A SYSTEMATIC REVIEW OF COVID-19 AND PRIAPISM

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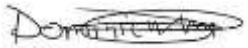
A research report submitted to the Faculty of Health Sciences of the University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Medicine

Johannesburg, 2022

DECLARATION

I, **Domenic Mpumelelo Malinga**, hereby declare that this research report is my own work and has not been submitted or presented for any other degree or professional qualification at this or any other institute. This research was undertaken in the Division of Emergency Medicine, University of the Witwatersrand, Johannesburg.

Signature of Student:  Date: 14/02/2022

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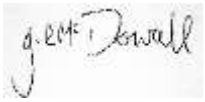
Signature of Supervisor 3:  Date: 14/02/2022

DEDICATION

This work is dedicated to my entire family, colleagues and friends for their support and patience with me during my academic commitments. Lastly, my loving wife Mrs Malinga who has been a great pillar of strength and motivation.

ACKNOWLEDGEMENTS

A special thank you to all my supervisors: Prof Abdullah Laher, Prof Ahmed Adam, & Mr Jared McDowall for their guidance, patience, and support. I would also like to extend my gratitude to Mr Devind Peter for the University of the Witwatersrand Health Sciences Library for his assistance with literature retrieval.

SUBMISSION FORMAT OF THIS RESEARCH REPORT

As per the University of Witwatersrand Faculty of Health Sciences guidelines, this research report is being submitted in the following format: submission for publication ready format. The article has been submitted to the journal, *Current Urology* and is currently under publication consideration.

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MANUSCRIPT

TITLE OF MANUSCRIPT

COVID-19 and priapism: an unexplored association?

RUNNING TITLE

COVID-19 and priapism

ARTICLE TYPE

Systematic review

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WORD, TABLE AND FIGURE COUNT

Abstract: 250

Manuscript: 2867

Tables: 2

Figures: 2

PRIOR PRESENTATIONS

None

FUNDING SOURCES/DISCLOSURES

None

ACKNOWLEDGMENTS

We are indebted to Mr Devind Peter for his kind assistance with the literature retrieval process (University of the Witwatersrand Health Sciences Library, Johannesburg, South Africa).

CONFLICTS OF INTEREST

The authors' hereby certify that this submission is not under publication consideration elsewhere and is free from any conflict of interest.

COVID-19 and priapism: an unexplored association?

ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) has an established impact on multiple organ systems including the vascular and urogenital systems. Vascular effects may include venous thromboembolic disease, which in theory may be a precursor to priapism, a urological emergency defined as an abnormal condition of prolonged penile erection of more than 4 hours in duration. To better explore this association, we have critically appraised all published COVID-19 cases associated with priapism.

Methods: After PROSPERO registration (CRD42021245257), a systematic search of Google Scholar, Scopus, Embase, Web of Science, PubMed, Cumulative Index to Nursing and Allied Health Literature, Global Index Medicus, and Cochrane Database of Systematic Reviews was performed using specific search terms. The following study metadata were extracted: age, requirement for respiratory support, cavernous blood gas findings, management of priapism, and patient outcomes.

Results: Fifteen single-patient case reports were included in this review. Of these, all of the patients presented with ischemic priapism, nine (60.0%) were >60 years of age, four (28.6%) reported more than a single episode of priapism, 11 (73.3%) presented with pneumonia, eight (53.3%) required mechanical ventilation, D-dimer was elevated in five of the six (83.3%) patients in whom this was reported, and four (26.7%) patients died.

Conclusion: Early reports suggest a prognostic relationship between COVID-19 and coexisting priapism. However, owing to commonalities in their pathophysiology and the small dataset reported in the literature, the probable association between COVID-19 and priapism is still theoretical. Further research is needed to confirm this association.

Key words: COVID-19, severe COVID-19, SARS-CoV-2, coronavirus, priapism, thromboembolism, thromboembolic disease, VTED

INTRODUCTION

Coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China, in December 2019, and spread rapidly worldwide [1]. Typical presentations of COVID-19 include dry cough, sore throat, loss of smell, and fever. In severe cases, patients may develop dyspnea requiring hospitalization. Up to 50% of patients with dyspnea require intensive care unit admission, of which 46%-65% develop respiratory failure and die. Evidence suggests that COVID-19 also affects other organ systems, including the haematological (venous thromboembolism), cardiovascular (myocarditis), and central nervous (encephalitis, Guillaine-Barre syndrome) systems [2].

The pathophysiology of COVID-19 includes the activation of the inflammatory and coagulation pathways. Studies have shown that patients with fatal COVID-19 have lower platelet counts and higher D-dimer levels than survivors [3,4]. Guidelines recommend that D-dimer and other coagulopathy markers should be monitored in hospitalized patients with COVID-19 associated coagulopathy [5]. Priapism has recently been reported as a possible thromboembolic complication of COVID-19 [6–20].

Priapism is a urological emergency defined as an abnormal condition of prolonged or constant penile erection lasting >4 h in duration. It can be categorized as either ischemic (low-flow or veno-occlusive) or non-ischemic (high-flow or arterial). Priapism is sometimes characterized by pain and may or may not be associated with sexual stimulation. The causes of priapism can be idiopathic or secondary to recreational drugs (e.g., cocaine), medications (e.g., antipsychotics, antidepressants), central nervous system pathology (e.g., spinal cord trauma, brain tumors), sickle cell disease, neoplasms (e.g., leukemia), metabolic diseases (gout, diabetes mellitus), spider bites, and scorpion bites [16,21].

