



A systematic review on COVID-19: urological manifestations, viral RNA detection and special considerations in urological conditions

Vinson Wai-Shun Chan¹ · Peter Ka-Fung Chiu² · Chi-Hang Yee² · Yuhong Yuan³ · Chi-Fai Ng² · Jeremy Yuen-Chun Teoh²

Received: 21 April 2020 / Accepted: 5 May 2020 / Published online: 27 May 2020
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Abstract

Purpose and objective We performed a systematic review on COVID-19 and its potential urological manifestations.

Methods A literature search was performed using combination of keywords (MeSH terms and free text words) relating to COVID-19, urology, faeces and stool on multiple databases. Primary outcomes were the urological manifestations of COVID-19, and SARS-CoV-2 viral RNA detection in urine and stool samples. Meta-analyses were performed when there were two or more studies reporting on the same outcome. Special considerations in urological conditions that were relevant in the pandemic of COVID-19 were reported in a narrative manner.

Results There were a total of 21 studies with 3714 COVID-19 patients, and urinary symptoms were absent in all of them. In patients with COVID-19, 7.58% (95% CI 3.30–13.54%) developed acute kidney injury with a mortality rate of 93.27% (95% CI 81.46–100%) amongst them. 5.74% (95% CI 2.88–9.44%) of COVID-19 patients had positive viral RNA in urine samples, but the duration of viral shedding in urine was unknown. 65.82% (95% CI 45.71–83.51%) of COVID-19 patients had positive viral RNA in stool samples, which were detected from 2 to 47 days from symptom onset. 31.6% of renal transplant recipients with COVID-19 required non-invasive ventilation, and the overall mortality rate was 15.4%.

Conclusions Acute kidney injury leading to mortality is common amongst COVID-19 patients, likely as a result of direct viral toxicity. Viral RNA positivity was detected in both urine and stool samples, so precautions are needed when we perform transurethral or transrectal procedures.

Keywords COVID-19 · SARS-CoV-2 · Viral RNA · Urine · Stool · Urology · Acute kidney injury

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00345-020-03246-4>) contains supplementary material, which is available to authorized users.

✉ Jeremy Yuen-Chun Teoh
jeremyteoh@surgery.cuhk.edu.hk

¹ School of Medicine, Faculty of Medicine and Health, University of Leeds, Leeds, UK

² S.H. Ho Urology Centre, Department of Surgery, 4/F LCW Clinical Sciences Building, Prince of Wales Hospital, The Chinese University of Hong Kong, 30-32 Ngan Shing Street, Shatin, New Territories, Hong Kong, China

³ Department of Medicine, McMaster University, Hamilton, Canada

Introduction

As cases of Coronavirus Disease 2019 (COVID-19) reaches the 1.7 million mark, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused over 100,000 deaths worldwide. Typical symptoms of COVID-19 include fever, cough, sore throat, fatigue, sputum production, shortness of breath and headache [1]. However, recent studies showed that COVID-19 could have other non-respiratory manifestations [2, 3]. As urologists, we manage patients with urological symptoms, and we perform both transurethral and transrectal procedures in our clinical practices. It is possible that we might encounter COVID-19 patients in our urological practices. To protect ourselves, our colleagues and our patients, it is important to understand thoroughly about the urological manifestations of COVID-19, and the possible routes of viral transmission via urine and stool. It is also important to understand whether there are any special

considerations in managing specific urological conditions under the circumstances of COVID-19. Therefore, we performed a systematic review to summarize the clinical manifestations, viral RNA detection and special considerations of COVID-19 from an urologist's perspective.

Material and methods

We systematically reviewed the literature on COVID-19 and its relevance to our urological practice. The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [4].

Literature search

A comprehensive literature search was performed using combination of keywords (MeSH terms and free text words) including 'COVID-19'/'SARS-CoV-2', 'Urology'/'Urogenital System', and "Stool"/"Faeces". MEDLINE, EMBASE and Cochrane library (CENTRAL and CDSR) were searched up to 8th April 2020. A limit of after 2019 was imposed since COVID-19 was first reported in late 2019. The search strategy was presented in Online Appendix 1. Additional articles were sought from the reference lists of the included studies.

Selection criteria

All articles identified from the literature search were screened by two independent reviewers (J.Y.C.T. and V.W.S.C.). We included studies on COVID-19 in adult patients. Case reports, case series, observational studies, non-randomized studies and randomised trials that were published in English were included in this review. Conferences abstracts, letters to editors, commentaries and editorials were also included. Studies related to obstetrics and gynaecology were excluded. Studies on severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) but not COVID-19 were excluded.

