

World Journal of *Methodology*

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ABOUT COVER

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INDEXING/ABSTRACTING

The *WJM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiang-Di Zhang; Production Department Director: Xu Guo; Editorial Office Director: Ji-Hong Liu.

NAME OF JOURNAL

World Journal of Methodology

ISSN

ISSN 2222-0682 (online)

LAUNCH DATE

September 26, 2011

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Bruno Megarbane

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2222-0682/editorialboard.htm>

PUBLICATION DATE

November 20, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Impact of gender-affirming hormone therapy on the development of COVID-19 infections and associated complications: A systematic review

Jennifer J Ferraro, Allie Reynolds, Sylvia Edoigiawerie, Michelle Y Seu, Sydney R Horen, Amir Aminzada, Alireza Hamidian Jahromi

Specialty type: Surgery

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Chavan RP, India; El Sayed S, Egypt

Received: April 11, 2022

Peer-review started: April 11, 2022

First decision: June 27, 2022

Revised: July 14, 2022

Accepted: October 5, 2022

Article in press: October 5, 2022

Published online: November 20, 2022



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Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can produce a wide range of clinical manifestations from asymptomatic to life-threatening. Various researchers have worked to elucidate the pathogenic mechanisms underlying these variable presentations. Differences in individual responses to systemic inflammation and coagulopathy appear to be modulated by several factors, including sex steroid hormones. Transgender men or non-binary individuals who undergo gender-affirming hormone therapy (GAHT) are a unique population of interest for exploring the androgen-mediated coronavirus disease 2019 (COVID-19) hypothesis. As the search for reliable and effective COVID-19 treatments continues, understanding the risks and benefits of GAHT may mitigate COVID-19 related morbidity and mortality in this patient population.

AIM

To investigate the potential role of GAHT in the development of COVID-19 infections and complications.

METHODS

This systematic review implemented an algorithmic approach using PRISMA guidelines. PubMed, Scopus, Google Scholar top 100 results, and archives of *Plastic and Reconstructive Surgery* was on January 12, 2022 using the key words “gender” AND “hormone” AND “therapy” AND “COVID-19” as well as associated terms. Non-English articles, articles published prior to 2019 (prior to COVID-19), and manuscripts in the form of reviews, commentaries, or letters were excluded. References of the selected publications were screened as well.

RESULTS

The database search resulted in the final inclusion of 14 studies related to GAHT COVID-19. Of the included studies, only two studies directly involved and reported on COVID-19 in transgender patients. Several clinical trials looked at the relationship between testosterone, estrogen, and progesterone in COVID-19 infected cis-gender men and women. It has been proposed that androgens may facilitate initial COVID-19 infection, however, once this occurs, testosterone may have a protective effect. Multiple clinical studies have shown that low baseline testosterone levels in men with COVID-19 are associated with worsening outcomes. The role of female sex hormones, including estrogen and progesterone have also been proposed as potential protective factors in COVID-19 infection. This was exemplified in multiple studies investigating different outcomes in pre- and post-menopausal women as well as those taking hormone replacement therapy. Two studies related specifically to transgender patients and GAHT found that estrogen and progesterone could help protect men against COVID-19, and that testosterone hormone therapy may increase the risk of contracting COVID-19.

CONCLUSION

Few studies were found related to the role of GAHT in COVID-19 infections. Additional research is necessary to enhance our understanding of this relationship and provide better care for transgender patients.

Key Words: COVID-19; Transgender; Gender-affirming hormone therapy; Gender affirmation; Testosterone; Estrogen

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Core Tip: Severe acute respiratory syndrome coronavirus 2 can produce a wide range of clinical manifestations from asymptomatic to life-threatening. Differences in individual responses to systemic inflammation and coagulopathy appear to be modulated by several factors, including sex steroid hormones. Androgens may facilitate initial coronavirus disease 2019 (COVID-19) infection, however, once this occurs, testosterone may have a protective effect. The role of estrogen and progesterone has also been proposed as potential protective factors in COVID-19 infection. Few studies have investigated the role of gender-affirming hormone therapy in COVID-19 infections. Additional research is necessary to enhance our understanding of this relationship and provide better care for transgender patients.

Citation: Ferraro JJ, Reynolds A, Edoigiawerie S, Seu MY, Horen SR, Aminzada A, Hamidian Jahromi A. Impact of gender-affirming hormone therapy on the development of COVID-19 infections and associated complications: A systematic review. *World J Methodol* 2022; 12(6): 465-475

URL: <https://www.wjgnet.com/2222-0682/full/v12/i6/465.htm>

DOI: <https://dx.doi.org/10.5662/wjm.v12.i6.465>

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent behind the coronavirus disease 2019 (COVID-19) global pandemic, has a wide array of clinical manifestations ranging from asymptomatic to life-threatening disease[1]. Various researchers have worked to elucidate the pathogenic mechanisms underlying these highly variable presentations, with many agreeing that the critical role of the immunological hyper-response (characterized by widespread endothelial damage, complement-induced blood clotting, and systemic microangiopathy) facilitates inflammation and disease progression[2]. Differences in individual responses to systemic inflammation and coagulopathy appear to be modulated by several factors, including sex steroid hormones[2].

