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COVID-19 pandemic impact on screening and diagnosis of prostate cancer: a systematic review

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ABSTRACT

Introduction The healthcare level has been greatly affected by the COVID-19 pandemic compared with before the outbreak. This study aimed to review the impact of COVID-19 on the screening and diagnosis of prostate cancer (PCa).

Method The current study was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020. The keywords used to perform the search strategy were COVID-19 and prostate neoplasms. The four primary electronic databases comprising PubMed/MEDLINE, Web of Science, Scopus and Embase were searched until 1 September 2022. After screening and selecting studies through the EndNote software, data were extracted from each included study by two independent authors. All studies were evaluated according to Newcastle–Ottawa Scale quality assessment tool.

Results As a result, 40 studies were included, categorised into two subjects. The majority of studies indicated a significant decrease in screening prostate-specific antibody tests during the COVID-19 pandemic compared with the pre-pandemic period, leading to delays in cancer diagnosis. The decrease in the number of diagnosed cases with low/intermediate stages to some extent was more than those with advanced stages. The PCa screening and diagnosis reduction ranged from nearly 0% to 78% and from 4.1% to 71.7%, respectively.

Conclusion Our findings showed that during the COVID-19 lockdown, delays in PCa screening tests and diagnoses led to the negative health effects on patients with PCa. Thus, it is highly recommended performing regular cancer screening to reduce the impact of the COVID-19 lockdown.

PROSPERO registration number CRD42021291656.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The COVID-19 pandemic has significantly impacted the healthcare system compared with the time before its outbreak. These changes are likely to have led to a wide range of disparities in cancer screening and diagnosis, as measures have been taken to control the risk of disease transmission.

WHAT THIS STUDY ADDS

⇒ The decline in screening rates caused by COVID-19 persists for an extended period, leading to a decrease in the number of diagnosed cases with low/intermediate stages to some extent more than those with advanced stages. The reduction in prostate cancer screening and diagnosis ranged from nearly 0% to 78% and 4.1–71.7%, respectively.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It is crucial for public health recommendations to emphasise the significance of early screening and diagnosis to motivate physicians to persist in screening and detecting cancers early, despite the ongoing pandemic.

INTRODUCTION

The COVID-19 pandemic and lockdown have brought about a sense of anxiety throughout the globe. Many uncertainties and worries about its nature, origins and course exist. The number of COVID-19 infections remains as the number of deaths rises.¹ The COVID-19 pandemic and lockdown may have greatly altered people's daily lives because of stress, concern for their families, isolation, unexpected school break, home restrictions in many nations, unpredicted bereavements, amplified time of connecting with the net and social media, as well as a concern for the economic future of their family and

country. Because of the disruption in social relations, people are staying at home.^{1 2}

Several guidelines have been performed by the Centers for Disease Control and Prevention to reduce exposure and transmission risk. Thus, these efforts are predicted to prevent the disease outbreak and decrease the pressure on the healthcare system.³ As a result, with the exponential progression of the COVID-19 infection, the healthcare system was forced to undergo sweeping changes to contain the spread of SARS-CoV-2 and reduce the likelihood of further outbreaks.⁴ Healthcare has accommodated short-term alterations to cancer care delivery, such as partially or completely changing to COVID-19 treatment facilities, delaying surgeries, and temporarily ceasing non-emergent cancer screening tests and other in-office cancer facilities to decrease transmission risk.⁵ Information from cancer centres across the globe has revealed an undesirable impact on the screening and diagnosing of cancer, and providing oncology services has significantly decreased during the COVID-19 outbreak.⁵ Some healthcare institutions of the COVID-19 and Cancer Research Network described reductions in cancer screening for several cancers, such as prostate cancer (PCa).⁶

PCa is a main public health problem, the second most common cancer worldwide and the leading reason for cancer death among men.⁷ PCa mortality has been reduced in numerous countries because of screening, diagnosing and early detection.⁸ On the other hand, localised PCa is heterogeneous cancer with no clinically significant or slowly progressive disease.^{7 9} Since most patients with PCa are initially presented asymptomatic, it is required to screen the candidate cases based on the serum levels of prostate-specific antibody (PSA) derivatives that can diminish a man's risk of having metastatic PCa and mortality.^{10 11} PSA is an enzyme normally produced by prostate epithelial cells.¹² This is secreted into urine or semen. Small amounts of PSA ordinarily circulate in the blood.¹² Thus, the PSA test can detect high levels of PSA that may show the presence of PCa.¹³ In suspected PCa, prostate biopsies can confirm the diagnosis and histological Gleason grade.¹³

Unavoidably, the COVID-19 pandemic delays PCa prevention and management.¹⁴ Several studies have reported disruptions in cancer screening and diagnosis after the initial wave of the COVID-19 pandemic, including cervical, colorectal and gastric cancers.^{14 15} Due to the importance of knowing about the decrease in the number of screening tests and diagnoses on forecasting the consequences in health planning during the pandemic, it is urgent to signify the impact of COVID-19 on PCa. Therefore, for the first time, we systematically reviewed the current literature conducted in diverse countries to provide efficient data for health policymakers to compensate for the decline and pave the way for the improvement of screening and diagnosis of cancer services during the COVID-19

crisis. The mentioned objectives were evaluated with a focus on studies that investigated the related features of patients with PCa comprising several biopsy/PSA tests, cancer detection rate, screening rate and stage at diagnosis before versus during COVID-19.

MATERIAL AND METHODS

Eligibility criteria

The eligibility criteria and research question have been determined using PICO: 'P' as Population, 'I' as Intervention, 'C' as comparator/control and 'O' as Outcome.¹⁶ According to PICO structures, the inclusion criteria were as follows:

- ▶ Asymptomatic men attending PCa screening programmes or symptomatic men with suspicious lesions.
- ▶ Observational studies (cross-sectional, cohort, case-control studies), grey literature (conferences papers, theses) and preprint studies related to our topic.
- ▶ Studies that compare the screening data (including several biopsy/PSA tests, cancer detection rate and screening rate), as well as diagnosis data (comparing the number of diagnoses, stage at diagnosis), of patients with PCa before versus during COVID-19 (initial, middle, long-term if applicable).

The investigations with the following criteria were excluded:

- ▶ Studies that report men with other cancers (unless the data for PCa screening/diagnosis are reported separately).
- ▶ Clinical studies, in vivo and in vitro studies.
- ▶ Reviews, meta-analyses, commentaries, case reports, case series, editorials, letters to editors and books.
- ▶ Studies with insufficient data or unavailable full text.

