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A Call for Quality: Substandard Research in Male Sexual and Reproductive Medicine During the COVID-19 Pandemic



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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has had a tremendous global economic impact and profound, long-lasting impact on people's lives. Since December 2019, when the first case of a severe atypical pneumonia caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was described from Wuhan, China, COVID-19 has caused over 4 million deaths worldwide (<https://coronavirus.jhu.edu/>). The medical community responded quickly, addressing key knowledge gaps about COVID-19 and ultimately developing highly effective vaccines.

Medical journals have been flooded with COVID-19 related submissions and many have provided rapid review of manuscripts and open access publications to further the timely dissemination of key findings. There are over 160,000 published articles on COVID-19, but less than one third are substantiated by evidence that would result in a change in clinical practice.^{1, 2} A majority of clinical studies registered on clinicaltrials.gov are not designed to produce Oxford Centre for Evidence Based Medicine (OCEBM) level 2 evidence.² A quarter of these publications are housed on pre-print servers and often do not undergo robust peer review.³ Over 114 papers related to COVID-19 have been retracted for reasons including methodological concerns, misinterpreted data and inappropriate conclusions, authorships concerns, research participant privacy concerns, and even data falsification (<https://www.legifrance.gouv.fr/loda/id/JORFTEXT000000886460/>). This number likely underestimates the true number of papers that warrant retraction. Even prominent, high impact medical journals have published research with high risk of bias and low reporting quality related to COVID-19.⁴ Most notably, two papers in the

New England Journal of Medicine and *The Lancet* evaluating medications for the treatment of COVID-19 derived from a large multinational database of hospital records were retracted due to concerns regarding data integrity.⁵⁻⁷ However, subsequent publications have relied on retracted work, with these two specific publications being cited over 100 times in peer reviewed journals, such as *Proceedings of the National Academy of Sciences*, even after these articles were retracted.⁸

Though we recognize that there is a balance between disseminating new research quickly—especially during a novel pandemic—with the need for rigorous studies and thorough peer review, substandard research has the potential to lead to misinformation and mistrust. Below we discuss several examples from the male sexual and reproductive medicine field that have been greatly overstated and taken out of context. This situation emphasizes the need for adequate description of limitations and biases of published work and improved science communication. Here, we present a call to raise the bar for investigations of COVID-19 and the SARS-CoV-2 virus and prioritize high quality scientific work with meaningful implications as we seek to move the field forward.

Substandard Research on COVID-19 in Male Sexual and Reproductive Medicine

Research topics in male sexual and reproductive medicine are commonly highlighted in the media, where substandard research is vulnerable to misinterpretation in part because complex topics are routinely dichotomized. One of the most notable headlines regarding substandard research in male sexual and reproductive medicine, were the series of retractions by *BJU International* due to inappropriate statistical analysis and data integrity in 2009 to 2010 (<https://retractionwatch.com/2015/04/24/urology-researcher-in-iran-up-to-six-retractions/>). Each of these studies had been cited over a dozen times. These retractions were damaging to the journal and the publisher, but more importantly demonstrated misrepresentation of research topics within male sexual and reproductive medicine for which there is limited literature.

We performed a PubMed/Medline search for publications between December 2019 and June 2021 using the criteria of “(SARS-CoV-2 OR COVID-19) and (erectile dysfunction or sexual transmission or semen or male infertility or semen analysis or testosterone).” A total of 395 articles were identified (Figure 1). Nearly a quarter represented qualitative review papers or expert opinion. A majority of the published work consisted of small observational cohort studies, case-control studies, or case series