Older age and male sex are known risk factors for more severe manifestations of the COVID-19 disease[3-5]. Even after controlling for other risk factors commonly found among men, such as a hypertension, smoking, and cardiovascular disease, the mortality rate of COVID-19 has been shown to be higher in cis-gender males compared with cis-gender females[6]. The molecular basis of the observation can be attributed to transcription of transmembrane protease serine 2 (TMPRSS2), a protease that processes SARS-CoV-2 spike proteins that bind angiotensin converting enzyme 2 (ACE2) receptors and mediate entry of the virus into host cells[7]. The expression of both TMPRSS2 and ACE2 appears to be androgen-mediated[8,9]. For this reason, androgens like testosterone, and other important sex hormones like estrogen and progesterone, have been investigated for their potential role in the age and sex-specific severity of COVID-19[10-12].

Given the risks associated with male sex hormones, patients with gender dysphoria (transgender men or non-binary individuals) who undergo gender-affirming hormone therapy (GAHT) have become another population of interest for exploring the androgen-mediated COVID-19 hypothesis[13]. Through GAHT, transgender women are prescribed natural or synthetic estrogens[14], while transgender men take exogenous testosterone titrated to physiological female range estradiol levels and male-range serum testosterone levels, respectively[15]. For the latter, there is a paucity of data on the safety and health risks associated with long-term testosterone administration in transgender men[16]. As the search for reliable and effective COVID-19 treatments continues, understanding the risks and benefits of GAHT (especially masculinizing treatments) may mitigate COVID-19 related morbidity and mortality in a unique and vulnerable patient population.

The purpose of this study was to perform a systematic review and meta-analysis of the literature pertaining to potential role of GAHT in the development of COVID-19 infections and associated complications.

MATERIALS AND METHODS

The current systematic review implemented an algorithmic approach to review all of the available English medical literature on the impact of GAHT on the development of COVID-19 infections using the preferred reporting items for systematic reviews and meta-analysis (PRISMA) principles (Figure 1). A comprehensive search of the medical literature in the "PubMed," "Scopus," "Reference Citation Analysis (RCA)," "Google Scholar" top 100 results, and previous issues of *Plastic and Reconstructive Surgery* was performed by two authors (A.R. and S.E.) on January 12, 2022 using the key words "gender" AND "hormone" AND "therapy" AND "COVID-19" as well as associated terms.

The search string was generated, and records that were not specific about GAHT or COVID-19 were excluded. Foreign language (non-English) articles were not eligible for inclusion. Articles published prior to 2019 were excluded as being prior to the COVID-19 pandemic and therefore not relevant to complications associated with COVID-19 infection. Titles and abstracts were screened by two authors (A.R. and S.E.) after which full-text articles were assessed for eligibility and inclusion. On initial and secondary searches, papers in review, commentaries, letters, or those without accessible full-text articles were excluded. References of the selected publications were additionally screened with the aforementioned inclusion criteria.

RESULTS

In total, 14 studies were included in this review per the inclusion/exclusion criteria (Figure 1). Two studies were laboratory-based research (Table 1), while the remaining were clinical studies, including one randomized-control trial (Table 2). Only two studies directly involved and reported on COVID-19 in transgender patients (Table 3).