Information sources

The four primary electronic databases comprising PubMed/MEDLINE, Web of Science (WOS), Scopus and Embase via Embase.com were searched until 1 October 2021, and updated on 1 September 2022. In addition, grey literature (conference papers and theses) and preprint websites (medRxiv and bioRxiv) were searched. To execute a comprehensive search and avoid missing data, references to included studies and key journals were also assessed.

Search strategy

This study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^{17 17} The keywords used to perform the search strategy were COVID-19 and prostate neoplasms. The search syntax was modified in other databases. There were not any language restrictions. The search syntax of the four electronic databases was exhibited in online supplemental table 1.

Selection process

There are three steps to select the study. First, we removed duplicate studies through EndNote software (V.X9.3.3, Thomson Reuters, Philadelphia, USA) and hand searching. Then, the title/abstract of the remaining studies was evaluated by two independent

authors (SMMZ and FT). Finally, two authors (SMMZ and FT) independently selected the studies by full text. In case of any disagreement between the two authors, it was resolved via a consensus and then was checked by the third author (EG).

Data collection process

Two authors (SMMZ and FT) extracted data from each included study separately. The attained data were entered into a 'data extraction form'. Discrepancies between the two authors were resolved by a consensus, then checked by the third author (JK).

Data items

Data extraction from each enrolled study was performed based on the following items: author's name, year of publication, country, sample size and age; information related to screening of PCa: number of biopsy/PSA tests, the average monthly number of PSA tests, PCa screening rate and main results; information related to diagnosis of prostate cancer: number of diagnoses, stage at diagnosis and main results.

Quality assessment

Two independent authors evaluated all studies according to the Newcastle–Ottawa Scale (NOS) tool (SMMZ and FT). The NOS tool comprises of three sections: selection, comparability, and exposure or outcome, with a score ranging from 0 to 9.¹⁸ The quality assessment result is divided into three categories: good, fair and poor. Our scoring criteria are four stars for selection, two stars for comparability, and three stars for exposure or outcomes. The findings of our quality assessment are categorised as good (three or four stars in the selection area, one or two stars in the comparability area, and two or three stars in the outcome/exposure area), fair (two stars in the selection area, one or two stars in the comparability area, and two or three stars in the outcome/exposure area) and poor (zero or one star in the selection area, zero star in the comparability area, and zero or one star in the outcome/exposure area). Any discrepancies between the two authors were resolved by a consensus and then checked by the third author (RG).

Protocol and registration

This systematic review has been registered in the PROSPERO (International Prospective Register of Systematic Reviews; <http://www.crd.york.ac.uk/PROSPERO/>), with the systematic review registration number: CRD42021291656 (available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021291656). Furthermore, the current systematic review protocol has been published in *BMJ Open* journal.⁴

RESULTS

Study selection

A literature search initially yielded 2545 references; of which 399, 997, 527 and 622 studies were retrieved from the PubMed/MEDLINE, Scopus, WOS and Embase databases, respectively, published from inception to 1 October 2021, and updated on 1 September 2022. Moreover, three studies were acquired from preprint websites. All studies were imported to the EndNote reference manager to remove duplicates (n=913) and review studies (n=175). From the remaining articles (n=1460), 1356 were excluded following the screening of titles and abstracts according to inclusion and exclusion criteria. Thus, 104 eligible studies remained for the selecting phase. Full text of the remaining studies was assessed; of these, 64 were excluded based on exclusion criteria, insufficient data and unavailable full text. As a result, 40 studies were included, which consisted of 13 screening tests and 27 diagnoses. A PRISMA flow chart of the eligible studies is exhibited in [figure 1](#).

Study characteristics

Totally, 40 studies were eligible according to the objectives. All of the included studies were published in English between 2021 and 2022. Geographically, most papers (n=14) were conducted in the USA, while the rest (n=15) were performed in other countries (Australia, the UK, Spain, Italy, China, Japan, Pakistan, Switzerland, Denmark, South Africa, Portugal, Sweden, Belgium, Canada and France). Of 40 studies, 13 reported the effects of COVID-19 on PCa screening (online supplemental table 1) and diagnosis (n=27) (online supplemental table 2). The study encompassed a diverse range of data points, including a sample size that spanned from 234 to 1 600 000, resulting in a total sample size of 3 876 856 participants. The age range of the patients was between 30 and 85 years. Additionally, the study comprised 5 distinct cohorts and 35 cross-sectional studies.

Quality assessment of studies

According to the NOS quality assessment tool, most of the included studies (n=24) had good quality, 10 had fair quality and 6 had poor quality. A summary of quality assessment for all eligible studies has been shown in [figure 2](#).

Screening

In this section, we aimed to discuss the possible lack of screening tests and their effect on cancer screening programmes before, during and after the lockdown. Routine cancer screening tests, including serum PSA, often detect asymptomatic cancer cases at an early stage and reduce PCa-specific mortality rates.¹⁹ The decline in screening rates caused by COVID-19 persists for an extended period, leading to delays in cancer diagnosis.²⁰ Unfortunately, the COVID-19 pandemic has changed the medical landscapes in these