Priapism is most commonly observed in adults, with an estimated incidence of 1.5 per 100 000 patients. Approximately 95% of presentations are of the ischemic type [22]. If treatment is not initiated timeously, permanent damage to the corpora cavernosa may occur, leading to ischemia, necrosis, and erectile dysfunction. Emergent treatments for priapism include ice pack

application, cavernosal aspiration, and intracavernous injections of sympathomimetic agents [23]. Apart from the emergent therapy required in its management, priapism carries a medical liability risk in cases of delay, omission, or neglect [24].

A limited number of cases of COVID-19 with coexisting priapism have been reported [6–19]. These cases must be reviewed to identify whether there is a potential association between these two conditions. Owing to the incidence and adverse events associated with priapism, coupled with the theoretical correlation between priapism and COVID-19 pathophysiology, we explored the potential relationship between the two by conducting this systematic review.

METHODOLOGY

Search strategy

Prior to commencement of the search, this systematic review was registered with the Prospective Register of Systematic Reviews (PROSPERO) (CRD42021245257). The following electronic databases were searched (09 February 2022): Google Scholar, Scopus, Embase, Web of Science, PubMed, Cumulative Index to Nursing and Allied Health Literature (CIANHL), Global Index Medicus, and the Cochrane Database of Systematic Reviews. The following search terms were used: ‘COVID-19’, OR ‘coronavirus,' OR 'SARS CoV-2’, AND ‘priapism’. The search was restricted to human studies. No language or date restrictions were applied.

Study selection

Studies included in the review met the following criteria: i) studies were clinical publications, ii) studies were limited to human subjects, and iii) publication text was available. All publications relating to the topic, including correspondence articles, letters to the editor, and conference proceedings, were eligible for inclusion. ‘Case report’ inclusion was pivotal in this review, since this early association had not been previously explored.

PICO (Participants/Intervention/Control)

Participants/Population: COVID-19-positive male patients with priapism.

Intervention/Exposure: Male patients were exposed and diagnosed with COVID-19 with concurrent priapism.

Comparator/Control: Male patients without a confirmed diagnosis of COVID-19 with the presence of priapism were excluded.

Review study definition of priapism

For the purpose of this systematic review, priapism was defined as a urological emergency characterized by prolonged or constant penile erection lasting >4 h in duration, with all subtypes considered for inclusion [21].

Data Extraction and methodology evaluation

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used to guide the electronic search [25]. Two independent reviewers (DM and JM) screened the articles using eligibility criteria. Using the inclusion criteria, a descriptive narrative for each article was compiled by the reviewers. All differences, disagreements, and conflicting entries were resolved by a third reviewer (AA). All points of interest were tabulated (country of origin, patient age, diagnosis, category of respiratory support required, number of episodes and duration of priapism, cavernosal blood gas, D-dimer level, management of priapism, patient outcomes, and authors' conclusions).

Data synthesis

The outcomes reported were summary data pertaining to the clinical presentation of priapism, severity of COVID-19 infection, relevant laboratory findings, patient outcomes, and management. Since all included studies were case reports, summative statistics and a narrative synthesis approach were primarily used to describe the findings.

Assessment of methodological quality of included articles

As all studies meeting the inclusion criteria were case reports, the tool proposed by Murad et al. was used to assess the methodological quality of the included manuscripts [26]. The tool comprises four domains, with eight questions in total. Since two questions related to drug

reactions were not relevant to our study, they were omitted. The overall methodological quality of each of the included articles was described as low, intermediate, or high quality. High quality was defined as a "yes" answer to four or more of the included questions; intermediate quality was defined as a "yes" answer to three of the included questions; and low quality was defined as a "yes" answer to less than three of the included questions (Table 1).

Table 1: Methodological quality assessment of the included reports

Author	Selection	Ascertainment		Causality		Reporting	Overall Quality*
	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	
Lamamri et al. [6]	Yes	Yes	Yes	Yes	Unclear	Yes	High
Lam et al. [7]	Yes	Yes	Yes	Yes	No	Yes	High
Silverman et al. [8]	Yes	Yes	Yes	Yes	Yes	Yes	High
Addar et al. [9]	Yes	Yes	Yes	No	Yes	Yes	High
Larrarte-Arenas et al. [10]	Yes	Yes	Yes	No	No	Yes	High
Grimberg et al. [11]	Yes	Yes	Yes	Yes	Yes	Yes	High
Giuliano et al. [12]	Yes	Yes	Yes	Yes	Yes	Yes	High
Carreño et al. [13]	Yes	Yes	Yes	Yes	No	Yes	High
Anderson et al. [14]	Yes	Yes	Yes	Yes	No	Yes	High
Ahmed et al. [15]	Yes	Yes	No	No	Unclear	Yes	Intermediate
Laaribi et al. [16]	Yes	Yes	Yes	Yes	Yes	Yes	High
Cruz et al. [17]	Yes	Yes	No	Yes	Yes	Yes	High
Brönimann et al. [18]	Yes	Yes	Yes	Yes	Yes	Yes	High
Ameyaw et al. [19]	Yes	Yes	Yes	Yes	Yes	Yes	High
Alsaedi et al. [20]	Yes	Yes	Yes	Yes	Yes	Yes	High

Questions 1-6 comprise the tool for assessing the methodological quality of each of the included articles:

1. Does the patient(s) represent(s) the whole experience of the investigator or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
2. Was the condition adequately ascertained?
3. Was the outcome adequately ascertained?
4. Were other alternative causes that may explain the observation ruled out?
5. Was follow-up long enough for outcomes to occur?
6. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?

*High quality: "yes" answer to four or more questions, intermediate quality: "yes" answer to three questions, low quality: "yes" answer to less than three questions.

