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RESEARCH ARTICLE

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SARS-CoV-2 infection affects the lower urinary tract and male genital system: A systematic review

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Abstract

PubMed, Scopus, and ISI Web of Knowledge databases were searched to identify studies published up to December 2020 on the involvement of urinary and male genital systems in COVID-19. Sixteen studies involving a total of 575 patients (538 males and 37 females) were included in this systematic review. The COVID-19 phase was available for 479 patients: 426 in the acute and 53 in the recovery phase. De novo lower urinary tract symptoms (LUTS) were observed in 43 patients and deterioration of pre-existing LUTS in 7. Bladder hemorrhage was observed in three patients and acute urinary retention in one. Regarding the male genital system, scrotal discomfort was observed in 8 patients, swelling in 14, pain in 16, and erythema in 1; low flow priapism was observed in 2 patients. Ultrasound examination identified acute orchitis in 10 patients, acute epididymitis in 7, and acute epididymo-orchitis in 16. A case–control study reported that patients with moderate COVID-19 show a significant reduction in sperm concertation, the total number of sperms per ejaculate, progressive motility, and complete motility. In contrast to what is known from the first studies on the subject, this review also includes subsequent studies that give evidence of the involvement of the lower urinary tract and male genital system in COVID-19.

KEYWORDS
coronavirus, disease control, COVID-19, infection, genital tract, SARS-CoV-2, urinary tract

1 | INTRODUCTION

The COVID-19 pandemic is one of the greatest recorded catastrophes in history, and has affected millions of human victims, severely limited the freedom of billions of people for long periods, and led to economic collapse in many countries; and everything is still going on.[1–4] However, doctors, researchers, politicians, and women and men of goodwill, each according to their abilities, have been able to give a concrete answer to this global disaster. In fact, about a year after its onset, basic research and clinical trials have greatly

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expanded knowledge on SARS-CoV-2 infection and the associated disease called COVID-19, patients are treated more effectively and most patients recover, the spread of the infection has been contained in many countries, and some vaccines against this virus have become available.

SARS-CoV-2 belongs to the β-coronavirus cluster.[1,5] Entry of SARS-CoV-2 into host cells depends on cellular expression of both angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2).[1,6–10] Zou et al. analyzed the RNA sequencing datasets of cells of major human physiological systems to evaluate the expression of the ACE2 receptor and constructed a risk map of the different vulnerability of various organs to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[11] This physiological variability is a biological background that may explain the different involvement of individual organs or tissues in the clinical presentation of COVID-19. Evidence has recently emerged that the lower urinary tract is a potential target for SARS-CoV-2 infection, due to a significant ACE2 expression in urothelial cells.[11] ACE2 has also been found in the human testis where it regulates the physiology of Leydig cells, Sertoli cell, and spermatogonia.[12] In addition, Song et al.[13] analyzed epithelial cells of the normal human prostate and found that ACE2 and TMPRSS2 are expressed in 0.32% and 18.65% of epithelial cells, respectively. Therefore, the urinary and male genital system is now regarded as at risk for SARS-CoV-2 infection and potentially responsible for some nonrespiratory symptoms of COVID-19.[7] The signs and symptoms relative to the involvement of the urinary and male genital systems are sometimes vague, and in any case, little known, therefore clinicians should pay particular attention to detecting them in their patients.[14,15]

The purpose of this systematic review is to highlight currently available literature data on the involvement of the urinary and male genital systems in SARS-CoV-2 infection, to offer young specialists in urology and infectious diseases an overview on this topic to better carry out their activity in this new clinical reality and, hopefully, develop the desire to perform in-depth studies and research on the subject.

2 | METHODS

This analysis was conducted and reported according to the general guidelines recommended by the Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[16]

2.1 | Literature search

A comprehensive literature search was performed using a combination of keywords (MeSH terms and free text words) including "COVID-19"/"SARS-CoV-2," "Urology"/"Urogenital System," "signs," "symptoms," "laboratory," and "radiology." Three databases (PubMed, Scopus, and ISI Web of Knowledge) were searched for articles published in English up to December 2020. Additional articles were sought from the reference lists of the included studies.

