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TOPIC PAPER

Scoping review: hotspots for COVID-19 urological research: what is being published and from where?

Liang G. Qu[1,2,3] · Marlon Perera[1,2] · Nathan Lawrentschuk[2,4,5] · Rainy Umbas[6] · Laurence Klotz[7]

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Abstract

Purpose Contemporary, original research should be utilised to inform guidelines in urology relating to the COVID-19 pandemic. This comprehensive review aimed to: identify all up-to-date original publications relating to urology and COVID-19, characterise where publications were from, and outline what topics were investigated.

Methods This review utilised a search strategy that assessed five electronic databases, additional grey literature, and global trial registries. All current published, in-press, and pre-print manuscripts were included. Eligible studies were required to be original research articles of any study design, reporting on COVID-19 or urology, in any of study population, intervention, comparison, or outcomes. Included studies were reported in a narrative synthesis format. Data were summarised according to primary reported outcome topic. A world heatmap was generated to represent where included studies originated from.

Results Of the 6617 search results, 48 studies met final inclusion criteria, including 8 pre-prints and 7 ongoing studies from online registries. These studies originated from ten countries according to first author affiliation. Most studies originated from China ($n=13$), followed by Italy ($n=12$) and USA ($n=11$). Topics of the study included pathophysiological, administrative, and clinical fields: translational ($n=14$), COVID-19-related outcomes ($n=5$), urology training ($n=4$), telemedicine ($n=7$), equipment and safety ($n=2$), urology in general ($n=4$), uro-oncology ($n=3$), urolithiasis ($n=1$), and kidney transplantation ($n=8$).

Conclusion This review has outlined available original research relevant to COVID-19 and urology from the international community. This summary may serve as a guide for future research priorities in this area.

Keywords COVID-19 · Urology · Uro-oncology · Training · Telemedicine · Kidney transplantation

Abbreviations

ACE2	Angiotensin-converting enzyme II
ADT	Androgen-deprivation therapy
AKI	Acute kidney injury
CI	Confidence interval
COVID-19	Coronavirus 19
EAU	European Association of Urology
ICU	Intensive care unit
OR	Odds ratio
PPE	Personal protective equipment
pRCC	Papillary renal cell carcinoma
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus
TURBT	Transurethral resection of bladder tumour
USA	United States of America

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✉ Liang G. Qu
liang.qu@austin.org.au

[1] Olivia Newton John Cancer Research Institute, Austin Health, Melbourne, VIC, Australia

[2] Department of Surgery, University of Melbourne, Melbourne, VIC, Australia

[3] Department of Urology, Austin Health, Heidelberg, VIC, Australia

[4] Department of Urology, The Royal Melbourne Hospital, Melbourne, VIC, Australia

[5] EJ Whitten Prostate Cancer Research Centre at Epworth, Melbourne, VIC, Australia

[6] Department of Urology, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia

[7] Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously 2019-nCoV), has had a worldwide impact. Health-care services in many nations have had to alter their operations due to the COVID-19 surge [1]. Previously ongoing research trials have been suspended due to the sudden shift in resources towards managing this pandemic [2]. In addition, surgical departments have had to prioritise and cancel surgeries, balance the safety of patients and staff, and assume the risk of operating where surgery is essential to life or limb [3, 4].

There is ongoing research in many medical specialties in areas that relate to COVID-19, and urological research is one of these. Studies have examined not only how COVID-19 may affect bodily systems in relation to pathophysiology, but also how it may impact routine care in a speciality, from an administrative and clinical practice perspective [5]. Original studies are required to inform guidelines, provide country-specific recommendations, and advise how health-care services may operate effectively.

Current guidelines amidst this COVID-19 pandemic frequently base recommendations on prior research [6–8]. Most of these publications consist of expert opinions, perspectives, or commentaries, with limited up-to-date research to guide these recommendations [9, 10]. Individual country-level recommendations seem warranted, given the vastly different impacts of COVID-19 on nations, and the circumstances that surround them.

