for “suspect” patients while awaiting rt-PCR results, and “COVID-19” dedicated unit for all SARS-CoV-2 carriers regardless of the presence of symptoms. COVID-19 patients presenting with severe symptoms were admitted and handled according to national guidelines. SARS-CoV-2 carriers were restricted to the dedicated unit for a duration of 28 days before being sent back to the conventional SARS-CoV-2-free HD unit.

The management of our HD patients (i.e., suspected/asymptomatic/SARS-CoV-2-positive) is summarized in Fig. 1.

### Symptom screening

Triage consisted in a brief anamnestic evaluation of possible symptoms and in measuring body temperature (with 37.5 °C as a red flag).

### Virological screening: viral culture and rt-PCR

In addition to clinical screening, asymptomatic patients were screened weekly by viral culture on a nasopharyngeal (NP) swab between the 16th of March, and the 16th of June, 2020. Virological screening was interrupted for SARS-CoV-2 carriers during their 28 days of isolation in the COVID-19 HD unit. On average, fourteen viral cultures were performed for each patient, except infected patients who had four less viral cultures, during their isolation period.

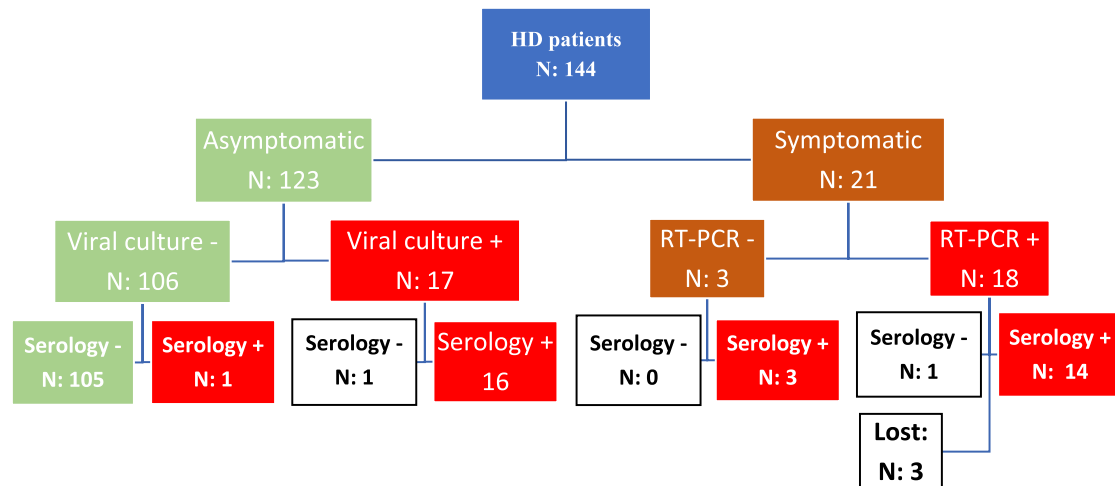
Viral cultures were performed by inoculating Vero (Vervet monkey) kidney cell lines with the vortexed nasopharyngeal swab supernatant and checked using a microscope for 14 days for any characteristic cytopathic effects. If cytopathic effects were noted, the virus was identified using antigen detection tests (COVID-19 Ag Respi-Strip assay, Coris Bioconcept, Gembloux, Belgium).

Reverse-transcriptase PCR (RealStar SARS-CoV-2 RT-PCR kit 1.0 Altona Diagnostics, Hamburg, Germany) was used as a diagnostic test for symptomatic patients.

Serology tests on peripheral blood samples were performed on the 15th and 16th of June, 2020, in all HD patients, except 3 patients (two patients were lost to follow up and the third one died before being tested). We used a qualitative serology test for SARS-CoV-2 IgG-IgM combined antibodies (Elecsys® Anti-SARS-CoV-2 assay, Roche Diagnostics, Mannheim, Germany).

### Imaging study

We performed a chest computed tomography (CT) in all HD patients with a suspected or confirmed SARS-CoV-2 infection, except in two patients who were lost to follow up (admitted to other hospitals).



**Fig. 2** Prevalence of SARS-COV-2 in our hemodialysis cohort according to virologic tests by RT-PCR, viral culture and retrospective serology

## Dialysis methods

During the COVID-19 epidemic, the duration of HD sessions was reduced from 4 h to 3.5 h. For all SARS-CoV-2 infected patients we used a Polymethylmethacrylate (PMMA) ‘FILTRYZER BG 1.8’ membrane, from Toray Industries, Inc.

## Results

We performed 1,802 viral cultures and 87 rt-PCRs on NP swab tests. Thirty-eight patients (26.3% of the total HD patients) were diagnosed with SARS-CoV-2 infection: 27 men (71%) and 11 women (29%) (sex ratio: 2.45), of a median age of 54 years [IQ range 19–90 years].