RESULTS

Search

The electronic database search yielded 351 records as follows: Google Scholar (n=253), Scopus (n=41), Embase (n=26), Web of Science (n=13), PubMed (n=12), CIANHL (n=5), Global Index Medicus (n=1), and Cochrane Database of Systematic Reviews (n=0). Of these, 299 titles were excluded (83 duplicates and 216 irrelevant to the topic). A further 16 records were excluded after abstract review. Of the remaining 36 records that were eligible for full-text assessment, 17

articles were not relevant to the topic, while five were review-type articles. Hence, 14 records were eligible for inclusion in this study. The details of this process are shown in Figure 1. Table 2 summarizes the findings of the manuscript included in the text.

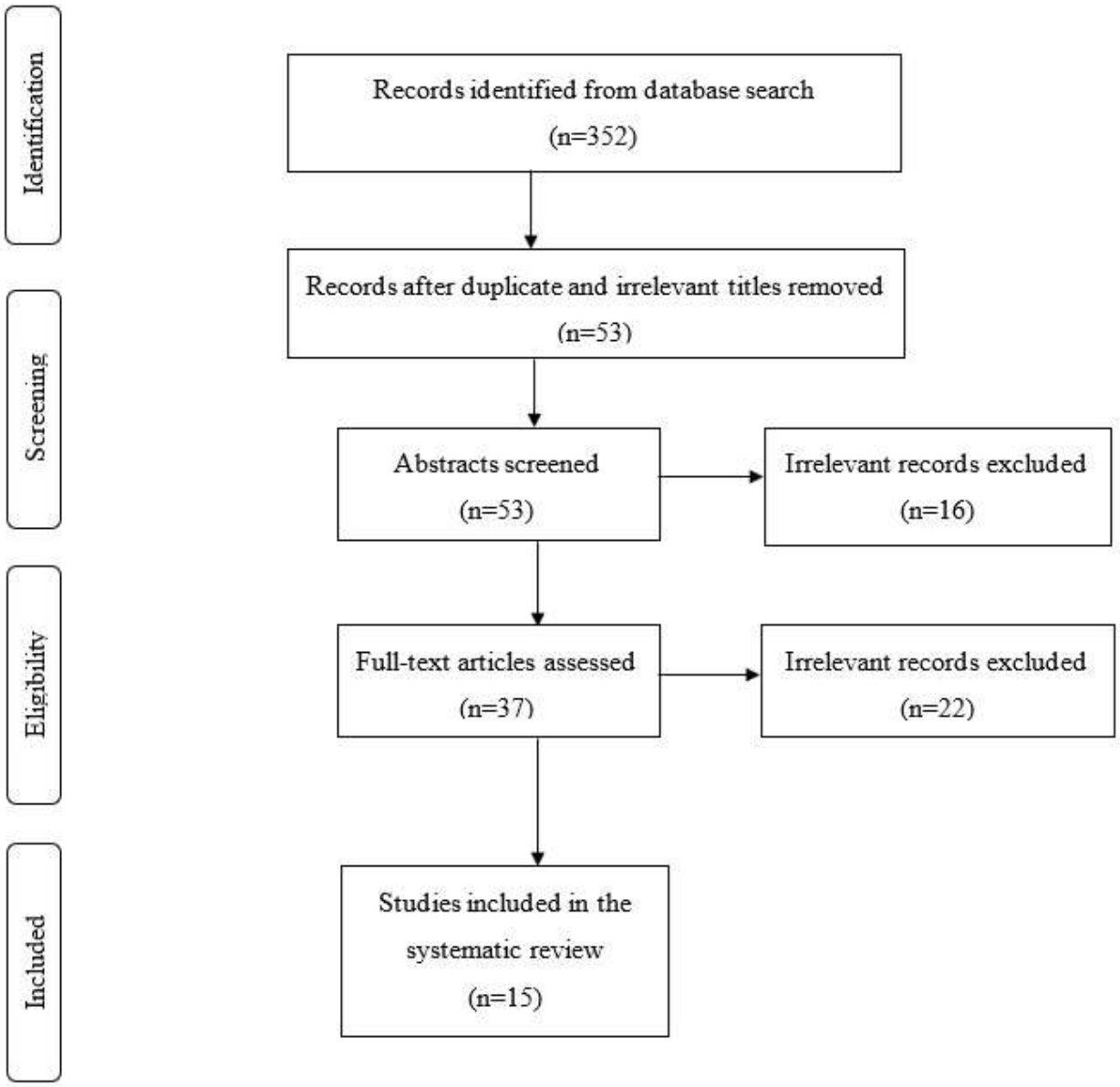

Figure 1: Study flow diagram

Table 2: Summary of literature included in the review

First author, study design & date of publication	Country of origin	Age	Diagnosis	Respiratory support	No. of episodes and duration of priapism	Cavernosal blood gas			D-dimer (ng/mL)	Management of priapism	Patient outcomes	Author's conclusion
						pH	PCO_2 (mmHg)	PO_2 (mmHg)				
Lamamri et al., CR, June 2020 [6]	France	62	COVID-19 pneumonia with priapism	MV	1 episode, >4 hours	6.98	121	68	2210	Ice packs, cavernosal aspiration, intracavernosal ethylephrine injection, enoxaparin	Survived to hospital discharge	Strongly suggests priapism related to SARS-CoV-2 infection.
Lam et al., CR, July 2020 [7]	United Kingdom	67	COVID-19 pneumonia with priapism	CPAP & HFNC	1 episode, duration not stated	NR	NR	NR	428	Conservative management due to rapid clinical deterioration of COVID-19 pneumonia	Deceased	Coagulopathy and possible microemboli formation secondary to COVID-19 infection may have led to obstruction of draining venules, resulting in low-flow priapism.
Silverman et al., CR, January 2021 [8]	USA	69	COVID-19 pneumonia with priapism	MV	1 episode, < 1 day	6.93	>98.3	<30.1	NR	Ice packs, cavernosal aspiration, intracavernosal phenylephrine injection, heparin	Deceased	The evidence has suggested an association between COVID-19 and hypercoagulability.
Addar et al., CR, April 2021 [9]	Saudi Arabia	62	COVID-19 pneumonia with priapism	HFNC	1 episode, 10 days	6.86	33.3	26.9	NR	Cavernosal aspiration, intracavernosal phenylephrine injection, enoxaparin	Survived to hospital discharge	NR
Larrarte-Arenas et al., CR, May 2021 [10]	Columbia	65	Mild COVID-19 with priapism, renal dialysis for the past 2 years	No oxygen required due to mild COVID-19 symptoms	1 episode, 30 hours	6.88	93.2	35	NR	Ice packs, cavernosal aspiration, intracavernosal epinephrine injection	Survived to hospital discharge	Haemodialysis and kidney disease may have predisposed the patient to priapism. Role of COVID-19 is unclear.
Grimberg et al., CR, June 2021 [11]	USA	45	COVID-19 pneumonia	MV	2 episodes 8 hrs apart, duration of	7.05	21	86	NR	Cavernosal aspiration, intracavernosal	Survived to hospital discharge	Priapism secondary to COVID-19 can occur while receiving

			with priapism		first episode was >4 hours					phenylephrine, enoxaparin		prophylactic doses of heparin. Priapism can be stuttering in nature. Corporal aspiration and injection are feasible and effective, even in prone patients.
Giuliano et al., CR, July 2021 [12]	Italy	34	Priapism post mild COVID-19	No oxygen required due to mild COVID-19 symptoms	1 episode, 36 hours	7.47	33	65	5855	Cavernosal aspiration, intracavernosal phenylephrine & spongio-cavernosal shunt all failed. Bilateral T-shunt relieved tumescence	Survived to hospital discharge	Priapism could occur due to mild COVID-19 infection.
