Detection of SARS-CoV-2 in semen samples: a scoping review

Detecção de SARS-CoV-2 em amostras de sêmen: revisão de escopo

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ABSTRACT

Background: many doubts about the infection of SARS-CoV-2 were raised, such as sexual transmission, sterility, and changes in fertility procedures; however, information is not clearly stated and organized. **Purpose:** to review and summarize scientific evidence on detection of SARS-CoV-2 in semen samples of Covid-19 patients. **Methods:** literature search in PubMed, Web of Science, Scopus, Medline and Embase databases, and followed Scoping Review protocol defined by Joanna Briggs Institute (JBI) after the guiding question "Is it possible to detect SARS-CoV-2 in the semen of adult patients with a confirmed diagnosis of Covid-19?" **Results:** 287 studies were identified, and, after discerning analysis, 9 studies published in the English language were selected. Three researchers analyzed the studies for SARS-CoV-2 presence in the seminal fluid, patients' severity, days since the onset of disease, diagnosis confirmation, semen collection method, viral analysis method, and sample numbers. **Conclusions:** it was not possible to find strong evidence to confirm the presence or absence of Covid-19 in the semen of adult patients. New studies on the subject should be better designed, taking into account the possible anatomical and functional conditions and changes of the male reproductive system during and after the infection by SARS-CoV-2.

Keywords: Semen, SARS virus, Infections, Detection.

RESUMO

Objetivo: Revisar e resumir as evidências científicas em pesquisas realizadas para detectar a presença de SARS-CoV-2 em amostras de sêmen de pacientes com COVID-19. **Métodos:** A pesquisa de literatura foi conduzida nas bases de dados PubMed, Web of Science, Scopus, Medline e Embase. Seguiu o protocolo de revisão de escopo definido por Joanna Briggs Institute (JBI) e baseou-se na pergunta norteadora "É possível detectar SARS-CoV-2 no sêmen de pacientes adultos com diagnóstico confirmado de Covid-19?". **Resultados:** 287 estudos foram identificados, 9 estudos publicados em língua inglesa foram selecionados após análise minuciosa. Três pesquisadores analisaram os estudos em busca de presença de SARS-CoV-2 no fluído seminal, gravidade do paciente, dias desde o início da doença, confirmação diagnóstica, método de coleta de sêmen, método de análise viral e número de amostras. **Conclusões:** Não foi possível identificar fortes evidências para confirmar a presença ou ausência de COVID-19 no sêmen de pacientes adultos. Novos estudos sobre o tema devem ser melhor projetados, levando-se em conta as possíveis condições anatômicas e funcionais e mudanças no sistema reprodutor masculino durante e após a infecção por SARS-CoV-2.

Palavras-Chave: Sêmen, SARS vírus, Infecções, Detecção.

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INTRODUCTION

The World Health Organization (WHO) declared Covid-19 as a pandemic threat and, in response, the Brazilian government - federal, state and municipal - decreed rules of restrictions and social isolation in order to hold the uncontrolled spread of the virus and health system overloading[1,2]. Those measures, in addition to exponential availability of access to information, created a general sense of fear of contracting Covid-19 and, therefore, drastically dropped the number of elective procedures and emergency attendance in cases without respiratory symptoms, leading to increased morbidity and mortality, and the consequent need of updating medical practice[3,4].

Previously to the COVID-19 pandemic, two coronaviruses epidemics, SARS-Cov and MERS-CoV (Middle East Respiratory Syndrome), arose in 2002 and 2012, respectively, but with much less spread than COVID-19[5]. A study with six patients suggested that SARS-CoV infection caused severe orchitis and was associated with destruction of germ cells, leading to a possible reproductive system impairment[6].

Little is known about the physiopathological mechanisms of SARS-CoV-2 and its possible sequels after the resolution of the infection[7]. Similarly to SARS-CoV, in order to invade the cell, SARS-CoV-2 uses the protease TMPRSS2 (Transmembrane Protease Serine 2) for spike protein priming, and, afterwards, connects to angiotensin-converting enzyme 2 (ACE2). In this way, ACE2 and TMPRSS2 are key factors for the onset of the infection by SARS-CoV-2[8,9]. Recently, the presence of ACE2 and TMPRSS2 was demonstrated to be found in the male reproductive system, with a higher concentration of ACE2 in spermatogonium, Leydig, and Sertoli cells, while TMPRSS2 was found in high concentrations in spermatogonia and spermatids cells. These findings suggest a strong potential for the male reproductive system, mainly the testis, as an aim for SARS-CoV-2[10,11].

