Secretion of severe acute respiratory syndrome coronavirus 2 in urine

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Purpose of review
Despite the plethora of publications discussing the severe respiratory coronavirus 2 (SARS-CoV-2), evidence of viral secretion in urine is sparse.

Recent findings
We could identify 34 publications including a total of 2172 patients. Among those, 549 patients were tested for SARS-CoV-2 secretion in urine, which was detected in only 38 patients (6.9%). Within the seven studies displaying positive results, the majority of positive patients (86.8%) was from not yet peer-reviewed studies including weak data and heterogeneous techniques for sample testing. Furthermore, none of the studies available in the literature addressed the virulence of detected viral RNA in urine.

Summary
Overall, only seven studies were able to detect SARS-CoV-2 secretion in urine, all of them with a considerably low rate of positivity. However, these studies were of rather low quality considering their methodology. Despite this, as SARS-CoV-2 has been detected in urine, it is of importance to discuss safety and urinary hygiene protocols. Until further research provides valid data on viral shedding and virulence in urine, potential risk of transmission through urine cannot be ruled out. Therefore, safety and hygiene measures need to be discussed.

Keywords
COVID-19, severe respiratory coronavirus 2, urine

INTRODUCTION

At the end of 2019, a new virus, called novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the causative pathogen responsible for COVID-19. Although the transmission occurs mainly via respiratory droplets, there is a lack of evidence about the pattern, duration, timing, compartmentalization and quantity of viral shedding in different specimens. SARS-CoV-2 can be detected in different fluids such as sputum, nasal swabs, blood and faeces. The evidence regarding the presence and virulence of the virus in urine is sparse. The WHO recently proposed in its guidelines to consider urine testing for all symptomatic patients and contact persons [1].

SARS-CoV-2 targets the angiotensin-converting-enzyme 2 (ACE-2) receptor for host cell entry [2]. ACE-2 not only occurs in epithelial cells of the human airway tract but is also abundantly expressed in the kidney, predominantly in the epithelial layer of the renal ducts [3]. Hence, the kidney could constitute a site of virus replication if it can dock at that site. As the presence of an active and contagious virus in urine could be a source and route of transmission, important hygiene and safety measures for the general population and healthcare workers (HCWs) might result.

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KEY POINTS

- The presence of SARS-CoV-2 in urine is poorly investigated in the current literature (0.6% out of 5674 articles).
- Overall, only 6.9% of patients in studies and case reports that analysed urine, were tested positive for SARS-CoV-2.
- Remarkably, 90% of the patients with multiple urine analysis displayed a positive RT-PCR only at one single point in time.
- The implementation of standardized procedures is crucial to reduce confounding factors resulting from preanalytical and analytical irregularities.
- The transmission risk and virulence of SARS-CoV-2 in urine have not been assessed so far, despite this, as SARS-CoV-2 has been detected in urine, safety and urinary hygiene protocols should be discussed.

To address this lack of knowledge, we performed a systematic review of all the available (published and unpublished) literature on COVID-19 to investigate the presence of SARS-CoV-2 in human urine.

Materials and methods

On the 14th of April 2020, we searched on PubMed, medRxiv, bioRxiv and COVID-19 Open Research database to assess the incidence of SARS-CoV-2 in urine. We only included articles published in the English language without restriction with regard to the publication period. The following keywords were used in our search strategy: 'COVID-19' OR 'nCoV' OR 'SARS-CoV-2' OR 'coronavirus'. Four investigators performed independently direct full-text screening of the articles based on the keywords 'urine, urinary'. We did not exclude reviews, editorials, letters and case reports. Discrepancies were resolved by Delphi consensus. Four investigators extracted independently the information from the included articles, and one-fifth made an independent review of all the extracted data (Fig. 1 and Table 1) [4–6,7▪▪,8–25,26▪,27–37].

RESULTS

Overall, 5674 publications were identified in the initial search (PubMed, 4530; medRxiv and bioRxiv, 1144). Among these, after full-text screening, 5637 articles were excluded including duplicates and nonrelevant articles according to our inclusion