Carreño et al., CR, September 2021 [13]	Columbia	39	COVID-19 pneumonia with priapism	MV	1 episode, >72 hours	7.32	46.6	66.8	865	Intracavernous injection of adrenaline, LMWH	Deceased	Potential association between ischemic priapism and COVID-19.
Anderson et al., CR, October 2021 [14]	USA	68	COVID-19 pneumonia with priapism	MV	4 episodes, duration of first episode was >4 hours	<6.8	19	86	NR	Cavernosal aspiration, intracavernosal phenylephrine	Deceased	Priapism may be a rare thromboembolic complication of severe COVID-19.
Ahmed et al., CR, October 2021 [15]	United Kingdom	58	COVID-19 pneumonia with priapism	MV	NR	NR	NR	NR	NR	Cavernosal aspiration	NR	We highlight the importance of vigilance for extra-pulmonary manifestations of Covid-19.
Laaribi et al., CR, December 2021 [16]	Morocco	67	COVID-19 pneumonia with priapism	MV	1 episode, prolonged duration with refractory priapism	NR	NR	NR	NR	Cavernosal aspiration, intracavernosal phenylephrine, caverno-cancellous shunt and posthectomy heparin	Survived to hospital discharge	Priapism is a rare thromboembolic complication of COVID-19 and requires rapid treatment in order to limit the often-irreversible sequelae.
Cruz et al., CR, December 2021 [17]	Argentina	62	COVID-19 pneumonia with priapism	MV	1 episode, 5 hours	7.2	60	80	4885	Ice packs, cavernosal aspiration, intracavernosal adrenaline, enoxaparin	NR	Failure to establish timely and effective treatment may lead to permanent sequela.

Brönimann et al., CR, January 2022 [18]	Austria	12	Priapism post mild COVID-19	No oxygen required due to mild COVID-19 symptoms	3 episodes in 4 days	6.95	3.1	85.1	NR	Ice packs, cavernosal aspiration, intracavernosal phenylephrine, etilefrine, enoxaparin	Survived to hospital discharge	The underlying SARS-CoV-2 induced pathophysiological mechanisms need to be confirmed by future studies.
Ameyaw et al., CR, February 2022 [19]	Ghana	9	Mild COVID-19 with priapism	No oxygen required due to mild COVID-19 symptoms	1 episode, 6 hours	NR	NR	NR	NR	Ice packs, conservative management with spontaneous resolution after an hour of hospital presentation	Survived to hospital discharge	Priapism may be a rare clinical feature of COVID-19 among children and should be looked for following COVID-19 infection.
Alsaedi et al., CR, February 2022 [20]	Saudi Arabia	66	COVID-19 pneumonia with priapism	HFNC	1 episode, 3 days	NR	NR	NR	200	Cavernosal aspiration, partial penectomy as the patient had clinical evidence of penile gangrene on presentation	Survived to hospital discharge	Strongly suggest the need for the diagnosis and prevention of thrombotic diseases in at-risk patients with COVID-19 infection.

CR – Case Report; MV – mechanical ventilation; CPAP – continuous positive airway pressure; HFNC – high flow nasal canula oxygen; LMWH – low molecular weight heparin; PCO2 – partial pressure of carbon dioxide; PO2 – partial pressure of oxygen; NR – not reported

Design of the included publications

All 15 included publications were single patient case reports [6–20].

Country of origin

Three cases (21.4%) originated in the USA [8,11,14]; two (14.3%) each from Columbia [10,13], the United Kingdom [7,15], and Saudi Arabia [9,20]; and one (7.1%) each from France [6], Italy [12], Morocco [16], Argentina [17], Austria [18], and Ghana [19].