Thus far, it is not known where urology-related COVID-19 research is published. This comprehensive review aimed to: identify all up-to-date original publications worldwide, reveal the origin of these publications, and summarise the studied topics in this field.

Materials and methods

This review has been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews-recommended checklist, with protocol available (Supplementary File 1) [11].

This review aimed to capture all original urological research related to COVID-19. Any manuscript was required to investigate COVID-19 and urology in: the study population, intervention, comparison, or outcome. Only original research observational or experimental studies were included. Included articles could be published, in-press, or pre-print awaiting peer-review. Case reports, editorials, reviews and guidelines were excluded. Commentaries and letters were included if they reported original data. Our review was not restricted by language. Articles were restricted to 01/01/2019 onwards.

Our comprehensive search strategy was performed on 17 May 2020. Our initial search was a combined search on MEDLINE and Embase. The key search terms consisted of: 'COVID-19', 'urology', 'kidney', 'ureter', 'bladder', 'laparoscopy' and 'robotic'. Our primary search was adapted to: CINAHL, Global Index Medicus, and The Cochrane Library. Grey literature was searched using Google Scholar. The top 30 urology journals by impact factor were also searched. A reference search was conducted from included manuscripts. A search of trial registries identified currently ongoing studies [12]. Registries included: Australian New Zealand Clinical Trials Registry, International Standard Randomised Controlled Trial Number registry, International Clinical Trials Registry Platform, and ClinicalTrials.gov.

After extraction and removal of duplicates, two authors (LQ and MP) contributed to the screening of initial titles and abstracts, and subsequent full texts for eligibility and final inclusion. Any disagreements were resolved through discussion.

Data recorded included metadata and study content. Data synthesis was presented in a narrative format. Available evidence was summarised and presented according to broad topic categories. A world heatmap was generated, using ArcGIS Desktop release 10.6 (Environmental Systems Research Institute, Redlands, CA, USA), demonstrating location of COVID-19-related urological publications by affiliated countries. This was overlaid with up-to-date COVID-19 case data at the time of our search strategy, according to the World Health Organization [13].

Risk of bias and quality assessment was performed using the Critical Appraisal Skills Programme checklist [14]. Studies were categorised as either poor, average, or good quality. All included studies were analysed due to the scoping nature of this review.

Results

The search strategy returned a total of 6617 initial search results (Fig. 1). After first-stage screening, there were 140 titles and abstracts for full text review. The primary reason for exclusion was for research that was not relevant or not original. In total, there were 48 studies included—8 manuscripts were pre-print manuscripts and 7 were ongoing studies from trial registries.

Quality assessment of included manuscripts (excluding seven registered trials) demonstrated 3/41 'good', 20/41 'average', and 18/41 'poor' studies. All studies were included in our subsequent narrative synthesis.