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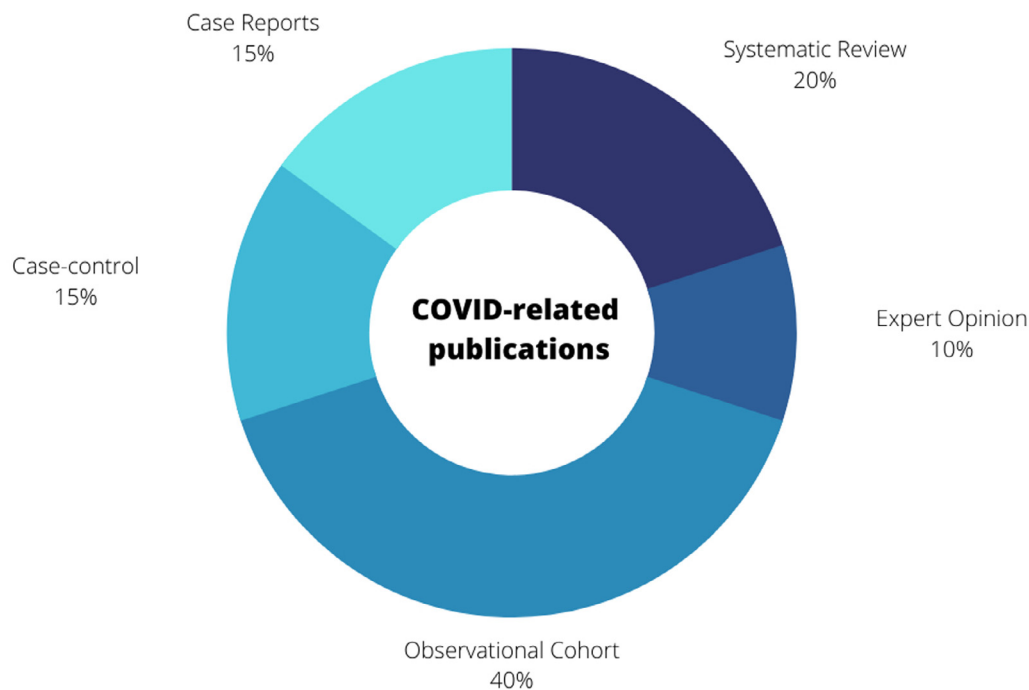


Figure 1. COVID-19 related publications in Male Sexual and Reproductive Medicine between December, 2019-June, 2021 (n = 395).

with high risk of biases and low reporting quality. The most common research topics have included SARS-CoV-2 in the seminal fluid, impact of COVID-19 on semen quality, the association between male androgens and COVID-19 and SARS-CoV-2 tropism for the male reproductive tract. There are currently no articles in male sexual and reproductive medicine that have been retracted or have an expression of concern (<https://retractionwatch.com/retracted-coronavirus-covid-19-papers/>).

However, there are several articles with a high risk of biases that have been highly sensationalized and even misinterpreted. We highlight several articles below that have received overwhelming media attention including over 50,000 news articles on COVID-19 and male infertility and over 100,000 articles on COVID-19 and erectile dysfunction from a web search.

One example is an early autopsy study of two men who died with COVID-19; one of the two men were noted to have testicular atrophy.⁹ Despite the small sample size and inability to control for confounding, subsequent post-mortem case series have relied on this citation to support the likelihood that SARS-CoV-2 may involve the testicle. However, these subsequent small post-mortem case series do not address any clinical implications of such findings.¹⁰⁻¹²

Early in the pandemic, there was tremendous interest in the possibility of SARS-CoV-2 in the semen. A research letter from a group at the Shangqiu Municipal Hospital suggested presence of SARS-CoV-2 in semen samples of 6 of 38 patients.¹³ The authors express a short statement regarding limitations of a small sample size and short follow-up, but do not offer the possibility of contamination of the semen samples with SARS-CoV-2 from other sources such as respiratory droplets. Other studies have been unable to confirm the presence of SARS-CoV-2 in the semen.¹⁴

More recently, a group studied the involvement of SARS-CoV-2 in the penile corpora cavernosa with a potential association with endothelial dysfunction resulting in erectile dysfunction.¹⁵ This series included 2 men with a prior history of hospitalization for COVID-19 and 2 men without history of COVID-19 hospitalization undergoing a surgical penile implant for ED. Both men with prior COVID-19 hospitalization had preexisting risk factors for ED including a history of radical prostatectomy and coronary artery disease, respectively. The authors offer two hypotheses for a potential role of SARS-CoV-2 in ED including systemic endothelial dysfunction and a direct role of SARS-CoV-2 in the corpora cavernosa itself contributing to endothelial dysfunction. However, based on the high risk of bias, these hypotheses are insufficiently supported by the findings of the study.

Ramifications of Publishing Substandard Research

Initially, very small cohort studies also helped clinically characterize unique patient populations affected by COVID-19. These research efforts were essential in providing important data where no data previously existed but should not represent the bar to which research should aspire for high quality investigation of COVID-19 and the SARS-CoV-2 virus. We must acknowledge the potential harms of continued emphasis on substandard research and disseminating the findings of methodologically flawed investigations, including sowing confusion, spreading inaccurate information, and leaving the healthcare community and lay public misinformed. All of these sequelae having wide ranging repercussions. Here, we present a call to arms for the research community at large. We urge researchers to prioritize the conduct of scholarly investigation that has high scientific value with meaningful implications, to maintain the principles of

scientific integrity and to set an expectation that clinical research should move the field forward.