The age range of study subjects

Nine (60.0%) patients were aged between 60-70 years [6–10,14,16,17,20]. There were two (13.3%) paediatric patients aged 12 [18] and 9 [19] years. The ages of the remaining four (26.7%) cases ranged from 34-58 years [11–13,15].

Subtype of priapism and likely aetiology

Low-flow (ischemic) priapism was diagnosed in all 15 cases [6–20]. In fourteen (93.3%) of these cases, the authors indicated that thromboembolic complications of COVID-19 was the most likely cause of priapism [6–9, 11–20]. In one case of mild COVID-19 infection, the authors were unsure whether the onset of priapism was precipitated by COVID-19 infection or whether it was a complication of the hemodialysis that the patient received two years prior [10].

Number of episodes and duration of priapism

Eleven (73.3%) publications reported a single episode of priapism [6–14,16,17,19,20], while one (6.7%) publication reported two [11], three [18], and four [14] episodes of priapism. The reported duration of priapism ranged from 4 to 10 days.

Severity of COVID-19

COVID-19 pneumonia was diagnosed in 11 cases (73.3%) [6–9,11,13–17,20], of whom eight (53.3%) required mechanical ventilation [6,8,11,13–17], one (6.7%) required a combination of continuous positive airway pressure (CPAP) non-invasive ventilation and high-flow nasal canal (HFNC) oxygen [7], and two (13.3%) required HFNC oxygen only [9,20]. Of the four (26.7%) remaining cases, all were reported to have mild COVID-19 infection and did not require supplemental oxygen [10,12,18,19].

Cavernous blood gas

Among the 10 cases in which cavernous blood gas was recorded [6,8–14,17,18], the pH was <7.25 in eight (80.0%) [6,8–11,14,17,18], $PaCO_2$ was ≥60 mmHg in four (40.0%) [6,8,10,17], and PaO_2 was <30.1 mmHg in two (20.0%) cases [8,9].

D-dimer

Of the six cases in which D-dimer levels were reported [6,7,12,13,17,20], only one had a D-dimer level of <500 ng/ml [7]. The highest recorded D-dimer level was 5855 ng/ml [12], while the lowest recorded level was 428 ng/mL [7].

Follow-up of survivors

Of the nine (60.0%) cases in whom survival to hospital discharge was reported [6,9–12,16,18,19], follow-up findings were recorded in five cases. Of these, the first publication reported that the patient was having night-time erections at two-week follow-up [9]; the second publication reported that the patient had complete erectile dysfunction at three-month follow-up [12]; the third publication only mentioned that the patient had no further episodes of priapism at 30-day follow-up [11]; the fourth publication reported that the patient required a glandulectomy, resection of non-viable corpora cavernosa, and a ventral penile urethrostomy due to extensive glandular necrosis [16]; and the fifth publication reported that the patient did not complain about priapism recurrence while confirming spontaneous physiologic erections, at eight-week follow-up [18].

Treatment

Priapism was managed conservatively in two (13.3%) cases: one was a 67-year-old man who developed rapid clinical deterioration of COVID-19 pneumonia and died shortly after admission [7], and the other was a nine-year old boy who achieved spontaneous resolution of priapism an hour after hospital presentation [19]. Except for a single case that required a bilateral T-shunt (corpora-glandular) procedure [12], a case requiring a caverno-cancellous shunt and posthectomy [16], and another case that presented three days after the onset of priapism with established penile gangrene and required a partial penectomy [20], the remaining 10 (66.7%) cases responded to standard therapy that included a combination of ice pack application, cavernosal aspiration/irrigation, and intracavernosal sympathomimetic injections [6,8–11,13–15,17,18]. With regard to the treatment of concomitant COVID-19,

four cases required mechanical ventilation [6–8,13], while anticoagulation therapy was administered to eight (53.3%) [6,8,9,11,13,16–18].

Patient Outcomes

Of the 13 publications that reported on mortality outcomes, four (30.8%) died from COVID-19 related complications prior to hospital discharge [7,8,13,14].

DISCUSSION

Despite two years of the COVID-19 pandemic, the precise pathophysiology of the disease is not yet fully understood. COVID-19 enters the host cells via the S spike protein, which binds to angiotensin-converting enzyme 2 (ACE2). In addition to the direct injury caused by the virus itself, activation of the inflammatory and coagulation pathways, suppression of immune function, and downregulation of ACE2 also contribute to the pathophysiology of multi-organ pathology associated with COVID-19 infection [27,28].

Microangiopathic thrombosis is commonly observed in patients with COVID-19. A meta-analysis of 42 studies comprising 8271 patients found that 21% of patients infected with COVID-19 also developed venous thromboembolism (VTE), which was associated with a significantly higher likelihood of mortality (OR, 1.74; 95%CI 1.01 – 2.98; p = 0.04) [29].

Activation of the coagulation cascade secondary to COVID-19 infection is a complex sequence of events that is precipitated by viral-induced endothelial cell injury (Figure 2), resulting in activation of the intrinsic, extrinsic, and common pathways, thereby leading to the formation of blood clots. Additionally, SARS-CoV-2 induced thrombosis also leads to elevated levels of homocysteine, which further enhances the coagulation cascade [30].

Ischemic priapism is the most common form of priapism and results from occlusion of the venous outflow of the corpora cavernosa, leading to tissue ischemia. When aspirated, penile blood appears dark red, implying the presence of tissue hypoxia [31]. Penile cavernous blood gas analysis in the presence of ischemic priapism is commonly associated with a pH of <7.25, PCO_2 >60 mmHg, and PO_2 <30 mmHg [32]. In keeping with this, the penile cavernous blood pH was <7.25 in eight of the 10 included cases cavernous blood gas was recorded. Of the two cases in which the pH was >7.25, it was still below the normal range of 7.36 – 7.44 in one case [13], but within the normal range in the other article [12]. Notably,

the latter patient was a 34-year-old adult who presented with mild COVID-19 infection, a very high D-dimer level (5855 ng/mL), and refractory priapism that necessitated a bilateral T-shunt procedure.