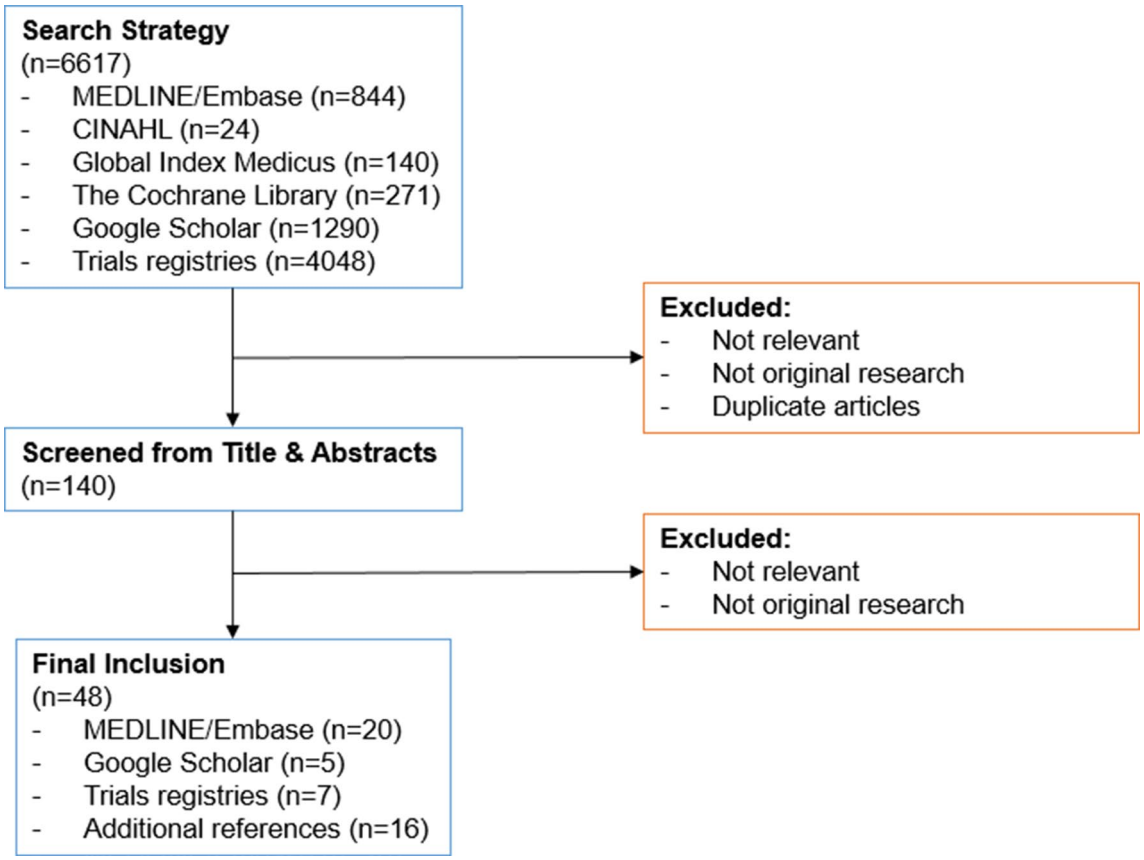

Fig. 1 Study selection flowchart. This scoping review searched several online databases, trial registries, and bibliographic references, to capture all relevant COVID-19 studies relating to urological research

Study metadata

Of the 48 included manuscripts and trials, 10 countries were represented from first author affiliations (Fig. 2a). China, Italy, and the USA were the major contributing countries. There were 15 countries represented by all co-authors (Fig. 2b). All currently registered trials were single-country trials: four from France; two from Italy, and one from Poland. The most commonly reported field of literature was translational ($n = 14$). Other commonly reported topics were kidney transplantation and telemedicine (Fig. 2a).

Translational

Current studies suggest SARS-CoV-2 may involve the urinary tract; however, the possibility of urinary transmission has not been conclusively answered. Farkash et al. investigated the link between SARS-CoV-2 and renal failure [15]. Using autopsy specimens, the authors demonstrated the presence of direct renal infiltration of SARS-CoV-2. Light microscopic examination demonstrated mild autolysis and some vacuolisation, which correlated to viral forms within tubular epithelial cells using ultrastructural analysis. Peng et al. examined the presence of viral RNA in pathological specimens using quantitative real-time polymerase chain reaction [16]. Of the nine patients with confirmed COVID-19, only one patient had detectable SARS-CoV-2 in urine, without any urinary tract symptoms. Pan et al. have reported 0/34 seminal samples from men with COVID-19 for SARS-CoV-2, with a median of 31 days from symptom onset to sample collection [17]. Song et al. reported negative semen samples in all men (0/13), but only one patient had a positive pharyngeal swab at the time of semen collection [18]. Quan et al. have reported 0/23 patients in their pre-print, but the presence of ongoing acute infection or time from symptom onset was not reported [19]. These findings suggest sexual transmission is unlikely, but further clarification is required relating to acutely infected individuals.