Publishing substandard research has ramifications for patients, clinicians, researchers, research funders, research regulators, research publishers, policymakers, and lay people. Authors must meet the criteria for authorship and share responsibility for the data and conclusions in published research findings. Substandard research can lead to unnecessary waste of valuable research resources, funding, and time. Manuscript retraction or expression of concern is much more serious and can reflect negatively on the authors, the institution, and the medical journal. Arguably the most important ramification of publishing substandard research during the pandemic is undermining the public health response to COVID-19. Many individuals obtain information from the mainstream media and social media that may overstate or misinterpret research findings.¹⁶ During the pandemic, clinicians and researchers were able to rapidly communicate and disseminate research findings to a variety of stakeholders using social media as the COVID-19 pandemic evolved.¹⁷ However, sharing of preliminary data with a high risk of bias can promote dissemination of misleading information.¹⁸ Although media coverage can bring renown to investigators and their institutions, these entities must consider that other professionals and the general public get health information through these outlets and must correct any misinterpretation or misinformation, regardless of the perceived personal or institutional gain brought by the exposure. Further, the authors must continually contextualize their study and describe it within its limitations to limit erroneous conclusions.

Maintaining High Quality Research and Publication Standards

With a better understanding of the diagnosis, prevention, and management of COVID-19, many researchers are recognizing the long-term consequences of COVID-19. As the initial sprint for COVID-19 research turns into a marathon, there must be a renewed focus on high quality research and evidence-based medicine. Indeed, as we look towards the future, there is a need for well-designed rigorous prospective studies, especially in areas where randomized trials are not feasible. Careful attention to collect detailed data on potential confounding and selection factors will enable application of analytic approaches to account for confounding and selection bias. Where possible, common data elements should be used to facilitate future data harmonization across studies such as the National Institutes of Health Common Data Elements Repository (<https://cde.nlm.nih.gov/home>). Considerations of appropriate sample size and innovative study designs, in conjunction with addressing common sources of bias is critical to raise the level of evidence and move the field forward. Importantly, even the most well-designed studies have limitations and researchers have the responsibility to carefully describe these limitations to improve dissemination of research findings and encourage thoughtful and clear science communication.

The peer review of scholarly manuscripts is critical to maintaining high quality research. The COVID-19 pandemic has increased the number of manuscript submissions and placed greater strain on peer reviewers. Often, journal peer reviewers provide a valuable, but uncompensated service to the research community that competes with other professional and personal pursuits. For journals, peer review assignments must be carefully considered, identifying experts in the same field that are able to provide a critical and unbiased appraisal of the authors' work. Rapid review has been offered by many journals during the pandemic, but this must not compromise the quality of the peer review process. Alternatively, journals and publishers should work to streamline the manuscript submission process and peer review assignment to hasten article turnaround times. Academic institutions must foster an individual's drive for high quality research and relieve pressures on faculty to "publish or perish."¹⁹ Academic institutions should continue to provide appropriate resources and mentorship especially to early career investigators to prioritize the scientific and societal value of research. In 2012, San Francisco Declaration of Research Assessment (DORA) called for the elimination of journal based metrics such as impact factor in funding, appointment, and promotion considerations and the need to assess research on its own merit rather than the basis of the journal in which the manuscript is published in (<https://sfdora.org/read/>). Researchers, institutions, publishers, and organizations that supply metrics should prioritize these recommendations.

The COVID-19 pandemic has brought out both sides of the research enterprise – how quickly research findings can be implemented to bring about vaccines and therapeutic approaches, as well as how substandard research can perpetuate, leading to misunderstanding, misdirection, sensationalism, and false claims. Through a concerted upholding of investigative standards, from investigator, to institution, to journal, to the lay press, dissemination of high quality, valid research findings with true beneficial impact can be achieved.

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- b. Acquisition of Data – N/A
- c. Analysis and Interpretation of Data – N/A

Category 2:

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- b. Revising it for Intellectual Content - Darshan Patel, Alexander Pastuszak, Lawrence Jenkins, Tung-Chin Hsieh, Faysal Yafi, John Mulhall, Sunni Mumford, James Hotaling

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- a. Final Approval of the Completed Article - Darshan Patel, Alexander Pastuszak, Lawrence Jenkins, Tung-Chin Hsieh, Faysal Yafi, John Mulhall, Sunni Mumford, James Hotaling

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