Epididymitis has been described in a cross-sectional study of adult men hospitalized for COVID-19 without scrotal complaints. Although orchitis was not found, 42.3% of men had ultrasound positive for epididymitis. No information was reported on seminal fluid positiveness for SARS-CoV-2[12].

Up to now, there are no reports of sexual transmission[13,14].

In this context, many doubts about the infection of SARS-CoV-2 were raised, such as sexual transmission, sterility, and changes in fertility, however, information is not clearly stated and organized. Therefore, the objective of this Scoping Review is to collect and summarize scientific evidence addressing the presence of SARS-CoV-2 in semen samples of COVID-19 patients in order to improve understanding of viral behavior and its consequences in the male reproductive system, as well as to guide diagnosis and treatment protocols for SARS-CoV-2 infection.

METHODS

A literature review was conducted according to what was proposed by The Joanna Briggs Institute (JBI) on Scoping Reviews[15]. All search and publications access was completed in July 2020.

The guiding question "Is it possible to detect SARS-CoV-2 in the semen of adult patients with a confirmed diagnosis of Covid-19?" was defined for the selection and search of the studies. This question was built through the PCC strategy, which consists of a mnemonic for the words: Population, Concept and Context. In this way, "P" was defined as adult patients, "C" as viral detection in semen samples, and the last "C" as Covid-19.

For the literature search, the following descriptors, its synonyms and keywords were used: "adult patients", "semen", and "SARS-CoV-2". The Boolean operators AND, NOT and OR were used between descriptors. Controlled descriptors were: "Adult Patient(s)", "Semen", and "SARS-CoV-2". Not controlled descriptors were "Adult(s)", "Patient(s)", "Seminal Analysis", "Sperm", "Detection", "Covid-19", and "Coronavirus(es)".

Databases accessed were PubMed, Web of Science, Scopus, Medline, and Embase. Inclusion criteria were English language, indexed sources, and primary studies and reviews.

Insightful reading of title, abstract and keywords was performed in order to select the articles according to inclusion and exclusion criteria formerly established. On the occasions that the title, abstract and keywords were not sufficient, the full text was also analyzed. All articles were called study, enumerated in chronological order, and evaluated by three researchers. Recommendations by JBI were adapted for the study singularities and used for data extraction. This article followed Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guideline and checklist developed under EQUADOR (Enhancing the QUAlity and Transparency Of health Research) Network guidance[16].

RESULTS

Following a database search, 287 potential studies were identified. After reading the title, abstract and keywords, 72 studies were selected, and 42 were excluded for being also found in different databases. The full text of the 30 remaining articles were read, and 21 were excluded for not answering the guiding question. Using the described methodology, a literature search found 9 articles that met all criteria. This process is shown in Figure 1.

Among the 9 studies analyzed, most of the studies were observational studies, while the other two were review articles. Most studies were conducted in China, being three studies exclusively in the country[17,18,19] and two in association with the USA[20,21]. Two studies were carried out in Italy[22,23], one in Germany[24] and one in India[25]. The first study was published on 10 April 2020[20] and the last study on 29 July 2020[19]. May was the month with the largest number of publications – 5 – on the topic[17,21,23-25], as shown in Figure 2.

Three researchers analyzed all articles regarding SARS-CoV-2 presence in the seminal fluid. Patients' severity, days since the onset of disease, diagnosis confirmation, semen collection method, viral analysis method, and sample numbers were also taken into consideration when analyzing the studies, as shown in Figures 3–5.