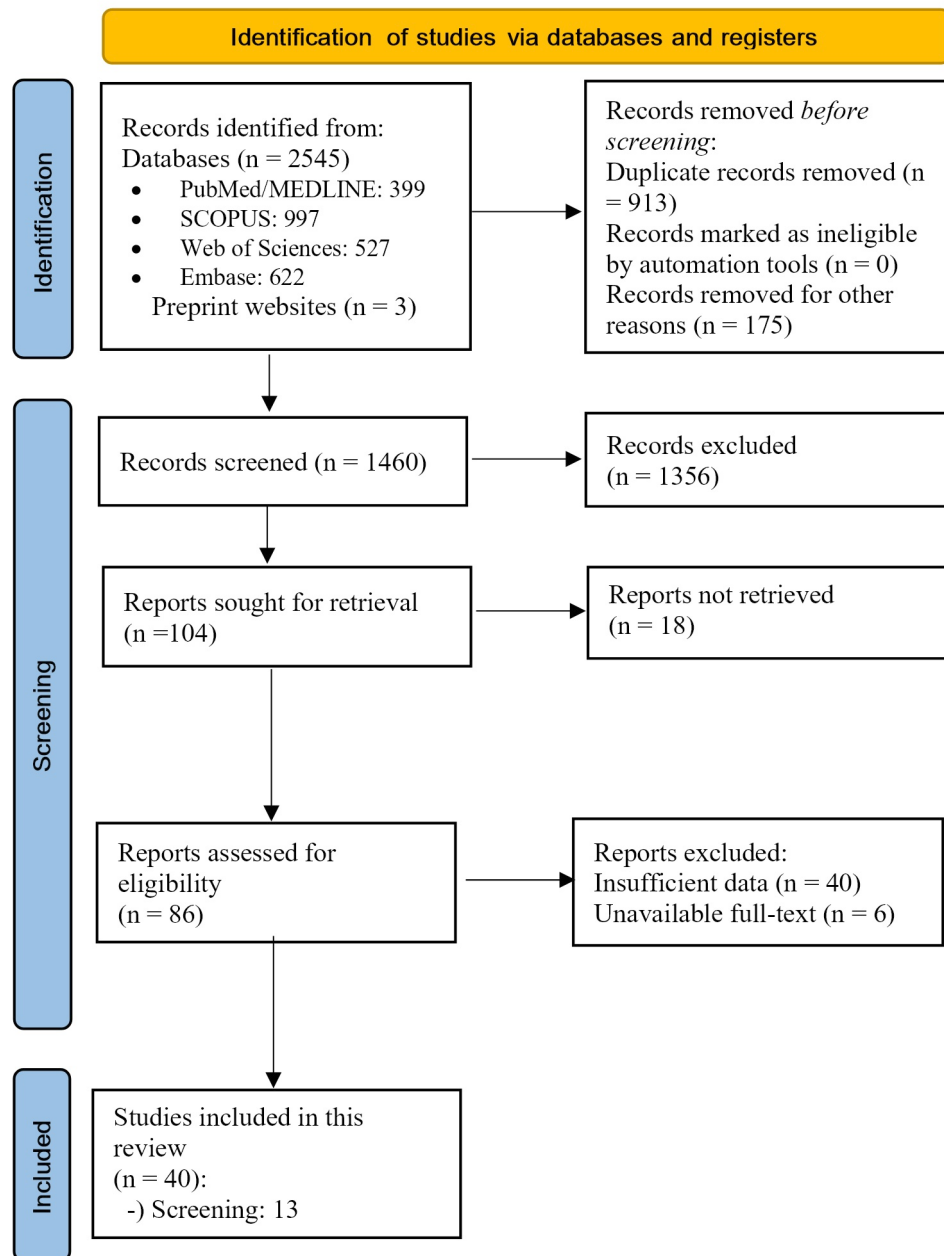


Figure 1 Flow chart for the search strategy according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

patients since they are being recommended to refrain from visiting medical facilities. Besides, critical and restrictive services on PCa screening have been altered considerably depending on the period and outcome of the study. As a result of these policies, PCa screening rates have drastically declined.²¹ This part was categorised into two subtitles: PSA and biopsy.

Prostate-specific antibody

All of the studies specifically analysed the impact of COVID-19 on the number of PSA tests performed during the pandemic versus the pre-pandemic period. In nine studies conducted in the USA, compared with the pre-pandemic period, a significant decrease in PSA

tests was reported in the early months of the COVID-19 pandemic, ranging from 13.2% to 74% during the stay-at-home and reopening phases.^{22–29} In the two Australian studies, the percentage rate of PCa testing using screening services dropped from 5% in 2019 to 2% in 2020 and 3% in 2020, respectively.^{30–31} In Pakistan, the number of PSA tests performed decreased throughout the year 2020 compared with data for 2019, indicating the highest percentage (–51.8%) decline for PSA tests during the 2020 lockdown period.³² In Italy, a significant decrease was observed during the local lockdown period (between 10 March and 17 May 2020), with an average decline of 62% in

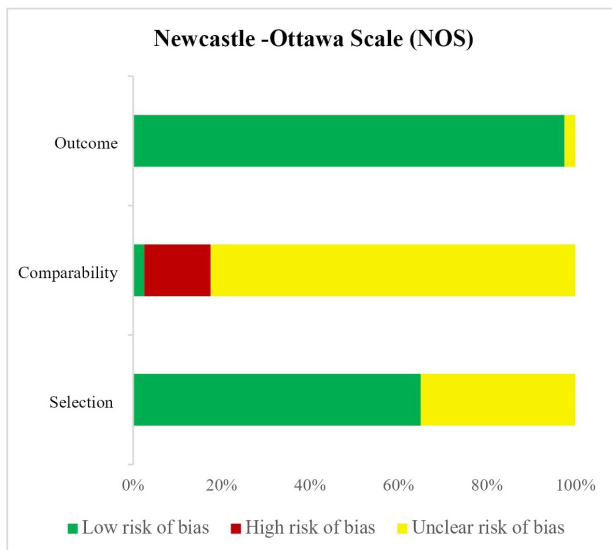


Figure 2 Summary of quality assessment.

total PSA tests, compensated by a 43% increase in total PSA tests in the post-lockdown period.³³ It has been reported that PSA testing rates were diminished by 34% in March, 78% in April and 53% in May 2020 in Switzerland; however, this reduction was compensated by June 2020 compared with pre-pandemic levels.²⁰

Biopsy

Three studies assessed the impact of COVID-19 on the number of biopsies during the pre-pandemic phase (2018–2019) compared with the pandemic period^{23 30 31}; of those, two were conducted in Australia that contradicted the trends across the world, which was unaffected in terms of prostate biopsy during 2020.^{23 31} Another one was performed in the USA, where the average monthly number of prostate biopsy results decreased by 37.9% during the early stage of the pandemic and rebounded to 18.1% during the late stage of the pandemic.³⁰

Diagnosis

Cancer diagnosis as a crucial healthcare service is one of the most ignored aspects negatively affected by the COVID-19 pandemic.³⁴ However, the long-term outcome of delay in cancer diagnosis is more challenging to measure. However, in the short term, disruption of cancer management, changes in treatment schedules and intervals, and delays in cancer treatment have already been documented.^{6 35–39} A decline in the number of new cancer diagnoses, including PCa, has been reported since the pandemic, affecting patients' clinical outcomes and advanced stages of the disease.^{34 40–42} In this section, the potential shortfall in cancer diagnosis and temporal relationship before, during and after different waves of COVID-19 was extrapolated.⁴³

Prostate-specific antibody

Most studies aimed to examine the decrease in cancer diagnosis and the stage of the disease during the first and second waves of the pandemic compared with the pre-pandemic phase.^{40 41 44 45} Furthermore, in some studies, the proportion of patients with late-stage PCa increased during the pandemic wave, which was likely to influence patients' clinical outcomes and treatment.^{41 46} In China, the proportion of PCa decreased by 4.1%, and delay of diagnosis or treatment was also reported in three patients with PCa, with a 29.2% decrease in hospital admissions and poor outcomes.⁴⁷ The decrease in screening tests has led to a reduction in subsequent diagnoses, accompanied by an increase in the percentage of positive PSA serum levels during the primary pandemic more than the other control periods (22.7% vs 9.9–13.2%) in the USA.²² The first wave of the pandemic in Australia and the second one, especially in Victoria alone, were notably reduced across all diagnostic and surgical procedures, with a 7% reduction in PSA levels.⁴⁸ A 14% decline in PSA tests has also been reported in another Australian study.⁴⁹ In addition, the median PSA level was diminished from 27.80 ng/mL in the pre-COVID-19 phase to 15.07 ng/mL in the post-COVID-19 phase among the Spanish population.⁵⁰