2.2 | Selection criteria

All articles identified from the literature search were screened by two independent reviewers (M. C. and N. L.) with any discrepancies resolved by a third author (C. S.). To assess the eligibility for the systematic review, PICOS (participants, intervention, comparisons, outcomes, study type) criteria were used. PICOS criteria were set as follows: (P)articipants—the subjects infected with SARS-CoV-2; (I)ntervention—the evaluation of signs, symptoms, laboratory or radiological findings relative to the urinary and/or male genital tract; (O)utcome—the evidence of signs and/or symptoms and/or laboratory findings and/or radiological evaluations indicative of male genital and/or urinary tract involvement; (S)tudy types—prospective and retrospective studies, review articles, meta-analysis, case series, case reports, letters to editors; studies related to nephrology, obstetrics, and gynecology were not included.

2.3 | Data collection

The following data were extracted from eligible studies: authors, year of publication, study period, study design, sample size, site of the study, patients' age and gender, disease state (acute vs. recovery), results of rhino-pharyngeal swab, SARS-CoV-2 antibody status, COVID-19 severity, signs and/or symptoms regarding the lower urinary tract or the male genital tract, symptom scores, findings from radiological and/or laboratory investigations regarding the lower urinary tract or the male genital tract, strategies adopted to manage these conditions.

3 | RESULTS

The search strategy revealed a total of 339 results. Screening of the titles and abstracts revealed 25 papers eligible for inclusion. Further assessment of eligibility, based on full-text papers, led to the exclusion of nine papers. Finally, 16 studies involving a total of 575 patients infected with SARS-CoV-2 who had been evaluated for urinary and/or male genital involvement between January and June 2020 were included in the final analysis[17–31] (Figure 1). The characteristics of selected studies are summarized in Table 1.

3.1 | Patients' demographics and COVD-19 characteristics

Patients' demographics are reported in Table 1. Overall, 199 patients were from China, 78 from Europe, 45 from the United States, and 253 from Jordan. The COVID-19 phase was available for 479 patients: 426 in the acute and 53 in the recovery phase. COVID-19 severity was available for 439 patients, but it was classified differently by the authors. The patients classified as asymptomatic or with mild, moderate, severe, and critical disease were 53, 166, 9,