Several studies suggest a possible association between angiotensin-converting enzyme II (ACE2), its co-receptor *TMPRSS2*, and COVID-19. Chai et al. reported the patterns of ACE2 expression and survival for patients with COVID-19 and cancers of over 30 types [20]. Although papillary renal cell carcinomas (pRCCs) had increased ACE2 expression, this was not associated with survival outcomes [20]. Yang et al. confirmed an association of

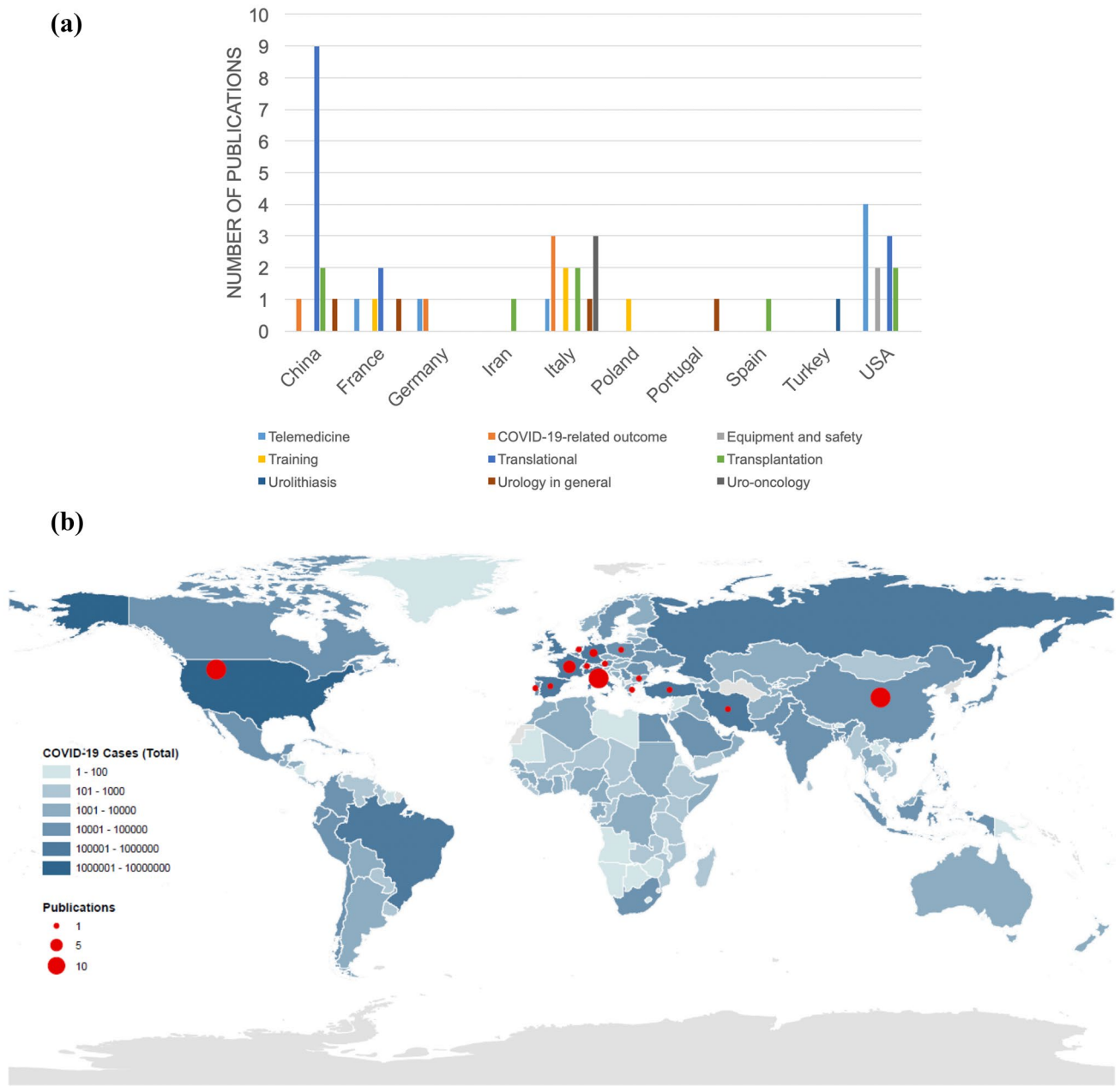

Fig. 2 COVID-19-related original research publications in urology by country and topic. **a** Of the included original research publications relating to the COVID-19 pandemic, most publication first authors were affiliated with China ($n=13$), followed by Italy ($n=12$) and the USA ($n=11$). **b** Total cumulative incidence of COVID-19 cases by country, as of 17 May 2020, has been illustrated (*shades of blue*). Affiliated countries of all co-authors of included publications were tallied and displayed for each country (*red circles*)