Data collection

For eligible studies, study information including first authors, site of study, inclusion and exclusion criteria, sample size, age and sex were recorded. A standardised form for data entry has been devised to focus on the following areas: (1) urological manifestations of COVID-19; (2) detection of viral RNA in urine and stool samples; (3) special considerations in urological conditions.

Data synthesis and statistical analysis

Primary outcomes of our study included urological manifestations of COVID-19, detection rates of SARS-CoV-2 viral RNA in urine and stool samples, and special considerations in urological conditions. For the urological manifestations and viral RNA detection rates, data were pool analysed using MetaXL and Microsoft Excel when there are two or more studies with at least four patients reporting the same outcome under the same definition. Random effects model was used. Double arcsine transformation was used to pool the proportions. The results were presented by forest plots, illustrating the prevalences, 95% confidence intervals and weightings. Cochran's Q test was used to detect heterogeneity, and a p value of <0.10 indicates significant heterogeneity. I^2 statistics was calculated to measure the proportion of total variation in study estimates attributed to heterogeneity with $I^2 > 50\%$ suggests substantial heterogeneity. Special considerations in urological conditions that were relevant in the pandemic of COVID-19 were reported in a narrative manner.

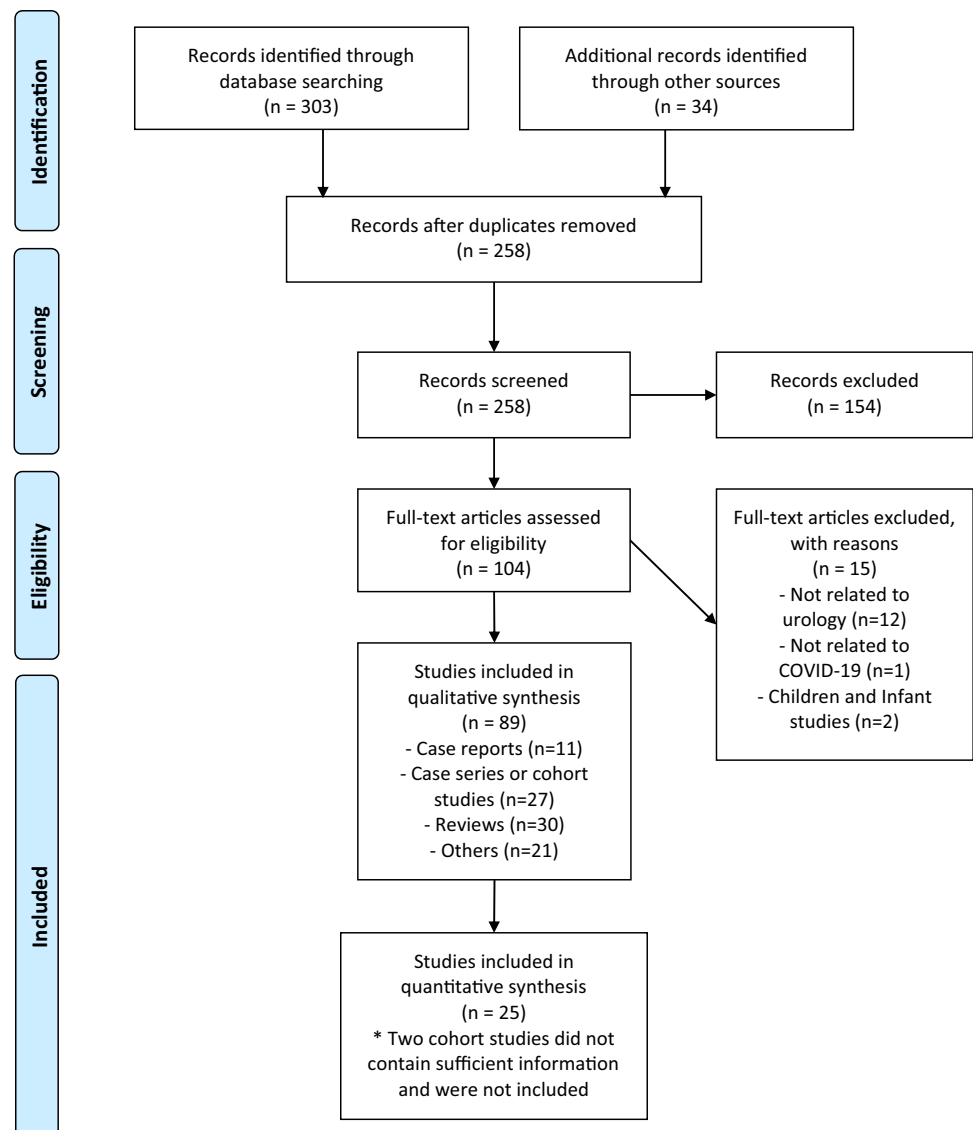
Results

The PRISMA flow diagram was shown in Fig. 1. A total of 303 records were identified upon literature search, and 34 additional records were sought from reference lists of the included literature. 258 records remained after removing duplicates. Among them, 154 were excluded upon initial screening, and 15 studies were excluded upon full-text review. Overall, 89 records were included in the qualitative synthesis and 25 studies were included in the quantitative synthesis. Table 1 summarised the study characteristics of the 25 studies [1, 5–28] that were included in the quantitative analysis.

Urological manifestations of COVID-19