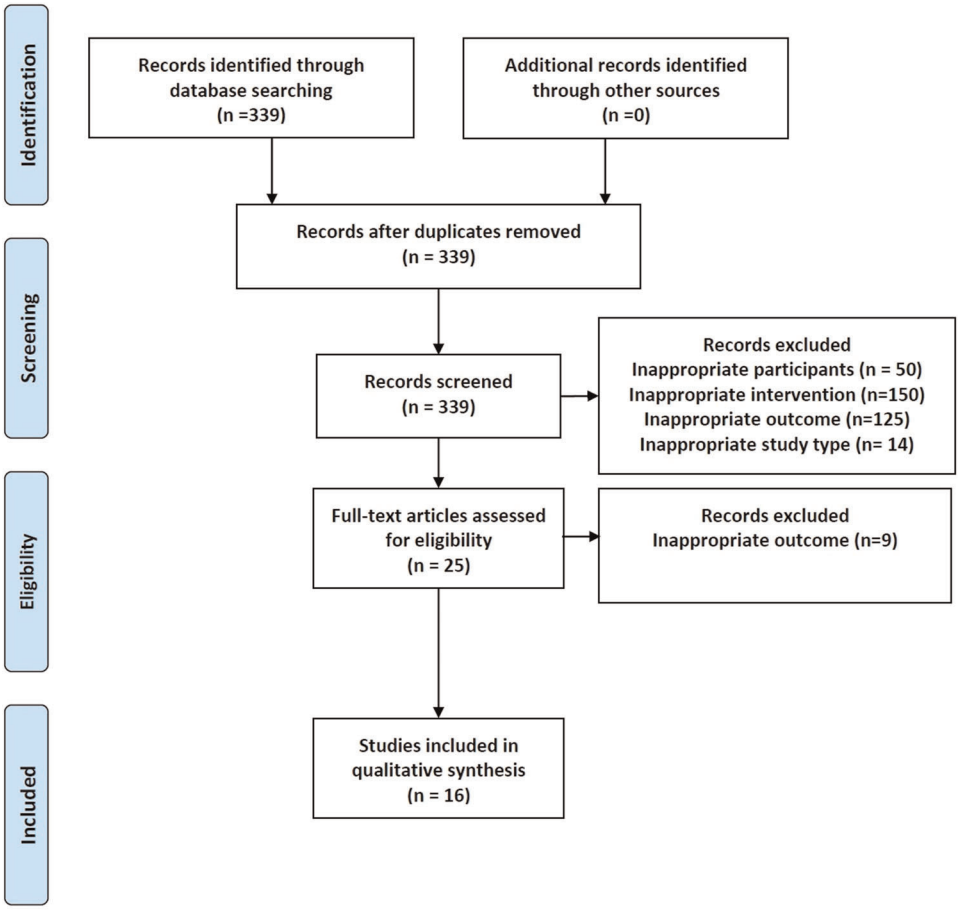

FIGURE 1 Flow diagram of the systematic review

37, and 14, respectively; Chen et al., however, merged patients with mild/moderate disease (83 cases) and those with severe and critical disease (59 cases).[20]

3.2 | Urinary tract involvement in COVID-19 patients

Urinary tract involvement was reported in five studies (Table 2).[26–29] In detail, *de novo* lower urinary tract symptoms (LUTS) and deterioration of pre-existing LUTS occurred in 43 and 7 patients, respectively. Validated questionnaires to score LUTS were adopted in two studies.[28,29] Dhar et al.[28] scored symptoms according to the Overactive Bladder Symptom Score and found a median overactive bladder symptom score of 18 in both men and women. Kaya et al.[29] adopted the International Prostate Symptom Score (IPSS) and the Urinary Symptom Profile (USP) for men and women, respectively and found, both in men and women, a statistically significant worsening in terms of both mean IPSS and mean UPS stress urinary incontinence/overactive bladder subscores.

Other signs of lower urinary tract involvement were bladder hemorrhage in three patients and acute urinary retention in one.[27] Microhematuria and leukocyturia were reported in three and two patients, respectively. Urine culture was negative in all 45 patients investigated. Radiologic data were not available in these five studies.

3.3 | Male genital tract involvement in COVID-19 patients

Male genital tract involvement was investigated in 11 studies[17–25,30,31] (Table 3). Scrotal discomfort was described in 8 patients, swelling in 14, pain in 16, and erythema in 1. Low flow priapism was reported in 2 patients.[23,30] Scrotal ultrasound was performed in 4 studies[20–22,24]: acute orchitis was found in 10 patients, acute epididymitis in 7, and acute epididymo-orchitis in 16[20, 22, 24]; one case of bilateral nonspecific intratesticular increased blood flow was also described.[21]

Alkhatatbeh et al.[22] observed 253 COVID-19 male patients and failed to observe symptoms or signs of orchitis across all age groups and different disease status. Two studies investigated spermatogenesis in patients with COVID-19 infection.[17, 19] Holtmann et al. investigated semen parameters in patients with mild or moderate COVID-19 infection after a mean period of 43.5 and 47.0 days from diagnosis, respectively. As compared with healthy controls and with patients with mild disease, those with a moderate COVID-19 infection showed a statistically significant reduction in sperm

TABLE 1 Study characteristics, demographic, and clinical characteristics of patients included