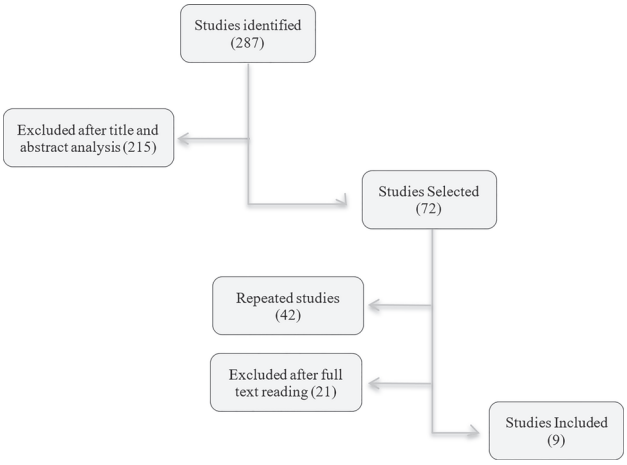

Figure 1. Process of inclusion

Figure 2. Information of authorship and jornal of publication

ID	Date	Country	Authors	Title	Journal
17	10-abr.	China, USA	F. Pan, et al.	No evidence of severe acute respiratory syndrome-coronavirus 2 in semen of males recovering from coronavirus disease 2019	Fertility and Sterility
19	16-abr.	Italy	D Paoli, et al	Study of SARSCoV2 in semen and urine samples of a volunteer with positive nasopharyngeal swab	Journal of Endocrinological Investigation
14	7-mai.	China	D. Li et al.	Clinical Characteristics and Results of Semen Tests Among Men With Coronavirus Disease 2019	JAMA Network Open
22	11-mai.	India	R. Vishvkarma, et al.	Could SARS-Cov-2 affect male infertility?	Andrologia: First International Journal of Andrology
18	26-mai.	USA, China	M. Yang, et al.	Pathological Findings in the Testes of COVID-19 Patients: Clinical Implications	European Urology Focus
20	27-mai.	Italy	G Corona, et al.	SARSCoV2 infection, male fertility and sperm cryopreservation: a position statement of the Italian Society of Andrology and Sexual Medicine (SIAMS) (Società Italiana di Andrologia e Medicina della Sessualità)	Journal of Endocrinological Investigation
21	29-mai.	Germany	N. Holtmann et al.	Assessment of SARS-CoV-2 in human semen - a cohort study	Fertility and sterility
15	17-jun.	China	L. Ma, et al.	Evaluation of sex-related hormones and semen characteristics in reproductive-aged male COVID-19 patients	Journal of Medical Virology
16	29-jul.	China	L. Guo et al.	Absence of SARS-CoV-2 in Semen of a COVID-19 Patient Cohort	American Society of Andrology and European Academy of Andrology

Figure 3. Information of objectives and methodology

ID	Objective	Methodology
17	To describe detection of severe acute respiratory syndrome (SARS)–coronavirus 2 (CoV-2) in seminal fluid of patients recovering from coronavirus disease 2019 (COVID-19) and to describe the expression profile of angiotensin-converting enzyme 2 (ACE2) and Transmembrane Serine Protease 2 (TMPRSS2) within the testicle.	Observational, cross-sectional study
19	To evaluate the possible presence of SARS-CoV-2 in semen and urine samples of a volunteer with confirmed Covid-19	Observational Case Report Study
14	Identify the presence of SARS-CoV-2 in the semen of patients with COVID-19 and in the recovering period	Cohort Study
22	Evaluate the possibility of an impact of SARS-CoV-2 infection on male fertility.	Review Article
18	To determine the pathological changes and whether SARS-CoV-2 can be detected in the testes of deceased COVID-19 patients.	Cross-sectional Descriptive
20	To summarize available evidence providing an official position statement of the Italian Society of Andrology and Sexual Medicine (SIAMS)	Review Article
21	To determine any possible implications of COVID-19 on male semen parameters; and analyze the semen for any presence of SARSCoV-2 RNA in recovered men and men with an active COVID-19 infection	Cohort Study
15	Collect semen samples from patients for SARS-Cov-2 virus and semen characteristics analysis. Moreover, compare sex-related hormones between reproductive-aged male COVID-19 patients and age-matched uninfected men.	Observational, cross-sectional study
16	To identify SARS-CoV-2 RNA in seminal plasma and determine semen characteristics from male patients in the acute and recovery phases of infection.	Cohort Study