There were a total of 21 studies reporting urinary symptoms and/or gastrointestinal symptoms, with a total of 3714 COVID-19 patients being included. Urinary symptoms were absent in all 3714 patients. Sighinolfi et al. briefly mentioned his encounter of two patients with indwelling urological devices (ureteral stent or nephrostomy tube), who had fever 'attributed' to urinary infection, but eventually turned out to be COVID-19 [29]. Yang et al. [23] reported one COVID-19 patient who suffered from urinary tract infection due to candida albicans during hospitalisation. To sum up, urinary symptoms is not a presenting symptom of COVID-19, but it can be a concomitant symptom due to other urological conditions.

Fig. 1 PRISMA flow diagram



Acute kidney injury (AKI) can be a manifestation of COVID-19 patients. Our meta-analysis included 12 studies and 3266 patients, and the pooled prevalence of AKI was 7.58% (95% CI 3.30–13.54%) (Fig. 2a). Amongst the 65 patients with AKI in three studies, the pooled mortality rate was 93.27% (95% CI 81.46–100%) (Fig. 2b). A cohort study by Cheng et al. also established associations between stage 1, 2 and 3 AKI, and in-hospital death, with hazard ratios of 1.90 (95% CI 0.76–4.75), 3.53 (95% CI 1.50–8.27) and 4.72 (95% CI 2.55–8.75) respectively [7]. Regarding the underlying pathophysiological mechanism, a recent molecular modelling study revealed that COVID-19 had a strong interaction with angiotensin converting enzyme 2 (ACE2) [30], and ACE2 had been shown to be a major receptor involved in the entry of COVID-19 into human cells [31]. Besides type II alveolar cells, proximal tubular cells of kidney also had abundant expression of ACE2 receptor [31–33].

Hence, the virus might be able to spread to the kidneys via the blood stream [34]. ACE2 were also expressed in other organs including testis and bladder [30, 31, 33], therefore it was postulated that these organs might be at risk of damage upon COVID-19. However, up to date, there were no reported cases of testicular or bladder manifestations following COVID-19 infection.

Detection of viral RNA in urine and stool samples

There were a total of 11 studies that reported the number of patients who had their urine tested for SARS-CoV-2 viral RNA. Amongst the studies, 195 patients were included and the pooled rate of RNA positivity was 5.74% (95% CI 2.88–9.44%) (Fig. 3a). It was difficult to determine the duration of viral shedding due to the relatively low rate of RNA positivity and the lack of serial testing [13, 15, 17].