Biopsy

In several studies, the diagnostic indices among the most 'underdiagnosed' malignancies showed that PCa diagnosis significantly reduced during the pandemic wave.^{40–42 44 45 51 52} In four UK studies, evaluation of PCa incidence and diagnosis in the COVID-19 lockdown period showed 42%, 56%, 10% and 51.4% reduction during the 3 months of the pandemic, respectively.^{40 41 44 45} Besides, in another population-based study in the UK, PCa diagnoses remained extensively lower at 10% below the expected numbers of pathological diagnoses.⁴⁵ In South Africa, the great decline reported in PCa diagnosis (58.2%) could mostly be attributed to the substantial de-escalation of routine prostate biopsies in 2019 compared with the matching period 2020.⁴² Despite the decline in the number of examinations in China, the positivity rate for the detection of malignant prostatic lesions increased significantly with a rate of 6.6%, along with a reduction in estimated cases (19.7%) during 2020 compared with 2019.³⁴ In Japan, the reduction in total hospital admissions and diagnosis of PCa cases was less than 10% in 2020 compared with the other types of cancer.⁵¹ Similarly, another study in Japan indicated that prostate biopsies and diagnostic practices decreased by 44% in May 2020 compared with 2019.⁵³ Furthermore, in three studies on the Spanish population, a drop in the rate of cancer diagnoses by 21% was presented in 2020 compared with 2019, with greater decline of 29.6%, 36.1% and 40% in PCa diagnosis, respectively.^{54 55} In another retrospective review of patients

with PCa biopsy at a Spanish tertiary hospital, a 40% decrease was observed during a 12-month period before and after COVID-19 with reduction in PCa biopsies from 82.16% to 71.53%.⁵⁰ In Australia, there was a 12% decline in PCa biopsies from January 2020 to December 2021 in comparison with the longer-term average trend.⁴⁹ In Belgium, a more evident decline in PCa diagnosis (57%) was seen in April 2020 relative to April 2019 and -6% in January–December 2020 relative to January–December 2019.⁵⁶ A Canadian study showed 1597 total missing cases and a 54.7% decline in weekly cancer incidence in 2020 compared with 2019.⁵⁷ In the US multi-institutional assessment of surgical and diagnostic delay for PCa, 55%, 43% and 12.8% were reduced in new PCa screening and diagnostic visits per week during the pandemic.^{58–60} In another study, the impact of COVID-19 on the rate of PCa biopsies and diagnoses in black versus white US veterans exhibited a significant decrease during the COVID-19 pandemic with no statistically significant changes by race.⁶¹ Findings of other studies in the USA showed a robust decrease in weekly diagnoses, with a total count of 5301 PCa cases during 2019–2020.⁶² Besides, an increase in the number of PCa diagnoses was observed up to 144.50% and 216.60% after the lockdown.⁶³ In France, the proportion of reduction was greater for PCa diagnostic services versus other urological malignancies from January to July 2020 than in the same period in 2019.⁶⁴

Stage

The findings of cancer staging comparison in UK patients presenting in 2020 vs 2019 revealed an overall 3.9% rise in advanced stages of the disease (stages III and IV), with an overall 6.8% rise in stage IV during this period.⁴¹ The numbers of PCa cases in early (I–II) versus late (III–IV) stages of the disease were 259 (65.1%) and 139 (34.9%) vs 84 (63.6%) and 48 (36.4%) at the time of cancer diagnosis, respectively.⁴¹ The most marked reduction in PCa diagnosis (75%) was mainly observed in low-grade and intermediate-grade lesions in the Italian population.³⁶ Similarly, the number of cancer diagnoses dropped roughly to 45% in other Italians, with a 21.7% fall in high-grade tumours in 2020 compared with the average numbers recorded in 2018 and 2019.³⁷ In Portugal, approximately 40% of PCa cases (from 1430 to 866) often diagnosed at advanced stages were decreased after the COVID-19 pandemic.⁴⁶ In an evaluation of the National Prostate Cancer Register data in Sweden, a 36% fall was observed in the registration of patients with PCa during 2020 compared with the corresponding periods in 2017–2019 (1458 vs 2285 cases), which was in men above age 75 years.⁶⁵ The number of cases diagnosed with low/intermediate versus advanced/metastatic stages decreased by 40% and 36%, respectively.⁶⁵ The total count of PCa screening tests has declined by 94% in the USA, and this number

has returned to the normal rate after removing restrictions. Similarly, the number of newly diagnosed cases, especially at advanced stages of the disease, has reached nearly zero during stay-at-home measures. However, after the elimination of restrictions, this number was lower than before COVID-19.⁶²

DISCUSSION

Globally, COVID-19 is believed to have interrupted cancer screening programmes, and PCa services have been on hold due to modified medical priorities.^{15 66} During the pandemic in many countries, patients' fear of COVID-19, risk of infection and possible transmission through diagnostic tests led to a substantial decrease in screening tests.¹⁴ Sometimes, diagnostic tests were not performed or postponed at the beginning of the COVID-19 pandemic for an unknown period.⁶⁷ To the best of our knowledge, this is the first systematic review designed to investigate the impact of COVID-19 on PCa screening and diagnosis, leading to more advanced or late-stage cancers.⁴¹

Following the US Preventive Services Taskforce recommendations regarding the PSA screening omission, findings of the Surveillance, Epidemiology, and End Results Programme showed a significant overall increase in metastatic PCa detection.⁶⁸ The PSA test continues to be a low-cost and highly sensitive tool, but non-specific for PCa.⁶⁹ It is undeniable that PSA screening revealed more patients with PCa than waiting for symptoms' presentation or incurable metastatic form of the disease.⁶⁹ Well-conducted studies comparing PSA-screened versus unscreened cases constantly revealed a clear 50% cancer-specific survival improvement in the screened groups in 10-year follow-up.⁷⁰ After mutual decision-making following the two abnormal PSA values, a biopsy is usually performed to confirm the diagnosis.⁷⁰ Likewise, at the beginning of the COVID-19 pandemic, a sudden shift was made in patient care approaches, especially in central healthcare services, which hindered diagnosis.⁵⁶

The impact of the COVID-19 crisis on various PCa screening methods can vary depending on the policies applied during the lockdown period.³² The findings of the enrolled studies demonstrated a decline in PSA screening^{20 22–30 32 33} and the number of patients who were pathologically diagnosed with PCa.^{22 34 36 40–42 45–51 53 54 56–62 64 65}