high ACE2 expression in pRCCs and improved overall survival (hazard ratio: 0.44) [21]. Song et al. investigated the expression of ACE2 and *TMPRSS2* in prostate epithelial cells and in lung cells. The authors reported a co-expression of 0.40–0.61% in normal prostate epithelial cells, compared to up to 16.1% in lung secretory cells, suggesting their co-expression may affect COVID-19 pathogenesis [22]. Using single-cell RNA sequencing, Wang et al. identified ACE2 expression predominantly in spermatogonia and Leydig and Sertoli cells [23]. Shen et al. report similar findings in their pre-print [24]. Another pre-print examining ACE2 expression throughout the urinary tract reported higher expression in testicular gametocytes and in renal proximal tubules [25]. Finally, Wu et al. report in their pre-print, the relationship between androgen receptor activation and ACE2 and

TMPRSS2 expression, and how this may contribute to the higher mortality from COVID-19 in males [26].

Currently, two ongoing studies from France are registered. One study is examining kidney involvement in COVID-19-infected patients (NCT04355624). Another study is investigating the predictive value of interleukin-6 and disease severity in kidney transplant patients (NCT04369456).

COVID-19-related outcomes

Two studies investigated androgens in patients with COVID-19, and associations with disease severity. In a pre-print by Ma et al., a case–control study was performed with 81 COVID-19 male patients and 100 controls [27]. Serum luteinising hormone to testosterone ratio was negatively associated with disease severity ($p = 0.0236$) on univariate regression, but was not associated on multivariate analysis. A pre-print by Schroeder et al. from Germany reported on 45 COVID-19 patients in intensive care [28]. Numerous male patients demonstrated low testosterone (68.6%) and low dihydrotestosterone (48.6%) levels, correlating to a greater mounted viral immune response, suggesting testosterone may be associated with a protective immune response.

Clinical studies have supported the concept of androgen deprivation and a protective effect against COVID-19 severity. An observational study in Italy with 9280 COVID-19 patients consisted of 786 (8.5%) men with prostate cancer. Montopoli et al. reported patients not on androgen-deprivation therapy (ADT) had significantly higher severity of COVID-19 compared to prostate cancer patients receiving ADT (odds ratio [OR]: 4.05; 95% CI 1.55–10.59) [29]. A pre-print by Duga et al. reported on 5α-reductase inhibitors and ADT in a longitudinal study of patients with COVID-19 ($n = 421$). The proportion of their sample on 5α-reductase inhibitors was lower compared to national population statistics (10.75% difference, 95% CI 7.74–12.52). This may suggest a protective effect from 5α-reductase inhibitors from developing COVID-19 infection; however, further clarification is required [30].

One retrospective study has investigated COVID-19 incidence post-urological procedures, comparing a COVID-19 referral hospital to a COVID-19-free hospital in Italy [31]. There were no cases of COVID-19 detected among the 63 patients in the referral hospital. In contrast, of the 76 patients at the COVID-19-free hospital, there were three COVID-19 patient cases and two treating urologists infected. These findings suggest benefits of stricter safety measures in reducing transmission of COVID-19.

Urology training

The impact of COVID-19 on resident well-being was assessed in a study from France. Abdessater et al. surveyed the impact of COVID-19 on 275 French urologists in training (55.5% response rate) [32]. Most respondents felt an increase in stress (91.6%). On multivariable regression, greater experience level (OR = 1.76, 95% CI 1.01–3.13) and a need to manage COVID-19 patients in the urology department (OR = 2.31, 95% CI 1.20–4.65) adversely affected the quality of their work.