Table 1 Baseline characteristics of the studies included in the meta-analysis

Study	City and Country	Type of study	Time frame	No. of COVID-19 patients	Age (years)	Sex (M/F)
Chen et al. [5]	Wuhan, China	Case series	20 Jan to 9 Feb	42	Median: 51 (IQR 42.75–62)	15/27
Chen et al. [6]	Wuhan, China	Cohort study (deceased vs recovered)	13 Jan to 12 Feb	274	Median: 62 (IQR 44–70)	171/103
Cheng et al. [7]	Wuhan, China	Cohort study (baseline creatinine vs elevated creatinine)	28 Jan to 11 Feb	701	Median: 63 (IQR 50–71)	367/334
Deng et al. [8]	Wuhan, China	Cohort study (deceased vs recovered)	1 Jan to 21 Feb	225	Deceased arm: 69 (IQR 62–74) Recovered arm: 40 (IQR 33–57) Whole cohort: NR	124/101
Guan et al. [1]	China	Case series	Up till 29 Jan	1099	Median: 47 (IQR 35–58)	640/459
Huang et al. [9]	Wuhan, China	Case series	16 Dec to 2 Jan	41	Median: 49 (IQR 41–58)	30/11
Lescure et al. [10]	Paris/ Bordeaux, France	Case series	24 Jan to 29 Jan	5	Median: 46 (IQR 30.5–64)	3/2
Li et al. [11]	Wuhan, Huangshi and Chongqing, China	Cohort study (COVID-19 vs other pneumonia)	6 Jan to 21 Feb	193	Median: 57 (IQR 46–67)	95/98
Lin et al. [12]	Zhuhai, China	Case series	17 Jan to 15 Feb	95	Mean: 45.3 (SD:18.3)	45/50
Ling et al. [13]	Shanghai, China	Case series	20 Jan to 10 Feb	66	Median: 44 (range 34–62)	38/28
Lo et al. [14]	Macau SAR, China	Case series	21 Jan to 16 Feb	10	Median: 54 (IQR 27–64)	3/7
Peng et al. [15]	Guangdong, China	Case series	NR	9	Median: 37 (IQR 28.5–47.5)	4/5
Shi et al. [16]	Wuhan, China	Cohort study (cardiac injury vs no cardiac injury)	20 Jan to 10 Feb	416	Median: 64 (range 21–95)	205/211
Wang et al. [17]	Wuhan, China	Case series	14 Jan to 13 Feb	116	Median: 54 (IQR 38–69)	67/49
Wang et al. [18]	Wuhan, China	Case series	1 Jan to 28 Jan	138	Median: 56 (IQR 42–68)	75/63
Wang et al. [19]	Hubei, Shandong and Beijing, China	Case series	1 Jan to 17 Feb	205	Mean: 44 (range 5–67)	140/65
Wölfel et al. [20]	Munich, Germany	Case series	From 23 Jan	9	NR	NR
Wu et al. [21]	Zhuhai, China	Case series	16 Jan to 15 Mar	98	NR	NR
Xie et al. [22]	Sichuan, China	Case series	NR	9	Median: 34 (IQR 25.5–52)	4/5
Yang et al. [23]	Wuhan, China	Cohort study (deceased vs recovered)	24 Dec to 26 Jan	52	Mean: 59.7 (SD: 13.3)	35/17
Young et al. [24]	Singapore	Case series	23 Jan to 3 Feb	18	Median: 47 (range 31–73)	9/9
Yu et al. [25]	Beijing, China	Case series	5 Feb to 19 Feb	76	Median: 40 (IQR 32–63)	38/38
Zhang et al. [26]	Wuhan, China	Case series	11 Jan to 10 Feb	82	Median: 72.5 (IQR 65–80)	54/28
Zhang et al. [27]	Wuhan, China	Case series	NR	39	NR	NR
Zhang et al. [28]	Jinhua, China	Case series	27 Jan to 10 Feb	14	Median: 41 (range 18–87)	7/7

All included studies were published in 2020 *IQR* Inter-quartile range, *NR* not reported, *SD* standard deviation