Studies [ref.]	Study design	Time frame	City and country	No. of COVID-19 patients	Age (years), mean (*SD*)	Sex (M:F)	Disease phase, *n*	Positive rinopharyngel swab, *n*	Positive antibody status, *n*	COVID-19 severity, *n*
Holtmann et al. [17]	CC	April–May 2020	Duesseldorf, Germany	14	42.7 (10.4)	14:0	Recovery (18)	17	IgA: 17	Mild (14)
Holtmann et al.[17]				4	40.8 (8.7)	4:0			IgG: 16	Moderate (4)
Pan et al.[18]	CS	January –March 2020	Wuhan, China	34	37 (31–49)[a]	34:0	Recovery (34)	34	n/a	n/a
Guo et al.[19]	CS	February –April 2020	Shandong, China	23	41.04 (11.56)	23:0	Acute (23)	23	IgM: 9 IgG: 22	Mild (18) Moderate (5)
Chen et al.[20]	R	February –March 2020	Wuhan, China	83	54.2 (38.0–69.0)[a]	83:0	Acute (83)	83	n/a	Mild and moderate (83)
Chen et al.[20]				59	64.0 (47.0–78.0)[a]	59:0	Acute (59)	59		Severe and critical (59)
Bridwell et al.[21]	CR	n/a	USA	1	37 (–)	1:0	Acute (1)	1	n/a	n/a
Gagliardi et al. [22]	CR	n/a	Versilia, Italy	1	14 (–)	1:0	Acute (1)	1	n/a	n/a
Lamamri et al.[23]	CR	n/a	Le Chesnay, France	1	62 (–)	1:0	Acute (1)	1	n/a	Critical (1)
La Marca et al.[24]	CR	April 2020	Modena, Italy	1	43 (–)	1:0	Acute (1)	1	n/a	Critical (1)
Kim et al.[25]	CR	n/a	USA	1	42 (–)	1:0	Acute (1)	n/a	n/a	n/a
Lamb et al.[26]	CC	n/a	MI, USA	4	68.2 (–)	1:3	n/a	4	n/a	n/a
Mumm et al.[15]	CS	March–April 2020	Munich, Germany	7	62 (59–78)[a]	7:0	Acute (1)	7	n/a	n/a
Luciani et al.[27]	CS	February –March 2020	Trento, Italy	3	74 (9.1)	3:0	Acute (1)	3	n/a	n/a
Dhar et al.[28]	CS	May–June 2020	MI, USA	39	63.5 (n/a)	32:7	Recovery (1)	39	n/a	n/a
Kaya et al.[29]	CS	May–June 2020	Turkey	19	38.9 (13)	19:0	n/a	n/a	n/a	n/a
Kaya et al.[23]				27	32.3 (8.9)	0:27				
Lam et al.[30]	CR	March 2020	Pembrokeshire, UK	1	67 (–)	1:0	Acute (1)	n/a	n/a	Severe (1)
Alkhatatbeh et al.[31]	R	March– May 2020	Amman, Jordan	253	43 (n/a)	253:0	Acute (253)	253	n/a	Asymptomatic (53) Mild (152) Severe (36) Critical (12)

Abbreviations: CC, case control; CR, case report; CS, case series; n/a, not available; R, retrospective; *SD*, standard deviation.

[a]Median (range).

TABLE 2 Studies describing urinary tract involvement

Studies [Ref.]	Pre-existing urological conditionstype(no./total[a])	Time from exposure/ diagnosis to onset of symptoms (days)mean (range)	Signs/symptomstype (no./total[a])	Symptom score	Laboratory findings		Management
					Urinalysispathologic findingtype no./total[b]	Urine culturefindingstype no./total[b]	
Lamb et al. [26]	n/a	n/a	De novo urgency (4/4) De novo urge incontinence (4/4) De novo frequency (4/4) De novo nocturia (4/4)	n/a	n/a	n/a	n/a
Mumm et al.[15]	BPH (1/7)	n/a	Increased urinary frequency (7/7)	n/a	Microhematuria (3/7) *Leukocyturia (2/4)*	Negative (6/6)	n/a
Luciani et al.[27]	Radiation cystitis (1/3) BPH (2/3)	6.3 (5-8)	Hematuria (3/3) Urinary retention (1/3)	n/a	n/a	n/a	Endoscopy (1/3) Embolization (1/3) Conservative (1/3)
Dhar et al.[28]	n/a	n/a	De novo urgency (39/39) De novo urge incontinence (39/39) De novo frequency (39/39) De novo nicturia (39/39)	Men: 18 (12–20)[c,d] Women: 18 (15–21)[c,d]	n/a	Negative (39/39)	n/a
Kaya et al.[29]	n/a	n/a	**n/a**	**IPSS total** Pre-COVID-19: 6.1 (7.3)[e] During hospitalization: 6.2 (7.5)[e] Post hospitalization: 5.7 (7.2)[e] (p: .148) **IPSS storage** Pre-COVID-19: 3.2 (4.1)[e] During hospitalization: 3.2 (4.3)[e] Post hospitalization: 2.8 (4)[e] (p: .054) **IPSS voiding** Pre-COVID-19: 2.9 (3.5)[e]	n/a	n/a	n/a