Amparore et al. reported the results of a survey of 351 urology residents (58% response rate), assessing the change in clinical and surgical activities in Italy. Involvement in training was reduced or suppressed in up to 81% of clinical and 62% of surgical activities. Compared to junior residents, final year residents experienced a significant reduction in involvement in open ($p = 0.03$) and minimally invasive ($p = 0.002$) surgical procedures [33].

An ongoing study in Italy with 1200 recruited participants has been registered, investigating COVID-19 and training across all surgical subspecialities (NCT04338945). Another study from Poland is investigating the impact on surgical wards and procedures, aiming to recruit 350 surgeons and surgical residents (NCT04368026).

Telemedicine

Several studies have reported increasing rates of telemedicine use across urology departments. In Italy, the implementation of a telemedicine outpatient clinic was examined over 4 weeks. Of the 928 scheduled patients, 45% had cancelled their appointments, and the resultant weekly proportion of face-to-face consultations decreased from 63 to 9%. Of face-to-face visits, 74% were regarding new or recurrent malignancies or dangerous clinical conditions, reflecting appropriate triaging of patients [34]. A pre-print study in the USA reported the effective uptake of telemedicine before and during the COVID-19 pandemic. Clinic video visits increased from mean 208 per week (7–18%) pre-COVID-19 to 1005 per week (54–68%) during the pandemic [35].

The level of patient satisfaction of the telemedicine consult has also been evaluated. In a study from Germany, up to 85% of patients preferentially opted for telemedicine consult over face to face, with no difference between oncological versus benign diseases (86% vs 85%, $p = 0.9$) [36]. Similarly, Davis et al. surveyed preference for telemedicine in a uro-oncology clinic over a 2-week period. Lower no-show rates were identified with audio-visual consults compared to face-to-face (17% vs 67%, $p < 0.001$), while 82% of patients reported a preference for telemedicine consults in the future [37]. A registered study in France (NCT04341714) is similarly assessing the efficiency and satisfaction of telemedicine

consults, aiming to recruit 400 patients from a neuro-urology clinic.

A study from the USA described the results from a risk-stratified triage strategy for inpatient urology consultations over 3 weeks. Up to 36% (19/53) of inpatient consultations were successfully performed via telemedicine, and 44% (8/18) of COVID-19-associated consultations were managed using telemedicine alone. There were no reported COVID-19 infections in urology team members [38].

Telemedicine in diagnostic procedures has also been studied. Lobo et al. compared the proficiency and diagnostic capability of telecystoscopy with traditional cystoscopy in the COVID-19 era. The authors reported 92% practitioner proficiency with telecystoscopy, while confidence in identification of abnormalities was equivalent [39].

Equipment and safety

In the USA, Sobel et al. reported personal protective equipment (PPE) use in urology to determine impact on limited resources. Of the 437 procedures, utilisation rates of masks, hats, gowns and gloves were higher in robot-assisted cases ($p < 0.0001$). Robot-assisted laparoscopic cystectomies required the most hats and masks (14.5 per case) [40].

Urology staff were surveyed regarding recommendations for urological procedures during COVID-19 in a single institution in the USA. In summary, the responders recommend maximising telemedicine, reducing in-room time, appropriately using PPE, and managing consumable supplies for bedside procedures [41].

Urology in general

Wang et al. reported the impacts of COVID-19 on surgical volume and ongoing research trials in China. The authors reported an 80% decrease in the number of procedures. All 110 patients in ongoing clinical trials experienced protocol deviations of 27 days on average [2].

Mandanelo et al. assessed the rates of urological emergency presentations before and during the pandemic in a single institution in Portugal. A retrospective analysis of 385 presentations demonstrated a 46.4% reduction in presentations, with an associated reduction in hospitalisation (11% vs 19%, $p < 0.05$) [42]. Similarly, Mantica et al. reported on emergency urological presentations in Italy. Over 60 days, consultations decreased from 63 to 17 patients; stone-related cases decreased from 35 to 6 patients; while haematuria cases decreased from 11 to 4 patients [43].