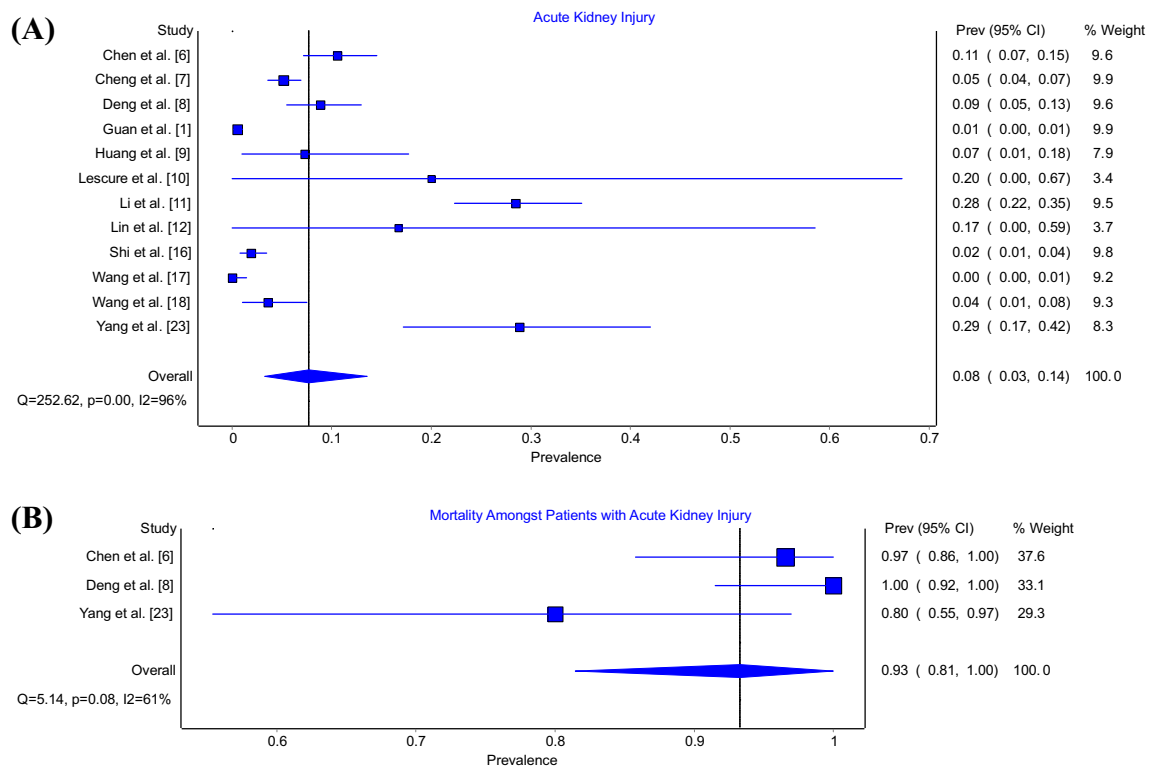


Fig. 2 a Pooled prevalence of acute kidney injury, and b pooled mortality rate in patients with acute kidney injury

Peng et al. reported positive urine sample for a patient on the 7th day of symptom onset. Ling et al. reported three out of four cases where urine samples remained positive even after throat swabs had converted negative, but the viral RNA conversion time was not precisely reported (at least 6 days from symptom onset) [13]. The duration of viral shedding in urine samples remained largely unknown.

Our meta-analysis included 12 studies that reported the number of patients with stools tested for SARS-CoV-2 viral RNA. Amongst the studies, 325 were included and the pooled rate of RNA positivity was 65.82% (95% CI 45.71–83.51%) (Fig. 3b). Due to a lack of a standardised serial testing protocol in the included studies, it is difficult to calculate the duration of viral shedding. However, positive viral RNA in stool could be detected as early as 2 days from symptom onset, [10, 14] and could be persistent up to day 47 from symptom onset despite a negative throat swab [21]. In a case series by Ling et al. 78.2% of the patients with positive stool samples were still positive after throat swabs had converted negative with a median delay of 2 days [13]. In the same study, the median days for RNA conversion in stool samples was 11 days, but it could be up to 20 days in patients who were on steroids.

Special considerations in managing specific urological conditions

Renal transplant recipients and COVID-19

There were six studies [35–40] reporting a total of 19 cases COVID-19 in renal transplant recipients (Table 2). The mean age was 47.4 ± 13.3 years. 21.1% of the patients were female. The majority of the patients had fever (94.7%) and cough (94.7%), and diarrhoea was present in 16.7% of them. 73.7% of the renal transplant recipients had elevated serum creatinine, and 31.6% required non-invasive ventilation. By the time of reporting, six patients were still under treatment in hospital. In the remaining 13 patients, 11 of them recovered (84.6%) and the remaining two patients died (15.4%). The proportion of patients requiring non-invasive ventilation and the mortality rate appeared to higher than the general population [1].

Urolithiasis and COVID-19

There were no reports on possible associations between COVID-19 and urolithiasis. However, non-steroidal anti-inflammatory drugs (NSAIDs), a medication commonly used to alleviate stone-related colicky pain has raised