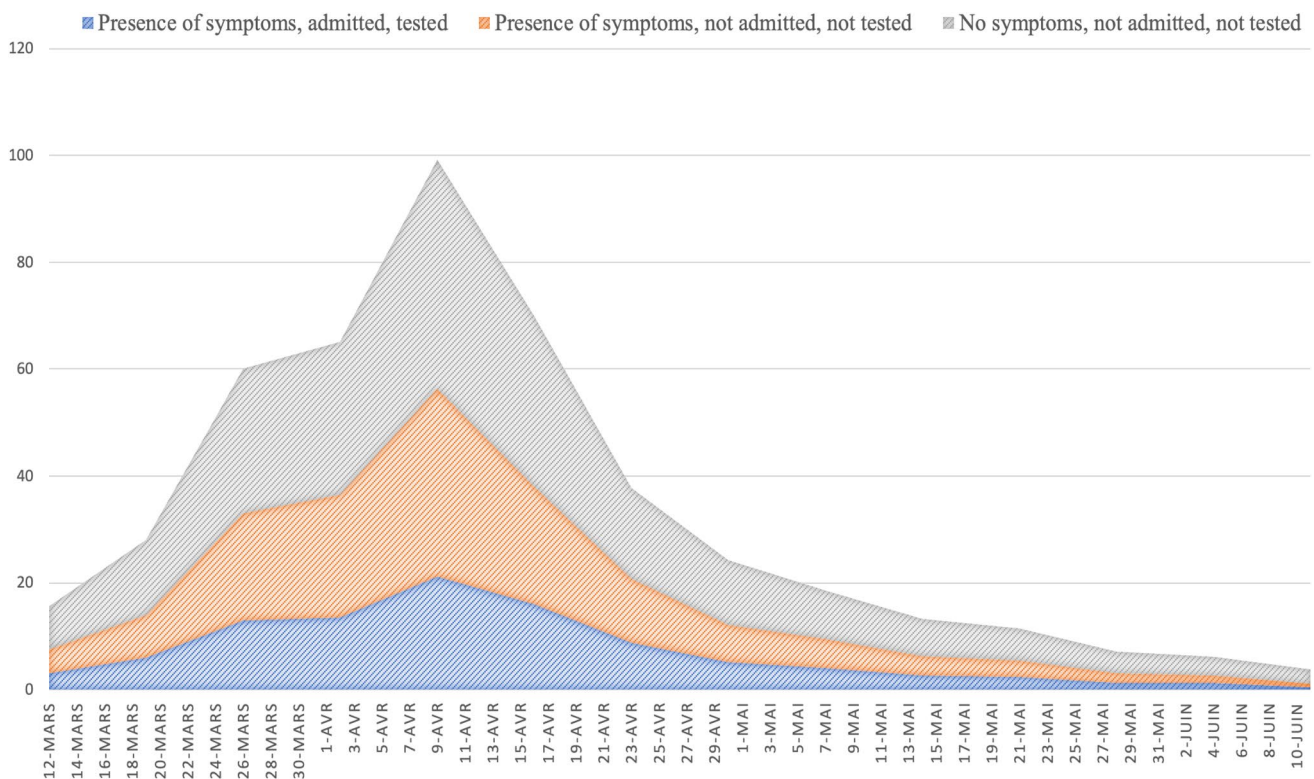
Among the 38 infected patients, 15 (39.4%) were admitted to a COVID-19 unit, while 4 patients (10.5%) were admitted to the intensive care unit (ICU). One patient (2.6%) died after two weeks in the ICU. Six other patients (4% of the total HD patients) died during the follow-up period (16<sup>th</sup> of March to 16<sup>th</sup> of June, 2020), 5 of whom had been infected by SARS-CoV-2 but died of other causes (severe post-intubation tracheal stenosis, acute lower extremity ischemia, septic shock, acute decompensated heart failure and withdrawal from dialysis), at least 28 days after

infection. The 6<sup>th</sup> patient died of hemorrhagic shock due to severe gastrointestinal bleeding.

Median time to positivity of viral cultures was 3 days (IQ range: 2–8 days), and 24 h for rt-PCR. Seventeen infected patients (45%) were asymptomatic and thus detected by viral culture. Among the symptomatic patients, 18 (47%) had a positive rt-PCR, while 3 patients (8%) were considered infected and isolated in COVID-19 HD shifts based on their symptoms and high suspicion on chest CT (Fig. 2).