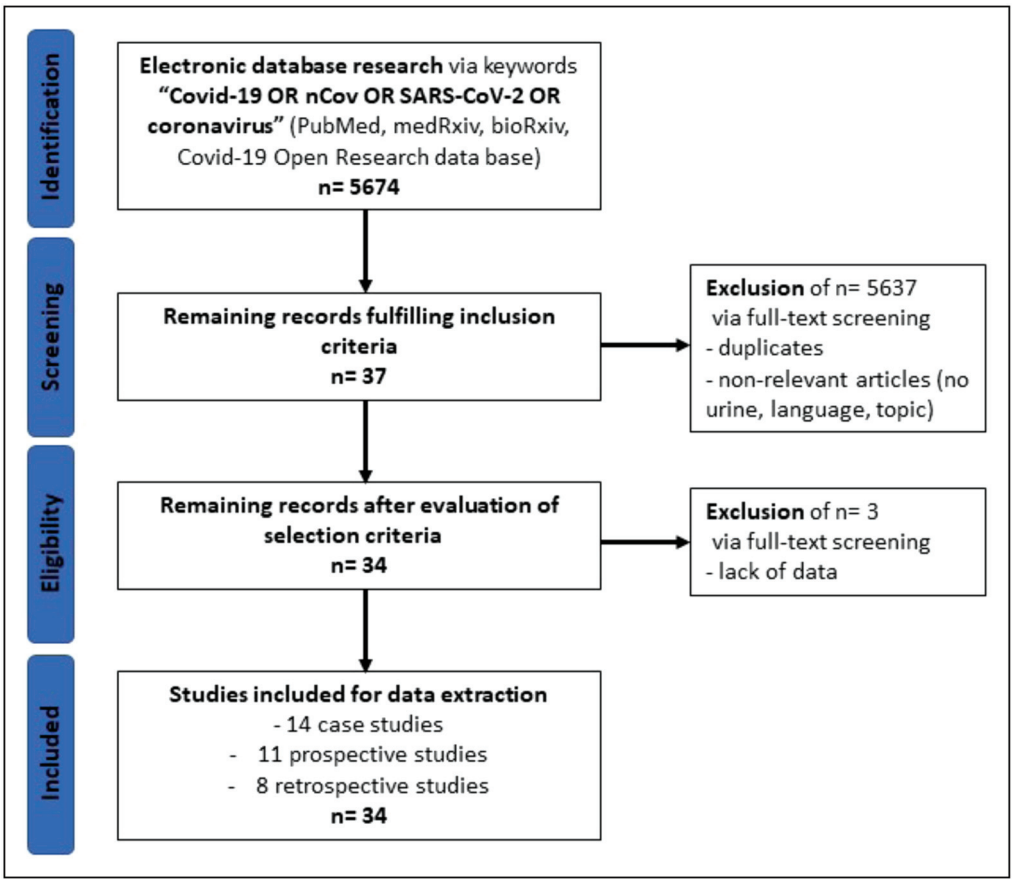

FIGURE 1. Study flow diagram. Selection of 34 studies including 2172 patients.

Table 1. Publications analyzing SARS-CoV-2 secretion in urine

Ref.	Date	Study type	Platform	Patients total	Patients urine tested	Positive in urine	Sampling time point
Chen *et al.* [8]	03 April 2020	Retrospective	PubMed	10	10	0	Multiple
Qiu *et al.* [9]	02 April 2020	Retrospective	PubMed	10	10	0	At diagnosis and sampling
Caly *et al.* [10]	01 April 2020	Case	PubMed	1	1	0	day 6, 8, 9, 11, 13 post symptom onset (day 1, 3, 4, 6, 8 post admission, respectively)
Wang *et al.* [11]	31 March 2020	Retrospective	medRxiv	116	53	4	Unknown (urine sediments)
Zhang *et al.* [12]	30 March 2020	Prospective	medRxiv	23	23	2	Day 16 and 21 post admission
Chan *et al.* [13]	30 March 2020	Retrospective	PubMed	15	15	0	Unknown
Yu *et al.* [14]	28 March 2020	Prospective	PubMed	76	14	0	Unknown
Xie *et al.* [15]	27 February 2020	Prospective	PubMed	19	19	0	Unknown
Lescure *et al.* [16]	27 March 2020	Case	PubMed	5	4	0	–One to five samples within up to 7 days post admission
Tan *et al.* [4]	26 March 2020	Prospective	medRxiv	67	67	12	Periodically (3–6 days interval) post admission
Klement *et al.* [17]	25 March 2020	Case	PubMed	1	1	0	Day 3,4,5 + 7 post diagnosis (= day 2,3,4 + 6 post symptom onset, respectively)
To *et al.* [18]	23 March 2020	Prospective	PubMed	23	18	0	Unknown
Fang *et al.* [19]	21 March 2020	Prospective	PubMed	32	32	0	Unknown
Hill *et al.* [20]	20 March 2020	Case	PubMed	1	1	0	Unknown
Cui *et al.* [21]	17 March 2020	Case	PubMed	1	1	0	Day 10 post symptom onset
Park *et al.* [22]	16 March 2020	Case	PubMed	1	1	0	Day 6 + 10 post symptom onset
Tan *et al.* [23]	16 March 2020	Case	medRxiv	1	1	0	Day 1, 11 and 18 post admission
Lo *et al.* [24]	15 March 2020	Retrospective	PubMed	10	10	0	Day 19 post symptom onset
Diao *et al.* [5]	13 March 2020	Prospective	medRxiv	259	19	14	Unknown
Ghinai *et al.* [25]	13 March 2020	Case	PubMed	2	2	0	2 weeks, every 2–3 days
Wang *et al.* [26▪]	11 March 2020	Retrospective	PubMed	205	72	0	Unknown
Wolfel *et al.* [7▪▪]	08 March 2020	Prospective	medRxiv	9	9	0	Day 2–4 post symptom onset
Holshue ML, *et al.* [27]	05 March 2020	Case	PubMed	1	1	0	Day 4, 7, 11, 12
Li *et al.* [28]	05 March 2020	Case	PubMed	2	2	0	Day 3,4,5,6,7 post symptom onset + day 1,2 post birth in infant
Chan *et al.* [29]	04 March 2020	Case	PubMed	6	5	0	Once at day 6–10 post symptom onset
Xiao *et al.* [30]	03 March 2020	Prospective	PubMed	73	73	0	Day 1–26 post admission
Young *et al.* [31]	03 March 2020	Prospective	PubMed	18	10	0	Daily
Guan *et al.* [32]	28 February 2020	Retrospective	PubMed	1099	Unknown	1	Unknown
Ling *et al.* [33]	28 February 2020	Retrospective	PubMed	66	58	4	During convalescence
Cheng *et al.* [34]	26 February 2020	Case	PubMed	1	1	0	Day 25 post symptom onset
Peng *et al.* [6]	25 February 2020	Prospective	medRxiv	9	9	1	Day 7 post symptom onset
Liu *et al.* [35]	25 February 2020	case	PrePrints	3 + 3 healthy children	2	0	Between day 1 and 5 post birth in infants
Kim *et al.* [36]	24 February 2020	Case	PubMed	2	2	0	Several samples at least 3 days post symptom onset
Pan *et al.* [37]	24 February 2020	Retrospective	PubMed	2	2	0	Several samples at day 3–15 post symptom onset