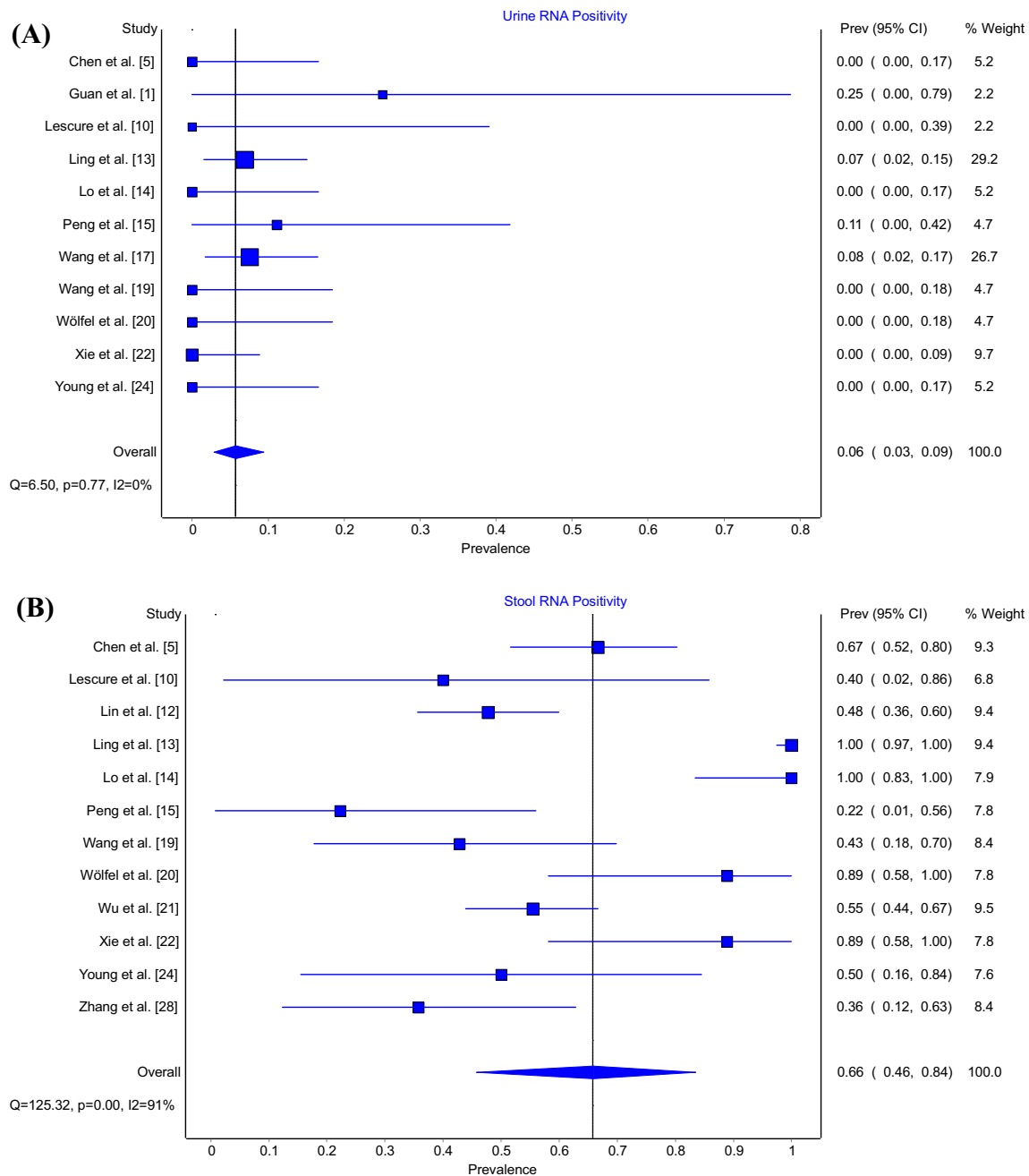


Fig. 3 **a** Pooled rate of urine RNA positivity, and **b** pooled rate of stool RNA positivity

concerns in the community. Fang et al. [41] reported that upregulation of ACE2 might increase the risk of developing severe and fatal COVID-19. NSAIDs also increases ACE2 and there is a worry that it might induce similar effect [41]. US Food and Drug Administration recently announced that there was not enough scientific evidence connecting the use of NSAIDs, such as ibuprofen, with worsening COVID-19

symptoms [42]. Therefore, the use of NSAIDs in renal colic management should still follow established indications.

Although urolithiasis is a non-malignant condition, stones can be obstructing and may lead to renal function deterioration if definitive surgery was delayed in the pandemic of COVID-19. Proletti et al. made recommendations on the priority of stone surgeries mainly based on patient and stone factors [43]. These recommendations