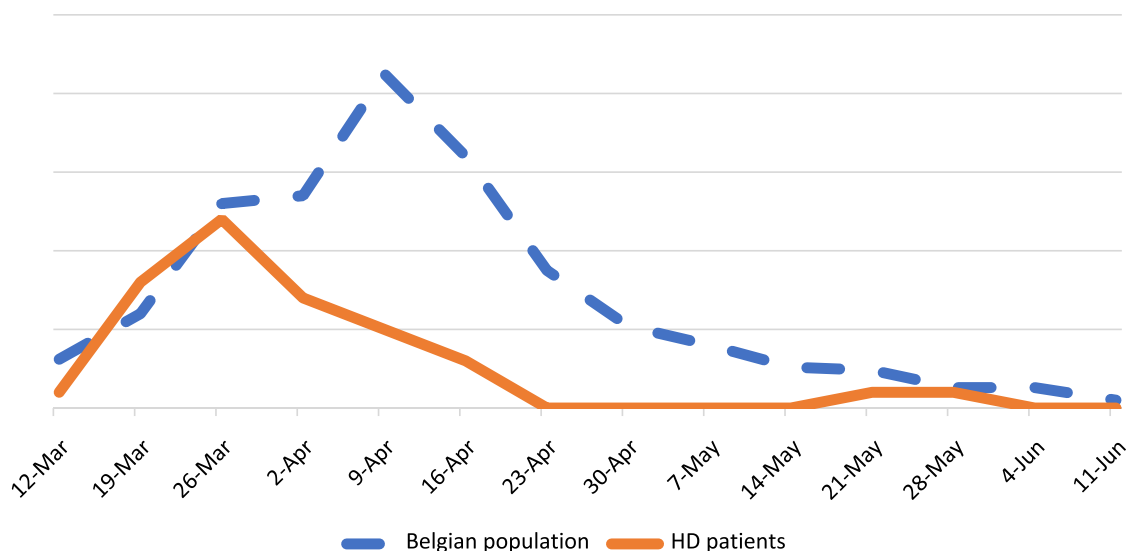
A chest CT scan was performed in 36 of the 38 SARS-CoV-2 infected patients, of whom 26 (72%) showed a high probability of COVID-19 based on their chest-CT results. Lesions in up to 40% of the lung parenchyma were observed in seven asymptomatic patients.

A SARS-CoV-2 serology test was performed in 141 patients. Among the 38 confirmed COVID-19 patients, three patients (8%) did not have a serology (two patients were lost to follow up and the third one died before being tested), 33 patients (94%) had a positive serology test and 2 patients (6%) had a negative test. Only one patient (0.6% of the 141 tested patients) who presented negative viral cultures on weekly screening and thus non detected, had a positive serology test (Fig. 2).



**Fig. 3** Influence of testing policy in SARS-COV-2 infection diagnosis





**Fig. 4** Evolution of SARS-COV-2 incidence in our HD unit compared to the Belgian population [12]

## Discussion

Long term health care facilities, like homes for the aged have been disproportionately affected by COVID-19 compared to the general population despite applying recommended precautions: social distancing, protective equipment, and hand washing. Owing to the impossibility to practice social distancing, many patients as well as healthcare workers were also affected by COVID-19 in hemodialysis facilities. That situation required organizational changes, screening, and isolation strategies to prevent the spread of SARS-CoV-2 while maintaining care delivery [9]. The best screening strategy for testing, tracing, tracking and isolating has yet to be determined [10]. Symptom-based screening is inefficient as up to 72% of patients are asymptomatic at the time of diagnosis [11]. Asymptomatic COVID-19 patients while less contagious contribute proportionally more than sick patients to disease propagation.

rt-PCR is the referent standard test for COVID-19 diagnosis [12]. However, sensitivity and specificity of RT-PCR varies according to the course of the disease. It has low specificity for COVID-19 late in, or after, the acute disease. Persisting positive rt-PCR tests weeks and even months after COVID-19 recovery can be misleading and interpreted as recurrence or persistence of the carrier state [13]. It has low sensitivity during incubation and in the early stages of the acute disease. If performed too early, rt-PCR misses up to 36% of SARS-CoV-2 infected patients, as subsequently evidenced by serology [14]. “Post hoc” serology might in fact be the gold standard for infection diagnosis even asymptomatic and a complementary test to rt-PCR [15].

In the early stages of the epidemic, access to rt-PCR was limited. Based on the national guidelines, only patients presenting hospitalization criteria were eligible for rt-PCR. Other patients were sent back home with a presumptive diagnosis of mild COVID-19. Under those conditions, it was not possible to weekly screen all our asymptomatic HD patients using rt-PCR. We chose to use viral cultures as screening in asymptomatic patients and reserve rt-PCR for symptomatic individuals in order to get faster results. We have shown that using serology as the surrogate marker for infection, sensitivity and specificity of viral cultures are 75% and 99%, respectively [16].

A seroprevalence study in slums in India showed 37 times more infected patients than those detected by rt-PCR [17]. The magnitude of affected patients, taking into account those with few, or no symptoms, might have been much higher than numbers reported by Public Health authorities [18] based on NP swab tests (Fig. 3).