(Continues)

TABLE 2 (Continued)

Studies [Ref.]	Pre-existing urological conditionstype(no./total[a])	Time from exposure/ diagnosis to onset of symptoms (days)mean (range)	Signs/symptomstype (no./total[a])	Symptom score	Laboratory findings		Management
					Urinalysispathologic findingtype no./total[b]	Urine culturefindingstype no./total[b]	
				During hospitalization: 3.1 (3.5)[e] Post hospitalization: 2.9 (3.4)[e] (*p* : .933)			
Kaya et al.[29]	n/a	n/a	**n/a**	**USP Scale (stress urinary incontinence)** Pre-COVID-19: 0.5 (1.9)[e] During hospitalization: 0.7 (1.9)[e] Post hospitalization: 0.5 (1.9)[e] (*p* : .05) **USP Scale (overactive bladder)** Pre-COVID-19: 2.2 (2.9)[e] During hospitalization: 2.3 (3)[e] Post hospitalization: 1.9 (2.6)[e] (*p* : .051) **USP Scale (slow current)** Pre-COVID-19: 0.1 (0.4)[e] During hospitalization: 0 (0)[e] Post hospitalization: 0 (0)[e] (*p* : .368)	n/a	n/a	n/a

Abbreviations: BPH, benign prostate hyperplasia; IPSS, International Prostate Symptom Score; USP, urinary symptom profile.

[a]Total patients with signs and/or symptoms and/or laboratory findings of urinary tract involvement.

[b]Total patients for whom the laboratory evaluation was available.

[c]Overactive Bladder symptom score.

[d]Median (range).

[e]Mean (standard deviation).

TABLE 3 Studies describing male genital tract involvement

Study [Ref.]	Prior andrological conditions, (n)	Signs or symptoms, (n)	Ultrasound data, (n)	Laboratory data	Management
Holtmann et al.[17]	0	-	-	Sperm concentration, mean (*SD*): 95.9 (50.5) 10^6/ml* Total no. progressive motility (*SD*) ($\times10^6$): 125.3 (96.4)* Total no. complete motility (*SD*) ($\times10^6$): 157.1 (120.8)* Total no. immotile (SD) ($\times10^6$): 86.6 (66.5)*	n/a
Holtmann et al.[17]	0	Scrotal discomfort (1)	-	Sperm concentration, mean (*SD*): 16.2 (22.4) 10^6/ml** Progressive motility ($\times10^6$): 2.4 (2.7)** Total no. complete motility (*SD*) ($\times10^6$): 4.7 (5.5)** Total no. immotile (*SD*) ($\times10^6$):7.2 (9.4)**	n/a
Pan et al.[18]	0	Scrotal discomfort (6)	-	n/a	n/a
Guo et al.[19]	n/a	n/a	n/a	Semen volume (ml): 2.3 (1.35–3.0) Sperm concentration: 95 (56–155.5) 10^6/ml Motility (PR, %): 50 (37.5) Motility (PR + NP, %): 65(57.5–76) Normal forms (%):16 (12–22)	n/a
Chen et al.[20]	n/a	Scrotal swelling/pain (3)	Acute orchitis (3) Acute epididymitis (3) Epididymo-orchitis (5)	n/a	n/a
Chen et al.[20]	n/a	Scrotal swelling/pain (10)	Acute orchitis (7) Acute epididymitis (4) Epididymo-orchitis (10)	n/a	n/a
Bridwell et al.[14]	n/a	Scrotal erythema (1) Scrotal discomfort (1)	Bilateral nonspecific increased blood flow (1)	Urinalysis: unremarkable	Acetaminophen + cefepime + azithromycin
Gagliardi et al.[15]	n/a	Scrotal pain and swelling (1)	Epididymo-orchitis (1)	Urinalysis: unremarkable Urine culture: sterile	Broad-spectrum antibiotics
Lamamri et al.[16]	n/a	Low flow priapism (1)	n/a	n/a	Cavernosal blood aspiration + intracavernosal injection of ethylephrine + thromboprophylaxis
Lam et al.[31]	Paraphimosis (1)	Low flow priapism (1)	n/a	n/a	Conservative management
La Marca et al.[24]	n/a	Scrotal pain (1)	Epididymo-orchitis (1)	n/a	Amoxicillin/clavulanic acid + azithromycin
Kim et al.[25]	n/a	Scrotal pain (1)	n/a	n/a	Cefpodoxime + azithromycin
Alkhatatbeh et al.[32]	0	0	0	n/a	n/a