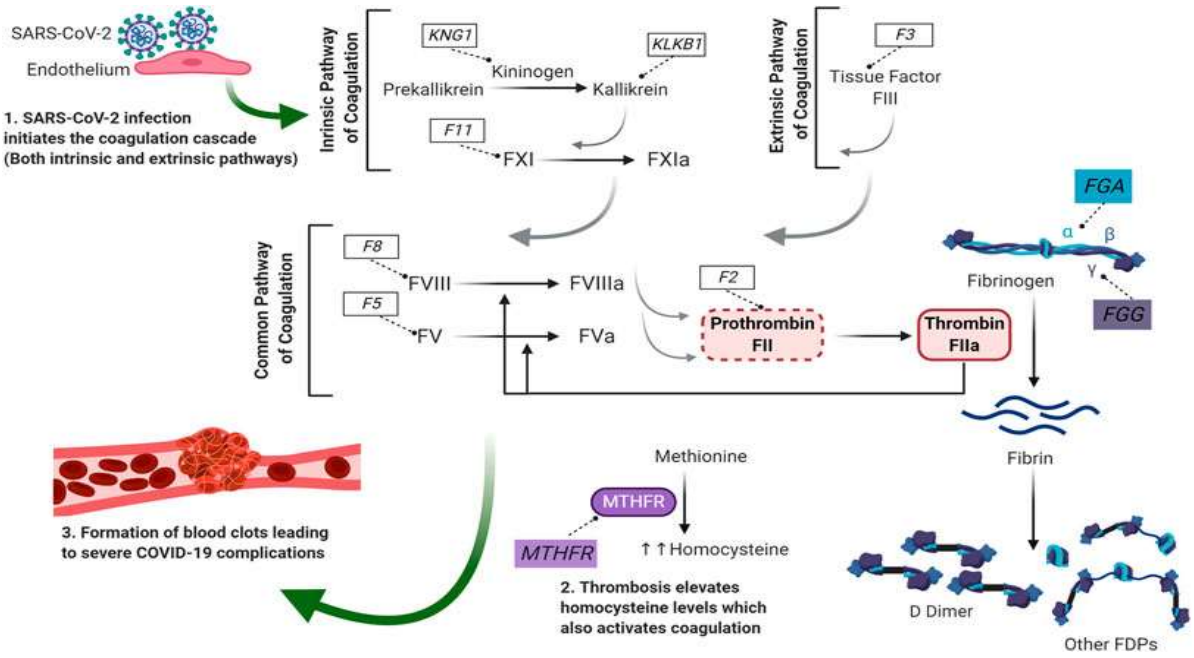

Figure 2: Illustration of SARS-CoV-2 (COVID-19) infection process in the human body. From "Prognostic Genetic Markers for Thrombosis in COVID-19 Patients: A focused Analysis on D-dimer, Homocysteine and Thromboembolism" by Abu-Farha M, Al-Sabah S, Hammad MM, Hebbar P, Channanath AM, John SE, Taher I, Almaeen A, Ghazy A, Mohammad A, Abubaker J, Arefanian H, Al-Mulla F and Thanaraj TA (2020). Front Pharmacol. 2020;11:e587451. Reused with permission.

Elevated D-dimer levels (>500 ng/ml) are a prominent feature of COVID-19 induced hypercoagulability [33]. Consistent with this, D-dimer levels were elevated in five of the six cases in which D- dimer levels were recorded [6,12,13,17]. This finding suggests that priapism could be listed as a thromboembolic complication of COVID-19. Thromboembolic complications of COVID-19 were postulated to be the most likely cause of priapism by the authors in 14 of the 15 included publications [6–13,15–19]. In the remaining publication, the authors indicated that priapism may have been secondary to hemodialysis rather than a complication of COVID-19 [10]. Haemodialysis has previously been described as a rare cause of priapism [34].

As COVID-19 has been associated with significantly higher mortality in the elderly [35], age may also play a role. Although the majority of patients in this study were aged between 60-70 years, four patients were below the age of 40 years [12,13,18,19], three of whom had mild COVID-19 infection [12,18,19], and two were in the pediatric age group [18,19]. This suggests that, although older patients with COVID-19 are more prone to developing priapism, it may also occur in younger patients.

Approximately three-quarters of the patients (73.3%) were diagnosed with COVID-19 pneumonia, more than half (53.3%) required mechanical ventilation, and one-third (30.8%) died prior to hospital discharge. This finding suggests that priapism may be an indicator of severe COVID-19. However, since COVID-19 infection was regarded as mild in 26.7% of patients who did not require supplemental oxygen, the relationship between priapism and severe COVID-19 is inconclusive.

An association between COVID-19 and other adverse effects in the male genital tract has also been reported [36]. Recently, Kresch et al. demonstrated the presence of COVID-19 virus particles in the penile tissue of two individuals with persistent severe dysfunction following recovery from COVID-19 respiratory symptoms [37]. Another study reported that sperm concentration was significantly lower in men previously infected with COVID-19 [38]. Hence, the findings of our systematic review shed further light on the impact of COVID-19 on sexual health in men.

The overall impact of COVID-19 has interrupted other urological surgical interventions during the pandemic, and an emphasis on giving priority to COVID-19 patients has been advocated. Since priapism is an established medical emergency, its management cannot be deferred [39,40].