criteria. After evaluating the selection criteria, we identified 34 articles (0.6%) reporting urinary detection of SARS-CoV-2.

We found 549 patients who had at least one urine specimen analysed. Seven publications reported at least one positive test for a total of 38 patients (6.9%). Among these positive patients, 26 (68.4%) were constituted by two studies that were not yet peer-reviewed of which one used nucleocapsid protein detection by fluorescence immunochromatography for virus detection [4,5]. The remaining studies ($n = 33$) performed RT-PCR to detect amplified viral RNA from urine samples. Remarkably, 90% of the patients with multiple urine analysis displayed a positive RT-PCR only at one single point in time during the study period. Twenty-seven studies (71%) testing urine in 342 patients (62.3%) did not detect any viral RNA in urine samples. Among the seven studies that reported SARS-CoV-2 secretion in urine, only one provided the viral copy number detected in RT-PCR, which was 3.22E^02 copies/ml [6]. All patients tested in the studies had COVID-19 symptoms. There was no article assessing the transmission risk and virulence of SARS-CoV-2 in urine.

DISCUSSION

Showing a high sensitivity and specificity, RT-PCR is currently considered the standard for fast and cost-efficient identification and quantification of SARS-CoV-2. Nonetheless, RT-PCR harbours the risk of false-negative and false-positive results. False-negative results are caused by low virus load and procedural errors such as inadequate sampling and processing, whereas false-positive results could result from cross-contamination occurring at some point in the entire testing procedure.

Despite WHO recommendations, the presence of SARS-CoV-2 in urine is poorly investigated in the current literature. However, urine rarely seems to contain SARS-CoV-2, even in symptomatic patients. Studies, which have been conducted so far were not designed to evaluate specifically SARS-CoV-2 in urine; therefore, most studies did not conduct multiple or systematic urine testing, which would be necessary to avoid selection bias. Potentially, the urinary secretion of the virus is highest early in the disease, when patients are not symptomatic yet and have a high virus load. Indeed, the inclusion of symptomatic patients only is a potential source of selection bias. In addition, studies failed to show consistently positive results in consecutive samples of previously positive tested patients. Urinary SARS-CoV-2 should, therefore, be measured at different disease states (e.g. asymptomatic, mild/moderate symptoms, severe symptoms and immune) and among different groups of the population (e.g. different ethnic groups, patients with renal insufficiency and so on). Moreover, validated and accurate sampling and testing strategies need to be implemented [7▪▪].

In summary, only seven studies were able to detect SARS-CoV-2 secretion in urine, all of them with a considerably low rate of positivity. However, these studies were of rather low quality considering their methodology. Despite this, as SARS-CoV-2 has been detected in urine, it is of importance to discuss safety and urinary hygiene protocols for HCW. There is a need for future studies to evaluate the virulence and risk of transmission via titre testing with virus purified from different fluid specimens such as urine.

CONCLUSION

Although the WHO recommends considering urinary testing for SARS-CoV-2 in symptomatic patients and contacts, it seems that the proportion of urine positivity is very low. Overall, we could only identify seven studies, which reported positive results, all of them with a considerably low rate of positivity. However, these studies were of rather low quality considering their methodology and none assessed the transmission risk and virulence of SARS-CoV-2 in urine. Until further research provides valid data on viral shedding and virulence in urine, a potential risk of transmission through urine cannot be ruled out. Therefore, safety and hygiene measures need to be discussed.

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