Chest CT was used as a screening test in some centers [19], as rt-PCR could yield up to 29% false negatives [20]. Some reports claim that chest CT was a more sensitive test than rt-PCR (98% vs 71%, respectively) [21]. However, CT scan has low sensitivity in asymptomatic patients [22], and low specificity due to their overlap with several other conditions, especially in HD patients [23].

In one Chinese series, 37 cases among 230 HD patients (16%) were diagnosed with COVID-19 and 6 patients (16%) died [19]. A prevalence of 8% with a mortality of 18% was registered in French-speaking Belgium HD centers. Those centers did not use a screening strategy, but only rt-PCR in symptomatic patients [24]. Our prevalence was higher, with 38 COVID-19 patients (26.3%) among 144 patients on HD,

with a lower mortality rate (2.6%). The higher prevalence in our center is explained by the systematic screening of all our HD patients allowing to detect even asymptomatic patients.

In a recent study, the seroprevalence of SARS-CoV-2 antibodies in a HD unit was 36% (129 patients), while only 22.2% (79 patients) of the total study population were detected by rt-PCR in symptomatic patients. Among the 129 patients with SARS-CoV-2 antibodies, 52 (40%) were asymptomatic or undetected by PCR testing alone [7]. These figures are compatible with our results. A prevention strategy based on testing solely the symptomatic patients is not only limited by the sensitivity of the rt-PCR, as three (8%) patients were not correctly diagnosed by rt-PCR (Fig. 2), but also by not detecting the asymptomatic carriers, as 45% of our infected patients were asymptomatic.

Our strategy allowed us to detect and isolate 97.4% of the infected patients, as proven by post-hoc serology. Only one patient, missed by clinical screening and sequential viral cultures, had positive serology.

SARS-CoV-2 serology also has its inherent limitations. In our study, two confirmed COVID-19 patients had negative serology. The first patient had negative serology two days after a positive viral culture, probably due to a short delay for seroconversion, as described by Egger et al. [25], and when serology was carried out using the the Elecsys® Anti-SARS-CoV-2 assay, seroconversion reached 100% positivity only 15–22 days after infection. This patient died shortly after diagnosis and further serological testing was not done. The other patient had negative serology approx. two months after a positive rt-PCR. The combined IgM–IgG immunoassay (Elecsys® Anti-SARS-CoV-2, Roche Diagnostics) reports 99.5% sensitivity over 14 days after symptomatic infection and 99.5% specificity, according to the manufacturer. However up to 5% of symptomatic patients and 15–40% of rt-PCR-positive asymptomatic patients remain seronegative [26]. This might explain the discordance between viral culture/rt-PCR and serological tests in our two patients.

The early detection of the infected patients and then the isolation of all carriers irrespective of symptomatology allowed us to rapidly control the local epidemic in our HD center. The peak incidence in our unit was reached two weeks after we applied systematic screening and was followed by a rapid decline of the incidence curve. In Belgium, in the absence of a universal screening and isolation strategy during the first COVID-19 wave, the incidence continued to increase for two more weeks, compared to our HD population [27] (Fig. 4).

The efficacy of that strategy might have been limited by the lack of involvement of healthcare workers who were tested only when symptomatic. However, nosocomial transmission is bidirectional between patients and staff. In a study, systematic screening of staff as well as patients permitted to identify 12% of staff members, about three times

more than HD patients themselves, with a SARS-CoV-2 rt-PCR positive test [28].

## Conclusion

We detected and isolated 97.4% of the infected patients thanks to our strategy based on the systematic screening of asymptomatic patients using viral culture and rt-PCR as a diagnostic test for symptomatic individuals. The screening strategy based on PCR testing of symptomatic patients could have missed 53% of infected patients in our unit. This allowed us to quickly control the spread of SARS-CoV-2 in our HD facility. Frequently repeated systematic screening based on virological assays for both patients and healthcare workers is probably the best testing/eviction strategy to limit the spread of SARS-CoV-2. Repeated follow-up seroprevalence studies should be carried out in various populations to assess the attack rate of SARS-CoV-2 infection.

**Authors' contributions** MTS: Conceptualization. Writing—original draft preparation. BM: writing—review and editing. PC: Conceptualization. Writing—review and editing. Supervision. EM: Review and editing. MM: Review and editing. IN: Writing—review and editing. Frederic Collart, MD: Conceptualization. Review and editing. Supervision.

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**Availability of data and material** The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

**Code availability** Not applicable.

## Declarations

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose.

**Ethics approval** Ethical approval was waived by the local Ethics Committee of the University in view of the retrospective nature of the study and because all the procedures being performed were part of the routine care.

**Consent to participate** Not applicable.

**Consent for publication** All the named authors consent to the publication of this manuscript.

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