In a study, the total count of PCa screening tests has reached near zero, and newly diagnosed cases, especially at advanced stages, were severely declined.⁶² Since primary care has shifted from face-to-face to telephone consultations, the relevant symptoms or signs of PCa may not be accurately recognised.⁴⁵ Furthermore, some patients with clinical symptoms refused in-person visits for anxiety about COVID-19 exposure.⁵⁶ With regard to resources and staffing, the diagnostic testing capacity in secondary care has been

limited following COVID-19.⁴⁵ Another confounding factor in primary and secondary care is the absence of healthcare staff due to the disease or self-isolation, dropping the number of patient assessments.⁴⁵

This review observed a significant decrease in PCa screening rates in several studies.^{20 22–30 32 33} The range of reduction in PCa screening and diagnosis varied from nearly 0% to 78% and from 4.1% to 71.7%, respectively. We observed that the worst affected group was those over 72 years old.⁶⁵

It has been reported that a 74% reduction in inadequate healthcare in the USA²⁴ and a 78% drop among men between 30 and 54 years were found in Switzerland during the pandemic.²⁰ The highest diagnosis deficit was observed mostly in the low-grade and intermediate-grade lesions.³⁶ Similarly, the data from the pathology laboratory in Portugal reported a considerable reduction (71.7%) in PCa cases, often diagnosed at more advanced stages.⁴⁶ Hamilton *et al*'s findings indicated that the PCa diagnosis lagging behind other cancers might reflect the lower contribution of men than women in healthcare.⁴⁵ Recent studies from Denmark and Poland have stated a 30% reduction in referrals for all cancers, including PCa, throughout the first wave of the epidemic.^{40 71} Reports from European countries revealed that the care facilities in 54% of centres were affected by COVID-19.⁷² Similarly, an international investigation described that 40% of referrals, 70% of radical prostatectomies and 80% of biopsies were postponed.⁷³ There have been several reasons for this drop, of which there is a reduction in promotion activities of healthcare services for cancer screening through the mass media.⁷⁴ In addition, the patients have been prevented from seeking care for routine and emergent issues to avoid exposure or transmission of the coronavirus.⁷⁴ Remarkably, the decline in diagnosis was observed especially in high-risk cases of cancer who were recommended self-isolation or diminished public contacts.⁷⁴ The largely tax-based primary diagnostic actions and medical referral system were the other aspects that acted as a barrier to attaining non-urgent consultations, leading to increased diagnosis duration in suspected cases.⁷⁵

In contrast, few studies have reported that the rate of prostate biopsies did not decline,^{20 30} and the differences in PCa testing delay were not significant.^{31 63} In some studies, this reduction was temporary and returned to normal after the restrictions ended.^{23 24 26 30 33 51 62} This could be partially explained by preserving and increasing of healthcare and diagnostic services.³⁴

In terms of failure in screening or diagnosis of patients with PCa with different stages of the disease, an observational study revealed a decline in the number of men diagnosed with low/intermediate-risk and high-risk/metastatic PCa by 40% and 36%, respectively.⁶⁵ Similarly, another study also observed a significant decrease in advanced cases, which could

explain the low number of newly diagnosed samples.⁸ In contrast, other studies reported an increase in the proportion of patients with late-stage disease and a delay in recognising pre-cancerous lesions.^{41 52} In a model-based UK cancer diagnosis study, an average 2-month delay in diagnosing patients with stages I–III PCa was predicted for 50% of referrals, leading to a 6% increase in deaths within 10 years.⁷⁶ Moving towards the advanced stages at diagnosis might intensify the burden on both patients and oncological care programmes, as these late-stage cancers may need more extensive handling because of delay treatment and prognosis of patients. Of note, only the temporary consequences of the COVID-19 pandemic can be evaluated at this time, and it will take more time to evaluate the effect of a pandemic on cancer especially in the advanced stages of the disease.^{46 65}

The main strength of our work is that this is the first systematic review of the effect of the COVID-19 pandemic on PCa screening and diagnosis. Furthermore, population-based data and nationally representative samples were used, which are adequate to generalise PCa screening and diagnosis.

This study also has several limitations, one of which was that studies' data were not comprehensive. Aside from not having enough data in all studies, they also had high heterogeneity of information that was not suitable for performing the meta-analysis. In addition, there was not enough information about the stage of the PCa in the screening section. It is also worth noting that there was a lack of available data on the impact of COVID-19 on healthcare access and utilisation by racial inequities. The search strategy employed in this study encompassed electronic databases until 1 October 2021, with the latest update being on 1 September 2022.

Nevertheless, it is important to acknowledge that the possibility of transitioning to a new normal may be constrained. Given the retrospective and unblinded nature of all the studies included in our analysis, there is a possibility of bias in outcome assessment and data reporting. This reflects the observational nature of the comparisons and the need for timely data reporting during a global pandemic. However, considering the highly objective nature of the outcomes measured in our study, we believe that the risk of reporting or selection bias is minimal.

CONCLUSION

The COVID-19 pandemic has had an effect worldwide, with varying impacts across each country; particularly, delays in cancer diagnosis negatively affect health outcomes. These findings indicated a statistically significant decrease in PCa screening, PSA tests and cancer diagnosis. It was mainly due to the effect of the restriction on lockdowns following the high prevalence of SARS-CoV-2 in diverse populations. Where the spread of COVID-19 has intensified, and

the restrictions have been imposed more than once, the zigzag effect can be realised among populations. Public health recommendations must highlight the importance of early screening and diagnosis, encouraging physicians to continue screening for early detection of cancers despite the ongoing pandemic.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval As this systematic review was only based on published data already in the public domain, ethical approval is not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository.