Table 2 Baseline characteristics of the studies included in the meta-analysis

Patient	Age	Sex	Fever	Cough	Diarrhoea	Elevated serum Cr	Maintenance immunosuppressants	IVIG	Other treatments	Non-invasive ventilation	Outcome
Zhu et al. [38]											
1	24	Male	Yes	No	No	Yes	Tacrolimus Mycophenolate Mofetil Prednisolone	No	Antivirals (Non-specified)	No	Recovered
2	55	Male	No	Yes	No	Yes	Tacrolimus Mycophenolate Mofetil Prednisolone	Yes	Antivirals (Non-specified)	Yes	Recovered
3	29	Male	Yes	Yes	Yes	Yes	Tacrolimus Mycophenolate Mofetil Prednisolone	No	Antivirals (Non-specified)	No	Recovered
4	30	Male	Yes	Yes	No	Yes	Tacrolimus Mycophenolate Mofetil Prednisolone	Yes	Antivirals (Non-specified)	No	Recovered
5	50	Male	Yes	Yes	No	No	Tacrolimus Mycophenolate Mofetil Prednisolone	Yes	Antivirals (Non-specified)	No	Recovered
6	65	Female	Yes	Yes	Yes	No	Tacrolimus Mycophenolate Mofetil	Yes	Antivirals (Non-specified)	Yes	In-hospital
7	52	Male	Yes	Yes	No	No	Tacrolimus Mycophenolate Mofetil Prednisolone	Yes	Antivirals (Non-specified)	No	Recovered
8	49	Male	Yes	Yes	Yes	No	Tacrolimus Mycophenolate Mofetil	No	Antivirals (Non-specified)	No	Recovered
9	59	Male	Yes	Yes	No	Yes	Cyclosporin Mizoribine	Yes	Antivirals (Non-specified)	Yes	Death
10	37	Female	Yes	Yes	No	Yes	Tacrolimus Mycophenolate Mofetil Prednisolone	Yes	Antivirals (Non-specified)	No	Recovered
Gandolfini et al. [37]											
11	75	Male	Yes	Yes	No	No	Tacrolimus Mycophenolate Mofetil Steroids (non-specified)	NR	Lopinavir/Ritonavir Antibiotics Hydroxychloroquine	Yes	Death
12	52	Female	Yes	Yes	No	Yes	Tacrolimus Mycophenolate Mofetil Steroids (non-specified)	NR	Darunavir/ Cobicistat Antibiotics (Non-specified) Hydroxychloroquine	Yes	In-hospital
Guillen et al. [35]											
13	50	Male	Yes	Yes	No	Yes	Tacrolimus Everolimus Prednisone	NR	Lopinavir/Ritonavir Ceftazolin Meropenem Interferon-Beta Hydroxychloroquine	Yes	In-hospital

Table 2 (continued)

Patient	Age	Sex	Fever	Cough	Diarrhoea	Elevated serum Cr	Maintenance immunosuppressants	IVIg	Other treatments	Non-invasive ventilation	Outcome
Zhang et al. [39]											
14	38	Male	Yes	Yes	No	Yes	Glucocorticoids Calcineurin Inhibitors	No	Antivirals (Oseltamivir or Arbidol)	No	Recovered
15	64	Male	Yes	Yes	No	Yes	Glucocorticoid Mycophenolate Mofetil Rapamycin	Yes	Antivirals (Oseltamivir or Arbidol) Cefixime	No	In-hospital
16	37	Female	Yes	Yes	No	Yes	Glucocorticoids Calcineurin Inhibitors	Yes	Antivirals (Oseltamivir or Arbidol) Cefixime	No	In-hospital
17	47	Male	Yes	Yes	No	Yes	Glucocorticoids Calcineurin Inhibitors	No	Antivirals (Oseltamivir or Arbidol)	No	In-hospital
18	38	Male	Yes	Yes	No	Yes	Glucocorticoids Calcineurin Inhibitors	No	Antivirals (Oseltamivir or Arbidol)	No	Recovered
Wang et al. [40]											
19	49	Male	Yes	Yes	NR	Yes	Cyclosporine A Mycophenolate Mofetil Prednisone	NR	Lopinavir/Ritonavir Ribavirin Interferon α -2b Methylprednisolone	No	Recovered

Cr creatinine, IVIG intra-venous immunoglobulin, NR not reported

will be useful in prioritising stone surgeries especially if the COVID-19 situation worsens with time.

Urological cancers and COVID-19

There were no reports demonstrating a definite association between COVID-19 and urological cancers. Interestingly, Liang et al. [44] reported a cohort of 1590 COVID-19 positive patients; it was noted that 18 cases (1%) had a history of cancer, which appeared to be of a higher incidence than the overall Chinese population (0.29%). Furthermore, cancer patients were found to have a higher risk of requiring invasive ventilation or death (39% in cancer patients vs 8% in non-cancer patients, $p=0.0003$). However, among the 18 patients, only one patient had history of urological cancer (bladder cancer). The results were at most hypothesis generating and more data would be needed on this aspect.