An obvious limitation of this systematic review was that only 15 publications were eligible for inclusion, all of which were single-patient case reports. This is understandable, as the possible association between priapism and COVID-19 has only recently been described. Another limitation is that most studies did not report on laboratory tests pertaining to inflammatory biomarker levels or coagulation profiles; hence, we were unable to determine whether there was an association between these tests and the risk of developing priapism.

CONCLUSION

Priapism was more common in cases of severe COVID-19 infection than mild infection, suggesting a possible prognostic relationship between the two conditions. However, priapism has also been described in mild COVID-19 cases. Despite the described theoretical association between the two conditions, there is still a scarcity of data in international literature. Regardless of insufficient evidence outlining a significant association between COVID-19 and priapism, the management of priapism still constitutes a medical emergency that requires urgent conventional intervention. Further research is required to confirm the probable association between COVID-19 infection and priapism.

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RESEARCH PROTOCOL

A systematic review of COVID-19 and priapism

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China, in December 2019 and spread rapidly throughout the globe [1]. The typical presentation of COVID-19 includes a dry cough, sore throat, loss of smell, and fever. In severe cases patients may develop dyspnoea requiring hospitalization. Up to 50% of patients with dyspnoea will require intensive care unit admission, of which 46%-65% will develop respiratory failure and die. Evidence suggests that COVID-19 also affects other organ systems, including the haematological (venous thromboembolism), cardiovascular (myocarditis) and central nervous (encephalitis, Guillaine-Barre syndrome) systems [2].

The pathophysiology of COVID-19 includes activation of the inflammatory cascade as well as the coagulation pathway. Studies have outlined that patients with fatal COVID-19 had lower platelet counts and a higher D-dimer levels than survivors [3,4]. Guidelines recommend that D-dimer and other markers of coagulopathy should be monitored in hospitalised patients with COVID-19 associated coagulopathy [5].

COVID-19 enters the host cells via the S spike protein which binds to angiotensin-converting enzyme 2 (ACE2). In addition to the direct injury caused by the virus itself, activation of the inflammatory and coagulation pathways, suppression of immune function and downregulation of ACE2 also contribute to the pathophysiology of multiorgan pathology associated with COVID-19 infection [6,7]. Microangiopathic thrombosis has been a common observation in patients with COVID-19. A meta-analysis of 42 studies comprising 8271 patients found that 21% of patients infected with COVID-19 had also developed venous

thromboembolism (VTE), which was associated with a significantly higher likelihood of mortality (OR, 1.74; 95%CI 1.01 – 2.98; p = 0.04) [8].

The coagulation abnormalities could cause Priapism as one of the complications. Further, frequent findings suggest that low platelet counts, widespread thrombosis, and significantly elevated concentration of Lactate Dehydrogenase (LDH), which also occur in patients with COVID-19, may be linked to an increased prevalence of priapism [9].

Priapism as a possible thromboembolic complication of COVID-19 has recently been reported [10]. Priapism is a urological emergency defined as an abnormal condition of prolonged or constant penile erection of greater than 4 hours in duration. It can be categorised as either ischemic (low-flow or veno-occlusive) or non-ischemic (high-flow, or arterial) types. Priapism may be characterized by pain and may or may not be associated with sexual stimulation. Causes of priapism may be idiopathic or secondary to recreational drugs (e.g., cocaine), medications (e.g., antipsychotics, antidepressants), central nervous system pathology (e.g., spinal cord trauma, brain tumours), sickle cell disease, neoplasms (e.g., leukaemia), metabolic diseases (gout, diabetes mellitus), spider bites and scorpion bites [11,12].

Priapism can be categorised into two subtypes. Ischemic (low-flow or veno-occlusive) priapism is the most common form of priapism and results from occlusion of the venous outflow of the corpora cavernosa, leading to tissue ischemia. The penile blood, when aspirated, appears dark red implying the presence of tissue hypoxia[13]. Penile cavernous blood gas analysis is commonly associated with a pH <7.25, $PC0_2$ >60 mmHg and $P0_2$ <30 mmHg. Non-ischemic (high-flow, or arterial) priapism is most commonly as a result of perineal trauma. Penile blood, when aspirated, is oxygenated, and appears bright red. The penile cavernous blood gas analysis is commonly associated with a pH 7.36 – 7.44, $PC0_2$ <40 mmHg and $P0_2$ >90 mmHg [13,14].

Causes of priapism may be idiopathic or secondary to recreational drugs (e.g., cocaine), various medications, central nervous system pathology (e.g., spinal cord trauma, brain tumours), sickle cell disease, neoplasms (e.g., leukaemia), metabolic diseases (gout, diabetes mellitus), spider bites and scorpion bites [11,12]. Medications known to cause priapism include vasoactive erectile agents, antianxiety agents, anticoagulants,

antidepressants, antipsychotics and antihypertensives [15]. Similarly, COVID-19 may potentially also cause of priapism [10]

Current evidence suggests that COVID-19 has unprecedented effects on the male reproductive system and sexual health in general [16]. There is a paucity of data pertaining to priapism with co-exiting COVID-19. It is also uncertain whether medications used to treat COVID-19 may also cause priapism.

Priapism should be promptly managed to reduce the risk of long-term complications. If treatment is not initiated timeously, permanent damage to the corpora cavernosa can occur, which may lead to ischaemia, necrosis, and erectile dysfunction. Emergent treatment for priapism includes ice pack application, cavernosal aspiration, and intracavernous injections of sympathomimetic agents [17]. This treatment guideline may need to be reviewed should there be an association with COVID-19.