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Table 1. Main characteristics of the screening studies

Author, publication year	Country	Sample size	Age (mean+/- SD or range)	Number of Biopsy/PSA tests	Average monthly number of PSA tests	Prostate cancer screening testing rate	Results	Quality
Ahmed, S, 2021 (19)	Pakistan	NA	NA	PSA: 54,769	-) 2020: Total period: 12778 Lockdown period (March 1 and April 9, 2020): 759 No lockdown period: 12019 -) 2017-2019: Total period: 13997 Lockdown period (March 1 and April 9, 2020): 1576 No lockdown period: 12421	Total period: -8.7% Lockdown period: -51.8% No lockdown period: -3.2%	Highest percent (51.8%) decline during the 2020 lockdown period was seen for PSA.	good
Bakouny, Z, 2021 (20)	USA	NA	59.6 (12.2)	NA	NA	prostate specific antigen screenings (22.7%vs 9.9%-13.2%).	This study reports a significant decrease in the number of patients undergoing screening tests for cancer. PSA screenings declined 13.2%	good
Chen, R, 2021 (21)	USA	1,600,000	50-69	NA	NA	-0.64	PCa screening declined sharply in March through May of 2020 compared with 2019, with the sharpest decline in April (-63.4%)	good
Ferrari, A, 2021 (22)	Italy	NA	NA	PSA: 723	-) Test requests in 2020: Total period (February 25-Dec 10): 171 (126-196) Lockdown period (March 10 and May 17): 52 (29-76) No lockdown period: 181 (165-201) -) Test requests in 2016-2019: Total period (February 25-Dec 10): 138 (117-151) Lockdown period (March 10 and May 17): 146 (129-147) No lockdown period: 135 (116-151)	During the lockdown period (Verona), -62% (IQR, -79% to -41%) During periods of 2020 without lockdown restrictions: + 43% (IQR, 24%to 54%)	A dramatic decline was observed during the local lockdown period (between March 10 and May 17, 2020), with median decrease of 62% for total PSA.	good
Pelzman, D., 2021 (23)	USA	NA	NA	-) Pre-pandemic: 2031 screening PSA labs, and 8173 total PSA labs/monthly -) 2020: 1613 screening PSA labs, and 6237 total PSA labs/monthly	NA	NA	Between March and May 2020, these numbers declined from 5731 screening visits, 2031 screening PSA labs, and 8173 total PSA to 3858, 1613, and 6237 monthly encounters, respectively.	good
Ip, C, 2021 (24)	Australia	NA	50-69	PSA:2,055,577 biopsy:62,950	NA	NA	Using the 2018–2019 year as a baseline, there was a 5% reduction in PSA tests in 2019–2020 (34 553 tests), and a 2%	good

							uptrend in 2020–2021 (14,067 tests). There was not any reduction in prostate biopsy.	
Kaufman, H, 2021 (25)	USA	NA	62.4 66.4	PSA: 16,365,833 biopsy:48,819	Prepandemic:465187 Early-pandemic:295786 Late-pandemic:483374	PSA Test Early-pandemic: -36.4% Late-pandemic: +3.9% Biopsy pre-pandemic: 1,453 early-pandemic: 903 (-37.9%), late-pandemic: 1,190 (+18.1%)	The average monthly number of PSA tests declined from 465,187 pre-pandemic to 295,786 early-pandemic (36.4% decrease) before rebounding to 483,374 (3.9% increase) late-pandemic. The average monthly number of prostate biopsy results decreased from 1,453 pre-pandemic to 903 early-pandemic (37.9% decrease) before rebounding to 1,190 late-pandemic (18.1% decrease).	good
Khan, M, 2021 (26)	USA	2,430		NA	Jan 2020:390 (Reference) Feb 2020:428(-10%) March 2020:303 (-22%) April 2020:108 (-72%) May 2020:209 (-46%) June 2020:266 (-32%) July 2020:373 (-4%) August 2020:353 (-9%)	NA	Screening volume declined (72%) rapidly after January 2020, with the nadir for prostate cancer site occurring in April 2020.	fair
Kim, A, 2021 (27)	USA	NA	55-69	NA	NA	March-June 2019: -28.7% March: -24.8% April: -61.8% May: -32.6% June: 8.5%	Routine cancer screening rates from March-June 2020 showed 28.7% reductions.	good
PVP, L, 2021 (28)	USA	NA	NA	NA	NA	NA	In Brazil, prostate cancer screening tests were reduced by 39.7%. In Colombia, prostate cancer screening tests were reduced by 25.6%. A monthly average of 981.0 (6 139.1) prostate biopsies were performed in 2019, while 466.8 (6 349.4) were performed in 2020, representing a 52.4% decrease.	good
Epstein, M, 2022 (29)	Switzerl and	198,367	-) 2019: 30–54: 35,055 (54%) 55–69:21,970 (34%) 70–85:8287 (13%) -) 2020: 30–54:35,159 (53%) 55–69:22,482 (34%) 70–85 :8755 (13%) -) 2021: 30–54: 34,191 (51%) 55–69:22,873 (34%) 70–85 :9590 (14%)	NA	2019: 16.6 tests per 1,000 men 2020: 19.9 per 1,000 2021: 19.9 per 1,000	NA	PSA testing rates decreased 34% in March, 78% in April, and 53% in May 2020. Decline in PSA testing in April 2020 between 73 and 84% compared to April 2019. The rate of prostate biopsies did not decline.	good
Kelkar, A, 2022 (30)	USA	8,984	NA	NA	NA	NA	In the early months of the COVID-19 pandemic, significant decrease (74%) in cancer screening was observed.	good
Jain, A, 2022 (31)	Australia	NA	NA	PSA: 891,650 Biopsy: 25,605	NA	NA	For 2020 nationwide the percentage change for prostate cancer testing was minor with 97% as many PSA tests and 105% as many prostate biopsies as the average for the preceding years.	good