A currently registered study in France is assessing patients undergoing elective and emergency urological procedures to identify variables that affect post-operative outcomes (NCT04352699). The study aims to assess 120 patients to assist with limiting access to surgical care.

Uro-oncology

Uro-oncological management has been examined in three studies from Italy. Campi et al. described the burden of high-priority uro-oncological surgeries from three Italian high-volume referral centres. Of 2387 major surgeries, 32% were classified as high priority, suggesting that up to two-thirds of major surgeries could be safely postponed [44]. Ficarra et al. further characterised the proportion of uro-oncological surgeries, including transurethral resection of bladder tumours (TURBTs). Of 51 non-deferrable oncological procedures, 24 were major surgeries and 27 were TURBTs. There were 16 patients who preferred to opt for treatment postponement, of which 10/16 were planned for TURBTs [45].

A survey of medical oncologists managing urological cancers was conducted to investigate management changes with COVID-19. The majority of oncologists would still pursue first-line therapy where indicated without delay, with the primary treatment consideration still being survival benefit rather than risk of COVID-19 transmission [46].

Urolithiasis

A cross-sectional survey assessed practice changes in stone management from expert European endourologists [47]. The survey achieved a 61% response rate from primary authors of the EAU section of urolithiasis working groups. Most experts reported managing patients with COVID-19 by planning elective readmissions for definitive stone management. Up to 17% of respondents did not perform surgery, while up to 11% did not accept COVID-19-positive patients.

Kidney transplantation

COVID-19 in patients with kidney transplantation has been described. There were six case series included [48–53] and one case–control study comparing patients with and without kidney transplants (Table 1) [54]. Sample sizes ranged from 5 to 33 patients, with reported median ages of 45–59 years. A range of 0–83% of patients required intensive care admission, while 0–67% patients died. Almost all studies reported immunosuppressant cessation or reduction for the patients studied—Zhu et al. however described one patient with mild COVID-19 symptoms, who did not withhold immunosuppressants, and was subsequently discharged [54].

Currently, one ongoing study from Italy has been registered, investigating hospitalisation for COVID-19 in patients with transplantations of kidney, pancreas or pancreatic islet (NCT04377776).

Table 1 Summary of studies reporting COVID-19 infection in patients with kidney transplantations

First authors	Publication country	Study design	Sample size	Age (median, years)	Transplant vintage (median, years)	Requiring hospital admission	AKI	ICU admission	Deaths
Montagud-Marrahi [48]	Spain	Case series	33	57	10.7	26 (79%)	–	13 (52%)	2 (6%)
Nair [49]	USA	Case series	10	57	7.7	9 (90%)	5 (50%)	5 (50%)	3 (30%)
TCUKTP [50]	USA	Case series	15	51	4.1	15 (100%)[a]	6 (50%)	4 (27%)[b]	2 (13)
Alberici [51]	Italy	Case series	20	59	13	20 (100%)[a]	6 (30%)	4 (20%)	5 (25%)
Abrishami [52]	Iran	Case series	12	48	13	12 (100%)[a]	–	10 (83%)	8 (67%)
Zhang [53]	China	Case series	5	45	1	5 (100%)[a]	–	0 (0%)	0 (0%)
Zhu [54]	China	Case–control[c]	10	49.5	Range 0.5–12years	10 (100%)[a]	6 (60%)	–	1 (10%)

Altogether, there were six case series and one case–control study that reported on COVID-19 outcomes in patients with kidney transplants

AKI acute kidney injury, *ICU* intensive care unit, *TCUKTP* The Columbia University Kidney Transplant Program, *USA* United States of America

[a]Study population consisted of only hospitalised patients with COVID-19 with prior kidney transplantation

[b]Reported intubation rate rather than intensive care unit admission

[c]Results of compared controls ($n = 10$) are not displayed in this table

Discussion

Our review aimed to highlight the current landscape of urological original research during the COVID-19 pandemic. 48 studies were included, investigating pathophysiological, administrative, and clinical outcomes relating to COVID-19 and urology.