Systematic reviews have been proven to be a highly effective method of research which has the capability of generating rigorous evidence. The systematic review study design is ranked as one of the best evidence in the hierarchy of research evidence, particularly in the healthcare sector [18]. In this study, The researcher will perform a systematic review of cases of priapism that were associated with COVID-19 and reported in the literature thus far. This is to increase the understanding and knowledge of the potential association between the two entities. Increased awareness in these cases would aid clinicians in initiating early and appropriate interventions. A preliminary review of the PubMed database identified at least 11 related manuscripts, thus suggestive of sufficient studies to conduct a systematic review.

STUDY AIM

To conduct a systematic review of the literature pertaining to priapism associated with COVID-19

STUDY OBJECTIVES

1. To determine the overall number of published cases pertaining to priapism and co-existing COVID-19.
2. To describe the clinical characteristics of patients with priapism and co-existing COVID-19.

3. To determine the disease severity and outcomes in patients with priapism and co-existing COVID-19.

METHODOLOGY

Study design

This study will be a systematic review that will be performed in accordance with the PRISMA statement. The PRISMA statement is a framework of components that should be included in a systematic review to ensure transparency and reproducibility (Appendix A).

Search strategy

Prior to commencement of the search, a registration application to the Prospective Register of Systematic Reviews (PROSPERO) will be processed. The following electronic databases will be searched Google Scholar, Scopus, Embase, Web of Science, PubMed, Cumulative Index to Nursing and Allied Health Literature (CIANHL), Global Index Medicus and the Cochrane Database of Systematic Reviews. The following search terms will be used: “COVID-19”, “priapism”, “coronavirus”, “SARS CoV-2” and “priapism”.

Study population

Males with a history of priapism and current or recent COVID-19.

Study selection

After excluding duplicate and irrelevant title, abstracts of the remaining articles will be analysed and screened for inclusion/exclusion criteria. The full text of all remaining articles will be assessed for eligibility. All necessary attempts to source full-text articles will be made utilizing the services of the university librarian. The final search strategy will be described and presented in the format of a flow diagram.

Inclusion criteria

- All cases of priapism with current or recent COVID-19
- Studies that are clinical publications
- Studies that are limited to human subjects
- Availability of full publication text

Risk of bias

The methodological quality of included studies will be assessed using the appropriate tool based on the type of studies identified (e.g., appropriate CASP checklist [19] or the tool proposed by Murad et al., for assessing the quality of case reports [20]).

Data extraction

Data will be extracted from the pool of eligible studies using the text articles and entered into a data collection sheet (Appendix B). An attempt will be made to collect the following data: first author, study design and date of publication, country of study origin, age of patients, final diagnosis, requirement for respiratory support pertaining to severity of COVID-19, number of episodes and duration of priapism, cavernosal blood gas findings, D-dimer levels, management of priapism, patient outcomes and author's conclusions (Appendix B).

DATA ANALYSIS

Since most publications are likely to be case reports, summative statistics and a narrative synthesis approach was primarily utilised to describe the findings. If appropriate, mean and/or median data will be calculated.

ETHICAL CONSIDERATIONS

Since this study will be a systematic review of published articles an application for an ethics waiver will be requested from the University of Witwatersrand Human Research Ethics Committee. There will be no active human participants in the study.

LIMITATIONS

Since COVID-19 emerged within the past one and a half years, there are currently a handful of publications relating to the topic, hence, data availability may be limited.

FUNDING

The research project will be self-funded with an estimated cost as follows:
Stationery and printing: R1000
Travel expenses & phone calls: R1000
Approximate total cost: R2000)

TIMING OF THE RESEARCH

	May 2021	June 2021	July 2021	Aug 2021	Sep 2021	Oct 2021	Nov 2021	Dec 2021	Jan 2022	Feb 2022
Literature review										
Protocol preparation										
Protocol submission										
Ethics clearance										
Data collection										
Data analysis										
Writing-up										
Submission										

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APPENDIX A: PRISMA Checklist for reporting a systematic review

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4		
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information, including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8		
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in a systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe the data extraction method from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used to assess the risk of bias of individual studies (including specification of whether this was done at the study or outcome level) and how this information is used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, the difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of the risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on the risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of the risk of bias across studies (see Item 15).	
Additional analysis	23	If done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]), give results of additional analyses.	
DISCUSSION			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each primary outcome; consider their relevance to critical groups (e.g., healthcare providers, users, and policymakers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias) and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	
FUNDING			
Funding	27	Describe funding sources for the systematic review and other support (e.g., the supply of data), the role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. Used with permission.

APPENDIX B: Data collection sheet

1. First author, study design and date of publication : _____
2. Country of origin: _____
3. Age of patient: _____
4. Diagnosis: _____
5. Number of episodes and duration of priapism:_____
6. Cavernosal blood gas analysis
    A. pH:_____
    B. PCO2(mmHg):_____
    C. PO2(mmHg):_____
7. D-dimer:_____
8. Management of priapism: _____

_____

9. Patient outcomes:_____

_____

10. Author's conclusion:_____

_____

ETHICS WAIVER CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Innovation)

TO: Mr/Professor DM/A Malinga/Adam
School: Clinical Medicine
Department: Medicine
Division: Emergency Medicine
Medical School
University
E-mail: dominic.malinga6@gmail.com

CC: Supervisor: Professor A Laher <abdullalaher@msn.com>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 20/12/2021

REF: *R14/49*

PROTOCOL NO: W-CBP-211220-01 (This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)

PROJECT TITLE: *A systemic review of COVID-19 and Priapism*

Please find attached the Ethics Waiver Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/ClearScanWaiver.wps

TURN-IT-IN REPORT

D.M Malinga Final draft 1.11-4.docx

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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4	S.A. Azer. "COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics", New Microbes and New Infections, 2020 Publication	<1%
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