Table 2. Main characteristics of the diagnosis studies

Author, publication year	Country	Sample size	Age (mean+ SD or range)	Number of diagnoses	Stage at diagnosis	Results	Quality
Purushotham, A., 2021 (32)	UK	628	NA	628	NA	51.4% fall in PCa diagnoses was observed.	fair
Skovlund, C. W., 2021 (33)	Denmark	NA	NA	NA	NA	Slight differences were seen for PCa (42%).	good
Van Wyk, A. C., 2021 (34)	South Africa	NA	2019: 67 (66 - 68) 2020: 65 (63 - 67)	NA	NA	Substantial declines were seen for PCa (58.2%).	poor
Vardhanabhuti, V., 2021 (35)	China	1939	NA	1939	NA	Analysis on confirmed malignant pathological diagnosis revealed a statistically significant reduction (19.7%) in PCa.	good
Itoshima, H., 2021 (36)	Japan	16,045	73 (68, 78)	12,475	NA	Cases of prostate cancer reduction in hospital admissions, the number of hospitalizations was less than 10% in May 2020 compared with other types of cancer.	good
Morais, S., 2021 (37)	Portugal	866	NA	66 (7.6)	NA	The one of the largest decreases were observed for PCa (71.7%).	good
De Vincentiis, L., 2021 (38)	Italy	NA	NA	2018–2019:32.5 2020:8	low- grade and intermediate-grade lesions High grade (prostatic cancer grading groups 4 and 5)	Regarding the prognostic indices the reduction mainly involved low- grade and intermediate- grade lesions. Prostate cancer had 75% decrease and there is no reduction in metastatic cancer.	poor
Fallara, G., 2021 (39)	Sweden	1458 cases in 2020 vs a mean of 2285 cases in 2017–2019	> 75 70–75 < 70	1458	low/intermediate-risk (T1-2)/ (Gleason score 6–7 and/or PSA ≤20 ng/ml) high risk/metastatic (≥ T3)/ (Gleason score 8–10 and/or PSA >20 ng/ml and/or N1 and/or M1)	There was a 51% decrease of new PCa cases among men above 75 years, a decrease of 37% among men aged 70–75, and a decrease of 28% among men under 70 years. The number of men diagnosed with low/intermediate-risk PCa decreased by 40%, The number of men diagnosed with high-risk/metastatic PCa decreased by 36%.	good
Mora, N., 2022 (40)	Spain	NA	NA	NA	NA	Reductions in 2020 and 2021 compared to 2019 accounted for 29.6% 11.2% in PCa, respectively.	good
Nossiter, J., 2022 (41)	UK	54,828	NA	2019: 32 409 2020: 22 419	Men diagnosed in 2020 were typically at a more advanced stage (Stage IV: 21.2% vs 17.4%) and slightly older.	There was a 30.8% reduction in the number of men with newly diagnosed PCa in 2020 after the start of the first lockdown, compared with the corresponding period in 2019.	poor
Papa, N., 2022 (42)	Australia	NA	NA	NA	NA	In comparison to the longer-term average trend, from Jan 2020 to Dec 2021 it is estimated that there were 14% fewer PSA tests, 12% fewer biopsies.	fair
Peacock, H. M., 2021 (43)	Belgium	NA	NA	NA	NA	One of the largest declines observed in April 2020 were seen for PCa (57%). Also, 6% reduction was seen in January-December 2020 relative to January-December 2019.	good
Ruiz-Medina, S., 2021 (44)	Spain	NA	NA	NA	NA	Decline in diagnosis was 36.1%.	good
Yamaguchi, S., 2022 (45)	Japan	NA	NA	NA	NA	The number of prostate biopsies, a diagnostic procedure for prostate cancer, decreased by 44% in May 2020.	good
Eskander, A., 2022 (46)	Canada	37,479	65.1 (SD=15.4)	NA	NA	Decline in weekly cancer cases compared the prior mean weekly volume at 2020 showed 1,597 total missing cases and 54.7% reduction.	good

Ferrara, G., 2022 (47)	Italy	NA	NA	2019:429 2020: 236	NA	The diagnostic decrease in PCa (45%) was the most relevant among other malignancies; however, high-grade tumors were only moderately affected (21.7%).	fair
Li, Z., 2021 (48)	China	234	NA	2019:137 2020: 97	T4N2M1c T4N1M1 T3aN0M0	In patients with PCa the proportion decreased by 4.1%. Besides, we identified 3 cases with PCa that underwent delay of diagnosis or treatment with unfavorable consequences.	good
Maganty, A., 2021 (49)	USA	399	65 (61, 69)	Pre-COVID= 268 post-COVID=131	NA	We observed a 43% decline in new PCa screening visits during the pandemic.	fair
Drescher, C. W., 2021 (50)	USA	10,054	NA	2019:5371 2020:4683	NA	There was a cumulative year-over-year 12.8% decline in PCa.	fair
Antón-Juanilla, M, 2021 (51)	Spain	total: 752 March-2019 to February-2020: 471 March-2020 to February-2021: 281	NA	NA	NA	A 40% decrease was observed between March 2019-February 2020 and March 2020-February 2021.	poor
Bernstein, A, 2021 (52)	USA	NA	NA	NA	NA	Overall, there was a 55% and 39% decline in biopsy and prostatectomy volumes, respectively.	poor
Biondi, C 2021 (53)	Australia	2019: 704283 2020: 657687	NA	NA	NA	Reduction in PCa diagnosis was 7%.	poor
J. Y. Blay, 2021 (54)	France	NA	NA	NA	NA	7% drop was observed in PCa diagnosis.	fair
Concepcion, J, 2022 (55)	USA	2019:78,500 2020:191,930 2021: 248,530	NA	NA	NA	PCa screening was 49,014,200 and 49,713,150 in 2019 and 2020, respectively. It has been reported 1.43% increase in PCa screening in 2020. The number of PCa diagnoses increased from 78,500 in 2019 to 191,930 in 2020 (+144.50%) and 248,530 in 2021 (+216.60%). There was an increase in deaths from PCa from 31,620 in 2019 to 33,330 in 2020 (5.41%) and 34,130 in 2021 (7.94%).	fair
Carroll, R, 2022 (56)	USA	Screening Total:7572 Before: 3166 During:190 After:4216	NA	New diagnoses Total:5301 Before: 3661 During:92 After:1548	Advanced cases Total: 797 Before: 587 During: 17 After:193	The total count of PCa screening tests has reached near zero, and newly diagnosed cases especially at advanced stages of the disease were severely declined.	fair
Hamilton, A, 2021 (57)	UK	NA	NA	1st March to 12th September 2020: -21% 9th August to 12th September 2020: -10% compared to the same time periods in 2017–19	NA	PCa diagnoses remained considerably lower (10%), below expected numbers of pathological diagnoses.	good
Klaassen, Z, 2022 (58)	USA	Biopsy: Prior to the pandemic (January 2018 through February 2020): between 1230 and 1695/monthly	NA	October 2020: 752 cases expected, 655 cases observed. 97 cases missed April 2020: 794 cases expected, 221 cases observed. 573 cases missed	NA	Among 51 606 included men, the estimated number of missed PCa diagnoses from March 2020 through March 2021 ranged from 97 to 573 cases.	fair

Table S1. Search syntax of the four electronic databases.