In the pandemic of COVID-19, there has been increasing demand for ventilator-level care and we might need to consider triaging urological surgeries. Stensland et al. made recommendations on the priority of surgeries based on its potential impact on patient survival, and suggested alternatives that may spare the use of ventilators [45]. Such recommendations will be extremely helpful when prioritisation of surgeries is deemed necessary.

Discussion

The increasing number of COVID-19 cases has raised significant fear among healthcare professionals and the general population globally. While COVID-19 primarily affects the respiratory system, it is possible for the disease to have non-respiratory manifestations. It is extremely important for urologists to learn about the potential implications of COVID-19 on their clinical practices.

Our study showed that COVID-19 was unlikely to cause any urinary symptoms, so the presence of urinary symptoms alone should not raise any significant concerns of COVID-19. On the other hand, if the patient has additional symptoms such as fever on top of urinary symptoms, we cannot assume that the fever is attributed to an underlying urological cause and we must maintain a high level of suspicion for possible COVID-19 [29].

There have been suggestions on the use of procalcitonin to differentiate between COVID-19 and urological conditions presenting with fever. Procalcitonin levels are likely to rise in bacterial, parasitic and fungal infections but not viral infections [7, 29, 38]. Procalcitonin may serve as a marker to preliminarily differentiate between COVID-19 and urological infections [46]. On the other hand, rapid tests for detecting SARS-CoV-2 will be of utmost importance in case of any suspicion of COVID-19.

Our study showed that the prevalence of AKI in COVID-19 patients was 7.58%. AKI is a possible manifestation of COVID-19, and its occurrence usually indicates a severe disease with high mortality rate. The association of COVID-19 and AKI was believed to be related to ACE receptors [11, 30, 47]. As ACE receptors were also found in testis and bladder, it was postulated that COVID-19 might have manifestations in these organs [31, 33]. However, this is largely theoretical without any actual cases being reported. Further studies will be needed to determine whether such postulation is a genuine concern. Although concerns of acute kidney injury as an indirect effect of sepsis and multiorgan failure has been reported, Diao et al. has reported direct cytotoxicity of SARS-CoV-2 against kidney tubules as a result of a direct infection, initiation of CD68⁺ macrophage and complement C5b-9 deposition [48].

Our study showed that 5.74% of the COVID-19 patients had positive viral RNA in urine samples. However, none of the patients had urinary symptoms, so it would be difficult for us to determine the necessity of viral RNA testing without the presence of other symptoms (such as fever, respiratory and gastrointestinal symptoms). Currently, there is also insufficient data regarding the duration of viral shedding in urine. Further studies to investigate the duration of viral shedding in urine are needed to inform future clinical practice.

Our results also showed that viral shedding in stool could be persistent up to 6 weeks after symptom onset. We should incorporate this information when we manage suspected, active and recovering COVID-19 patients, and decide when it is safe to perform transrectal procedures when it is clinically indicated. When the transrectal procedure is considered mandatory in an urgent manner, the use of protective personal equipment must be ensured to protect healthcare workers from being infected.

To our knowledge, this is the first systematic review investigating COVID-19 with relevance to urology. In this study, the implications of COVID-19 on an urologist's daily practice has been comprehensively covered. However, there are several limitations in our study. First, COVID-19 has only started five months ago, and there is a lack of high-quality evidence in this area. Second, urological symptoms might be under-reported and urine viral RNA might be under-tested. Third, most of the studies included in this systematic review were based in China. The implications of COVID-19 may be different in other areas like Europe and America, where the pandemic is most severe now. Nevertheless, we believe that COVID-19 is a rapidly evolving crisis that warrants a timely systematic review and we hope the information will be useful for urologists in their clinical practices.

Conclusions

Our systematic review showed that urinary symptom is not a clinical manifestation of COVID-19. Acute kidney injury could occur in COVID-19 patients, and its occurrence was associated with high mortality rate. As viral RNA positivity was detected in both urine and stool samples, precautions are needed when urologists perform transurethral or transrectal procedures. Special considerations in managing specific urological conditions are also needed in the pandemic of COVID-19.

Author contributions VWSC: project development, data collection, data analysis, manuscript writing. PKFC: data analysis, manuscript writing. CHY: data analysis, manuscript writing. CYY: data collection, data analysis. CFN: data analysis, manuscript writing. JYTT: project development, data collection, data analysis, manuscript writing/editing.

Funding No funding or other financial support was received.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals/ ethics approval Not applicable.

Informed consent to participate Not applicable.

Informed consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

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