Figure 4. Description of the patients

ID	Collection Technique	Viral confirmation technique	Seminal analysis technique	Results and Conclusions
13	Masturbation	Quantitative RT-PCR of pharyngeal swab sample.	RT-PCR	SARS–CoV-2 was not detected in the semen of recovering patients. ACE2–mediated viral entry of SARS–CoV-2 into human testis cells is unlikely to occur.
14	Masturbation	RT-PCR of pharyngeal swabs	RT-PCR	Semen and urine samples search for SARS-CoV-2 RNA was negative.
15	Masturbation	RT-PCR of nasal and pharyngeal swabs	RT-PCR	SARS-CoV-2 was detected in the semen of 6 patients with Covid-19. SARS-CoV-2 may still be detected in the semen of recovering patients
16	-	-	-	The presence of ACE2 on testicular cells and the impact of previous coronaviruses on testes suggest that SARS-CoV-2 is highly likely to affect testicular tissue, semen parameters and male fertility.
17	Incisional biopsy	Positive nucleic acid testing of oropharyngeal swabs or bronchoalveolar lavage fluid, radiological features of viral pneumonia, and clinical symptomatology	RT-PCR	The mean number of Leydig cells in Covid-19 testes was significantly lower than in the control group. Viral RNA was detected in 1 out of 12 cases.
18	-	-	-	Available data do not support the presence of SARS-CoV-2 in plasma seminal fluid of infected subjects.
19	Masturbation	Positive swab result (Eswab collection kit; Copan) or positive Immunoglobulin IgA and IgG antibodies	Quantitative RT-PCR	No evidence of SARS-CoV-2 shedding in semen of recovered men or men with acute Covid-19
20	Group 1: Routine medical Purpose (blood) Group 2: Fertility Evaluation Group 3: Masturbation	Quantitative RT-PCR of pharyngeal swab sample or by serum virus antibody (IgM or IgG) detection using the colloidal gold test.	Quantitative RT-PCR	No SARS-CoV-2 was found in semen specimens. 8 out of 12 patients had normal semen quality. A higher serum luteinizing hormone (LH) and a lower ratio of testosterone (T) to LH were observed in the COVID-19 group.
21	Masturbation	Quantitative RT-PCR of pharyngeal swab	RT-PCR	All patients tested negative for SARS-CoV-2 RNA in semen specimens which indicates the unlikely possibility of sexual transmission through semen

Figure 5. Main outcomes of the articles

ID	Patients' age range	Nº of patients	Nº of samples	Patients' severity	Disease period
17	18 - 57 years (Median: 37 years)	34	34	Mild, in general. (All recovering)	Median: 31 days (table is given)
19	31 years old	1	2	Low risk	15 days since onset of symptoms
14	15 years and older	50	38	Unquoted	23 (60.5%) patients achieved clinical recovery and 15 (39.5%) were at the acute stage of infection
22	Review article				
18	42 – 87 years old	12	12	Postmortem	23 - 75 days since onset of symptoms
20	Review article				
21	Recovery patients: 42.2 ± 9.9 Control group: 33.4 ± 13.1	34	34	Control group: 14 Mild type: 14 Moderate type: 4	Already recovered from SARS-CoV-2 virus infection. Control group were not affected
15	Group 1: (119 men): 20 - 49 years (median: 39 years)	Semen (12) / Blood (119 patients and 273 control)	Semen (12) / Blood (119 patients and 273 control)	Group 1 (119 Men): Mild (3 - 2.52%), Moderate (100 - 84.03%), Severe (14 - 11.76%) and Critical (2 - 1,68%)	Group 1: Admission to hospital (from 5 to 31 March 2020), Last discharge (15 April)
	Group 2: (273 men): 24 -49 years (median: 39 years)			Group 2: control group	Group 2: control group
	Group 3: (12 men): 25 - 46 years (median: 31.5 years)			Group 3 (12 men): Mild (1 - 8.33%), Moderate (11 - 91.7%)	Group 3: 56 days to 109 days (with a median of 78.5 days)
16	20 – 62 years old	23	21	Mild type: 18 (78%) Moderate type: 5 (22%)	Recovery phase

DISCUSSION

It is important to highlight that countries faced the Covid-19 pandemic with many cases and deaths registered. It is presumed that its institutions have had contact with the virus for a longer time, and have also been able to study, ahead of others, SARS-CoV-2 consequences in the human organism, such as the search for the virus in the semen of infected patients. These findings explain that the first article published was developed in China, and the majority of the other studies were also developed by Chinese scientists[17-21].

Other countries followed this trend and began to promote studies on this subject as the number of confirmed cases grew. The studies carried out in Italy were published in April and May[22,23], a few days after the peak of weekly confirmed cases in the country. A similar situation occurred in Germany[24].