*P < .05: mild vs. moderate.

**P < .05: moderate vs. control.

concertation, the total number of sperms per ejaculate, progressive motility, and complete motility, whereas no statistically significant difference was found between controls and patients with mild disease.[17] Accordingly, Guo et al.[19] found total sperm count, total motile sperm count, and sperm morphology within normal ranges in a population mainly composed of patients with mild COVID-19, tested after a median interval of 32 days from diagnosis.

4 | DISCUSSION

The different expression in ACE2 and TMPRSS2 in human tissues is one of the main reasons for their different involvement in COVID-19. Although not considered among the systems most frequently and/or intensely affected by SARS-CoV-2 infection, the lower urinary tract and the male genital systems have nevertheless been identified by recent studies as part of COVID-19 pathology. It follows that urologists and infectious disease specialists should become aware of the recent evidence on this topic, to fully experience their clinical and research activity in this sector as well. Chan et al.[32] have systematically reviewed the data available in literature until April 2020 and, not having found the presence of patients with urogenital symptoms among those included in their analysis, concluded that involvement of the urogenital system in COVID-19 was unlikely. Subsequently, the persistence of the SARS-CoV-2 pandemic has stimulated further research on the topic, and this has led us to carry out an updated systematic review ensuring a timely systematic review of the available evidence. The results of this systematic review demonstrate that the male genital system and the lower urinary tract are both involved in COVID-19.

De novo LUTS or worsening of pre-existing LUTS represent the most common involvement of the lower urinary tract in COVID-19, with storage symptoms being the most remarkable complaints. Although considered multifactorial by some authors,[33-35] the pathogenesis of LUTS has not yet been elucidated.[34,35] Theoretically, the bladder could become infected with SARS-CoV-2 by the hematogenous route or by the propagation from urethral cells, where the presence of ACE2 receptors has been demonstrated.[15] However, if it is not fully understood which cells, luminal or basal urothelial, effectively express ACE2 receptor,[15] SARS-CoV-2 has been infrequently detected in the urine of infected individuals. A systematic review of the literature considering urine samples from 533 patients from 14 studies found evidence of SARS-CoV-2 in only 24 patients (4.5%).[35] The infrequent presence of SARS-CoV-2 in urine samples from infected subjects has been interpreted as a sign in favor of the spread of the virus from the urethral endothelium to the bladder.[15] Some authors have recently hypothesized that, in patients with COVID-19 and *de novo* severe urinary symptoms, an increase in inflammatory cytokines released into the urine and/or active in the bladder may be responsible for COVID-19 Associated Cystitis (CAC) and of the associated bladder dysfunctions.[26]

Recent literature data have reported that patients with CAC, both men and women, frequently refer to *de novo* lower urinary tract symptoms such as an increase in urinary frequency and nocturia, stressing the need that *de novo* urinary symptoms should be considered among the complex symptomatology of COVID-19. Therefore, physicians caring for COVID-19 patients, in ambulatory care, clinical wards, or emergency rooms, should be aware of CAC.