Current pathophysiological research appears to focus on characterising (1) the extent of detectable viral load in human pathological specimens, and (2) the role of ACE2, *TMPRSS2*, and androgens. Translational studies suggest ACE2 and *TMPRSS2* act as susceptible entry points for SARS-CoV-2 [55]. Given *TMPRSS2* is a previously described dysregulated gene in prostate cancer, studies have investigated its relation to SARS-CoV-2 [22]. This concept has been explored clinically, where androgen deprivation may downregulate *TMPRSS2* activity, which may in turn influence COVID-19 severity [29]. Although current findings are preliminary, they suggest that androgen deprivation may exhibit protective effects for patients from COVID-19.

COVID-19 infection rates have also been examined between different hospital urology units. Notably, a urology unit within a COVID-19 referral centre demonstrated no in-hospital COVID-19 infections, while a non-COVID-19 hospital recorded five new infections. Despite the expected greater risk of transmission at a COVID-19 referral hospital, the study findings suggest stricter safety measures employed at a referral centre may actually pose lower risk of viral exposure [31].

Current administrative research areas have been examined. The reduction of surgical activities of up to 62% for residents as reported by Amparore et al. should be addressed through careful restructuring of residency programmes. Urology surgical caseload has been associated with confidence and training satisfaction, as previously described for urology residents across Europe [56]. Telemedicine initiatives have also demonstrated efficacy in implementation and patient popularity. These programmes may lead other healthcare services to adopt urological telemedicine services in both the inpatient and outpatient settings.

Clinical fields of COVID-19-related urological research seem to focus on uro-oncology, urolithiasis, and kidney transplant recipients. In addition to studies reporting general changes in urological presentations, uro-oncology studies have examined prioritisation of non-deferrable surgeries and choice of therapies, while one study has reported on expert management opinions for urolithiasis. Studies of kidney transplant recipients are currently focused on characterising the clinical progress of COVID-19.

Of note, this comprehensive search did not identify any original research that examined endourology, reconstructive urology, paediatric urology, or functional urology. Because reviews were produced as results from the search pertaining to these topics, the search likely had adequate sensitivity [6, 57]. Rather, this finding may represent a deficiency in original research in these fields. Additional studies investigating SARS-CoV-2 in urine were not captured in this review [58, 59]. This was likely due to a study focus towards other pathological specimens given negative detection in urine. Likewise, authors from only 15 countries produced original publications. These findings do not reflect the total research output relating to COVID-19, and other countries may contribute in other fields. Of note, the countries contributing the most manuscripts were China, Italy, and the USA. These

countries represent some of the most affected nations across the world [13].

Although this review has highlighted key areas of current urological research during the COVID-19 pandemic, these must be interpreted with caution, especially when informing clinical practice. Studies were reported as if they represented entire nations when most were conducted within single institutions. Furthermore, eight pre-prints were included to increase the scope of our review—these must first undergo a peer review. Nevertheless, our review is the first to provide a comprehensive country-level analysis of current original urological research related to COVID-19.

Conclusion

This review summarised original research relating to COVID-19 and urology, spanning 15 nations, and covering pathophysiological, administrative, and clinical research topics. This comprehensive overview has provided a landscape of what research exists and where it has been published, reflecting areas of high COVID-19 burden across the world. This review may assist clinicians and researchers to identify current and future areas of study relating to their subspeciality or nation.

Author contributions LG Qu: project development, data collection/analysis, manuscript writing/editing. M Perera: data collection/analysis, manuscript writing/editing. N Lawrentschuk: manuscript writing/editing. R Umbas: manuscript writing/editing. L Klotz: manuscript writing/editing.

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Compliance with ethical standards

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

Data sharing Data will not be available online, but will be shared upon request.

Research involving human participants and/or animals Not applicable.

Informed consent Not applicable.

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