India and the USA are slightly different cases, because, until the date of the present study, they still had high numbers of confirmed cases and deaths per day. The studies conducted jointly with the USA were not carried out in its territory, but in China[20,21].

Most studies did not find viral SARS-CoV-2 RNA in semen samples[18-20,22,24]. Two studies found SARS-CoV-2 RNA in semen samples[15,19], however, results are still controversial.

The first one[17] was conducted in all male patients from a Municipal Hospital in Shangqiu, China. Six out of 38 patients who provided semen samples by masturbation had a positive result for viral RNA by Reverse Transcription Polymerase Chain Reaction (RT-PCR), but precautions for contamination were not defined. Masturbation is hardly a sterile procedure, and samples could be contaminated by exhaled droplets[22]. Positive patients ranged from 20s to 50s years old, and from 6 to 16 days since disease onset.

The second study[21] was developed in 12 postmortem patients. Testis samples were collected by incisional biopsy, and analyzed by light and electron microscopy, immunohistochemistry for lymphocytic and histiocytic markers and RT-PCR for viral RNA. Most of the samples identified moderate to severe tissue injury, but only one of them found SARS-CoV-2 RNA by RT-PCR method.

This specific patient had a high viral load in all other tissues analyzed (lung, kidney and spleen), which could have happened due to blood extravasation caused by tissue injury and disseminated intravascular coagulation[24], thus misinterpreting the results since the RNA detected could be present in the extravasated blood instead of in the testis – viral RNA was also positive in the blood samples. In spite of that, the objective of this study was to determine pathological changes in the testis only, not considering other reproductive organs.

Most studies used the gold-standard method, RT-PCR assay of naso-pharyngeal swabs, for COVID-19 diagnosis[17-20,22,24]. Ling Ma et al (2020)[18] also used serum virus antibody IgM and IgG detection using the colloidal gold-test. One study used the positive nucleic acid testing of swabs or bronchoalveolar lavage fluid[21]. One study used positive swab results (Eswab collection kit) or positive Immunoglobulin IgA and IgG antibodies[24]. Other two studies were review articles[23,25].

RT-PCR is recommended by WHO because it is the most common, effective and straightforward diagnostic method[27]. The use of the gold standard method for virus identification is essential to guarantee good quality and standardized studies carried out in different centers.

The two most frequent severity states of patients, when the data was presented, were mild and moderate, probably, given that masturbation, a non-passive method, was the main technique of semen collection, and, probably, individuals with high severity were excluded by not being able to provide samples. Nevertheless, the patient severity was unquoted in both studies that have found SARS-Cov-2-RNA in semen samples[17,21]. Thus, no linkage between severity state and presence or absence or SARS-Cov-2-RNA in semen was related.

Except for the postmortem study that used incisional biopsy to collect samples, masturbation was the chosen method for semen collection. As discussed earlier, the sterility condition of this technique is uncertain, and semen contamination by droplets has to be considered[22]. For the SARS-Cov-2 presence assessment in semen samples, the RT-PCR method was used in all studies since it corresponds to the gold standard test.

In spite of that, studies suggest that many factors could influence viral loads, such as patient age, comorbidities, and time since the beginning of the disease[28]. After the first week of symptoms onset, the viral load starts to gradually decrease, and, succeeding seroconversion, evidenced by immunoglobulin serum positivity, viral RNA is undetected[29], therefore disturbing results of viral RNA search in all infected fluid and tissue samples.

The semen studies were conducted with small numbers of patients (range, 1 to 50 patients), and, disregarding some patients whose semen samples were not possible to include, only a unique semen sample was available for each individual, corresponding to a range between 12 and 38 samples among the considered studies. These sample sizes seem insufficient to provide enough information for reaching clear conclusions.

CONCLUSION

According to the studies analyzed, it was not possible to find strong evidence to confirm the presence or absence of Covid-19 in the semen of adult patients, since important doubts were identified in the articles with positive results. However, this review has some limiting factors: only five databases were searched, and new studies on the theme are constantly being published, facts that might exclude relevant outcomes from this review. Therefore, novel studies on the subject should be better designed to consider the possible anatomical and functional conditions and changes of the male reproductive system during and after the infection by SARS-CoV-2.

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Author Contributions
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