Noteworthily, it has been also underlined that an increase in urinary frequency, in addition to fever, should be considered an important symptom of overlap with urosepsis in the context of the differential diagnosis of COVID-19.[15]

Scrotal discomfort or pain with radiological evidence of inflammatory changes of the testis and/or epididymis is the most frequently described male genital complaints in patients with SARS-CoV-2 infection. The pathogenesis of orchitis relies on the hematogenous spreading of SARS-CoV2 to testis tissue, where ACE2 is expressed in the Leydig cells, Sertoli cells, and spermatogonia.[20] Postmortem studies of patients who had died of severe acute respiratory syndrome (SARS) showed the presence of orchitis with histological evidence of immune-mediated inflammatory damage.[36] Alkhatatbeh et al.,[31] however, failed to observe any symptoms or signs of orchitis in their series, but the relatively small sample size might have failed to capture a rare complication; in addition, most patients in this study were asymptomatic or had mild-to-moderate symptoms and the authors hypothesized that viral threshold required to cross the blood–testis barrier could be not achieved.[31] The involvement of the male genital system in patients with SARS-CoV-2 infection may theoretically impair fertility. Available evidence demonstrates that although a mild COVID-19 infection is not likely to affect spermatogenesis, semen can be impaired after a moderate infection.[17] However, data about semen analysis performed before the outbreak of the pandemic were not available for patients involved in these studies thus limiting the diagnosis of pre-existing male infertility.[17] Moreover, the long-term effects of SARS-CoV-2 on male reproductive function are lacking.[17]

Low flow priapism was observed in two patients with severe COVID-19.[23,30] Once recognized by health-care professionals, low flow priapism should be treated promptly to prevent immediate and chronic functional complications.[23,30] The pathogenesis of priapism in patients with COVID-19 has been attributed to thrombotic complications. The reporting of further cases would be of interest to strengthen this evidence.[23,30]

We recognize the limitations of the data published so far on the involvement of the urogenital system by SARS-CoV-2, coming from a few studies, often carried out with low methodological quality, and including few patients, often heterogeneous and with short follow-up. Furthermore, demographics, epidemiological data, and symptoms were recorded in precoded questionnaires only in a few studies. As a result, available data on the involvement of urologic and male genital systems in COVID-19 are sparse and patchy. However, unlike what emerged during the first wave of the pandemic, we now know that this involvement occurs in 3%–5% of cases with SARS-CoV-2 infection and that in some cases the clinical manifestations are relevant.

5 | CONCLUSIONS

The data highlighted in this systematic review demonstrate that patients with COVID-19 may have signs, symptoms, and radiological and laboratory features indicative of involvement of the lower urinary tract and of the male genital system. *De novo* or worsening LUTS, and testis and/or epididymal discomfort or pain are the most common clinical findings. Moreover, spermatogenesis can be impaired in patients with moderate infection. Current knowledge is therefore sufficient to alert all health-care professionals involved in the management of patients with SARS-CoV-19 infection to focus their attention also on the lower urinary tract and male genital system.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceptualization: Massimiliano Creta, Caterina Sagnelli, Giuseppe Celentano, and Luigi Napolitano. *Methodology*: Massimiliano Creta, Caterina Sagnelli, Giuseppe Celentano, and Luigi Napolitano. *Validation*: Massimiliano Creta, Caterina Sagnelli, Giuseppe Celentano, Luigi Napolitano, Roberto La Rocca, Marco Capece, Gianluigi Califano, Armando Calogero, Antonello Sica, Francesco Mangiapia, Massimo Ciccozzi, Ferdinando Fusco, Vincenzo Mirone, Evangelista Sagnelli, and Nicola Longo. *Data curation*: Massimiliano Creta, Caterina SagGiuseppe Celentanonelli, Giuseppe Celentano, Luigi Napolitano, Roberto La Rocca, Marco Capece, Gianluigi Califano, Armando Calogero, Antonello Sica, Francesco Mangiapia, Massimo Ciccozzi, Ferdinando Fusco, Vincenzo Mirone, Evangelista Sagnelli, and Nicola Longo. *Writing—original draft preparation*: Massimiliano Creta, Caterina Sagnelli, Giuseppe Celentano, and Luigi Napolitano. *Writing—review and editing*: Massimiliano Creta, Caterina Sagnelli, Giuseppe Celentano, and Luigi Napolitano, and Evangelista Sagnelli. *Supervision*: Massimiliano Creta, Caterina Sagnelli, Giuseppe Celentano, and Luigi Napolitano. All authors have read and agreed to the published version of the manuscript.

PEER REVIEW

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