PubMed/MEDLINE
<p>(“COVID 19”[tiab] OR “COVID-19 Virus Disease*”[tiab] OR “COVID 19 Virus Disease” [tiab] OR (Disease[tiab] AND COVID-19 Virus[tiab]) OR (Virus Disease[tiab] AND COVID-19[tiab]) OR “COVID-19 Virus Infection*”[tiab] OR “COVID 19 Virus Infection” [tiab] OR (Infection[tiab] AND COVID-19 Virus[tiab]) OR (Virus Infection[tiab] AND COVID-19[tiab]) OR “2019-nCoV Infection*”[tiab] OR “2019 nCoV Infection” [tiab] OR (Infection[tiab] AND 2019-nCoV[tiab]) OR “Coronavirus Disease-19” [tiab] OR “Coronavirus Disease 19” [tiab] OR “2019 Novel Coronavirus Disease” [tiab] OR “2019 Novel Coronavirus Infection” [tiab] OR “2019-nCoV Disease*”[tiab] OR “2019 nCoV Disease” [tiab] OR (Disease[tiab] AND 2019-nCoV[tiab]) OR “COVID19” [tiab] OR “Coronavirus Disease 2019” [tiab] OR (Disease 2019[tiab] AND Coronavirus[tiab]) OR “SARS Coronavirus 2 Infection” [tiab] OR “SARS-CoV-2 Infection” [tiab] OR (Infection[tiab] AND SARS-CoV-2[tiab]) OR “SARS CoV 2 Infection” [tiab] OR “SARS-CoV-2 Infections” [tiab] OR “COVID-19 Pandemic*”[tiab] OR “COVID 19 Pandemic” [tiab] OR (Pandemic[tiab] AND COVID-19[tiab]))</p> <p>AND</p> <p>(“Prostate Neoplasm*”[tiab] OR (Neoplasm*[tiab] AND Prostate[tiab]) OR (Neoplasm*[tiab] AND Prostatic[tiab]) OR “Prostatic Neoplasm” [tiab] OR “Prostate Cancer*”[tiab] OR (Cancer*[tiab] AND Prostate[tiab]) OR “Cancer of the Prostate” [tiab] OR “Prostatic Cancer*”[tiab] OR (Cancer*[tiab] AND Prostatic[tiab]) OR “Cancer of Prostate” [tiab])</p>
Embase
<p>(‘COVID 19’:ti,ab OR ‘COVID-19 Virus Disease*’:ti,ab OR ‘COVID 19 Virus Disease’:ti,ab OR (Disease:ti,ab AND COVID-19 Virus:ti,ab) OR (Virus Disease:ti,ab AND COVID-19:ti,ab) OR ‘COVID-19 Virus Infection*’:ti,ab OR ‘COVID 19 Virus Infection’:ti,ab OR (Infection:ti,ab AND COVID-19 Virus:ti,ab) OR (Virus Infection:ti,ab AND COVID-19:ti,ab) OR ‘2019-nCoV Infection*’:ti,ab OR ‘2019 nCoV Infection’:ti,ab OR (Infection:ti,ab AND 2019-nCoV:ti,ab) OR ‘Coronavirus Disease-19’:ti,ab OR ‘Coronavirus Disease 19’:ti,ab OR ‘2019 Novel Coronavirus Disease’:ti,ab OR ‘2019 Novel Coronavirus Infection’:ti,ab OR ‘2019-nCoV Disease*’:ti,ab OR ‘2019 nCoV Disease’:ti,ab OR (Disease:ti,ab AND 2019-nCoV:ti,ab) OR ‘COVID19’:ti,ab OR ‘Coronavirus Disease 2019’:ti,ab OR (Disease 2019:ti,ab AND Coronavirus:ti,ab) OR ‘SARS Coronavirus 2 Infection’:ti,ab OR ‘SARS-CoV-2 Infection’:ti,ab OR (Infection:ti,ab AND SARS-CoV-2:ti,ab) OR ‘SARS CoV 2 Infection’:ti,ab OR ‘SARS-CoV-2 Infections’:ti,ab OR ‘COVID-19 Pandemic*’:ti,ab OR ‘COVID 19 Pandemic’:ti,ab OR (Pandemic:ti,ab AND COVID-19:ti,ab))</p> <p>AND</p> <p>(‘Prostate Neoplasm*’:ti,ab OR (Neoplasm*:ti,ab AND Prostate:ti,ab) OR (Neoplasm*:ti,ab AND Prostatic:ti,ab) OR ‘Prostatic Neoplasm’:ti,ab OR ‘Prostate Cancer*’:ti,ab OR (Cancer*:ti,ab AND Prostate:ti,ab) OR ‘Cancer of the Prostate’:ti,ab OR ‘Prostatic Cancer*’:ti,ab OR (Cancer*:ti,ab AND Prostatic:ti,ab) OR ‘Cancer of Prostate’:ti,ab)</p>
Scopus
<p>(TITLE-ABS-KEY(“COVID 19” OR “COVID-19 Virus Disease*” OR “COVID 19 Virus Disease” OR (Disease, AND COVID-19 Virus) OR (Virus Disease AND COVID-19) OR “COVID-19 Virus</p>

Infection*" OR "COVID 19 Virus Infection" OR (Infection AND COVID-19 Virus) OR (Virus Infection AND COVID-19) OR "2019-nCoV Infection*" OR "2019 nCoV Infection" OR (Infection AND 2019-nCoV) OR "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019-nCoV Disease*" OR "2019 nCoV Disease" OR (Disease AND 2019-nCoV) OR "COVID19" OR "Coronavirus Disease 2019" OR (Disease 2019 AND Coronavirus) OR "SARS Coronavirus 2 Infection" OR "SARS-CoV-2 Infection" OR (Infection AND SARS-CoV-2) OR "SARS CoV 2 Infection" OR "SARS-CoV-2 Infections" OR "COVID-19 Pandemic*" OR "COVID 19 Pandemic" OR (Pandemic AND COVID-19)))

AND

(TITLE-ABS-KEY("Prostate Neoplasm*" OR (Neoplasm* AND Prostate) OR (Neoplasm* AND Prostatic) OR "Prostatic Neoplasm" OR "Prostate Cancer*" OR (Cancer* AND Prostate) OR "Cancer of the Prostate" OR "Prostatic Cancer*" OR (Cancer* AND Prostatic) OR "Cancer of Prostate"))

WOS

(TS=("COVID 19" OR "COVID-19 Virus Disease*" OR "COVID 19 Virus Disease" OR (Disease, AND COVID-19 Virus) OR (Virus Disease AND COVID-19) OR "COVID-19 Virus Infection*" OR "COVID 19 Virus Infection" OR (Infection AND COVID-19 Virus) OR (Virus Infection AND COVID-19) OR "2019-nCoV Infection*" OR "2019 nCoV Infection" OR (Infection AND 2019-nCoV) OR "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019-nCoV Disease*" OR "2019 nCoV Disease" OR (Disease AND 2019-nCoV) OR "COVID19" OR "Coronavirus Disease 2019" OR (Disease 2019 AND Coronavirus) OR "SARS Coronavirus 2 Infection" OR "SARS-CoV-2 Infection" OR (Infection AND SARS-CoV-2) OR "SARS CoV 2 Infection" OR "SARS-CoV-2 Infections" OR "COVID-19 Pandemic*" OR "COVID 19 Pandemic" OR (Pandemic AND COVID-19)))

AND

(TS=("Prostate Neoplasm*" OR (Neoplasm* AND Prostate) OR (Neoplasm* AND Prostatic) OR "Prostatic Neoplasm" OR "Prostate Cancer*" OR (Cancer* AND Prostate) OR "Cancer of the Prostate" OR "Prostatic Cancer*" OR (Cancer* AND Prostatic) OR "Cancer of Prostate"))