DISCUSSION

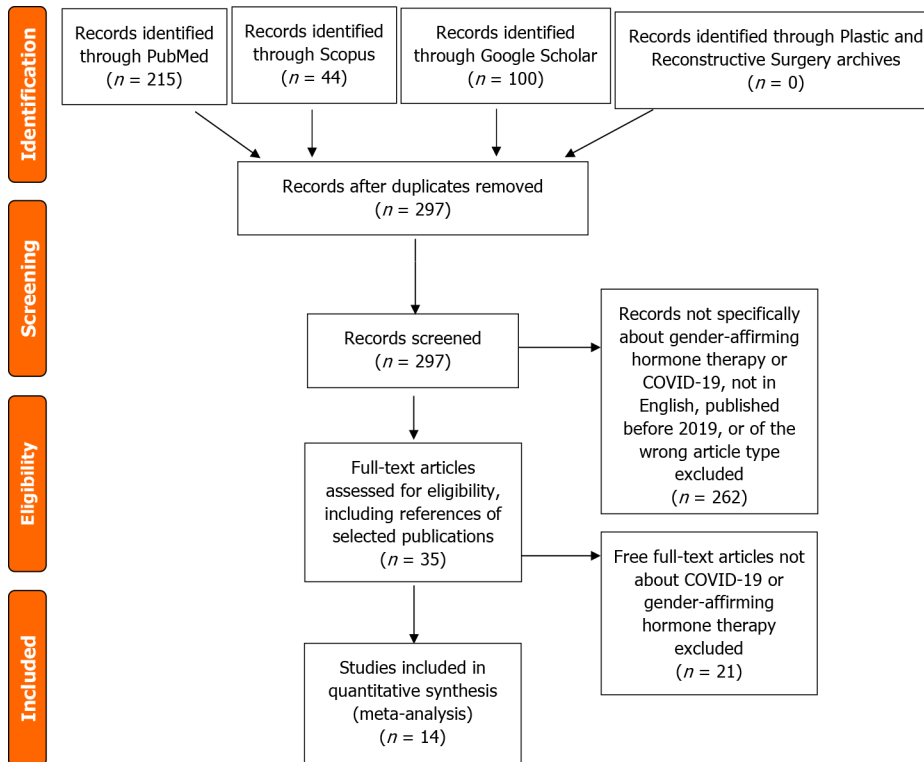
The sexual dimorphism seen in COVID-19 morbidity and mortality outcomes has contributed to the hypothesis that the male sex hormone, testosterone, may be an independent risk factor associated with COVID-19 infection and severity, while female sex hormones, estrogen and/or progesterone may endow a protective effect[17,18].

TESTOSTERONE AND COVID-19

It has been proposed that androgens are needed for initial entry of SARS-CoV-2 into the cell *via* the

Table 1 Laboratory studies

Ref.	Study type	Focus	Results
Youn <i>et al</i> [37]	<i>In vitro</i> cell line treatment	Investigated potential protective effects of estrogen on endothelial cells against oxidative stress induced by IL-6 and by SARS-COV-2 spike protein (S protein)	17β-Estradiol reversed S protein induced activation of NADPH oxidase isoform 2 (NOX2) and ACE-2 dependent ROS production, as well as ACE2 upregulation and induction of pro-inflammatory gene monocyte chemoattractant protein-1 (MCP-1) in endothelial cells, effectively attenuating endothelial dysfunction completely Implications: Estrogen inhibits initial viral response and attenuation of cytokine storm induced endothelial dysfunction, especially in men and post-menopausal women. Data supports hypothesis that estrogen may be used to alleviate viral infection and cytokine storm-induced endothelial dysfunction, a critical mediator of ARDS/multi-organ failure. Thus, attenuating disease progression, severity and mortality
Samuel <i>et al</i> [42]	<i>In vitro</i> stem cell lines and high throughput drug screens	Established a screening strategy to identify drugs that reduce ACE2 levels in human embryonic stem cell (hESC)-derived cardiac cells and lung organoids. Target analysis of hit compounds revealed androgen signaling as a key modulator of ACE2 levels	Inhibitors of 5-α reductase, which dampen androgen signaling reduced ACE2 levels in target cells; Treatment with antiandrogenic drugs reduced ACE2 expression and protected hESC-derived lung organoids against COVID-19 infection; Study also found that clinical data on COVID-19 patients with prostate cancer, which is associated with elevated androgen levels, are significant risk factors and that genetic variants that are associated with higher androgen levels are associated with higher diseases severity



DOI: 10.5662/wjm.v12.i6.465 Copyright ©The Author(s) 2022.

Figure 1 Search strategy for our systematic review to find the currently published medical literature describing the impact of COVID-19 infections on gender-affirming hormone therapy.

activation of TMPRSS2, whose expression is increased by testosterone[8,9]. This gave rise to the theory that higher androgen levels in cis-gender men may account for the higher rates of infection and worse outcomes compared with their cis-gender women counterparts. Likewise, based on this logic, clinical trials have begun to look at the use of anti-androgens and TMPRSS2 inhibitors as prophylactic agents in the setting of SARS-CoV-2 infections[19]. However, once the initial infection occurs, testosterone is hypothesized to have a protective effect by limiting the collection of free radicals in cells and reducing the risk of a cytokine storm and subsequent development of acute respiratory distress syndrome (ARDS)[20]. Taken together, these two androgen dependent theories suggest that while low testosterone may reduce the risk of initial infection, testosterone later protects against more severe forms of disease and may prevent detrimental outcomes in individuals with COVID-19 infections. Further complicating the role of male sex hormones in gender outcome differences, testosterone levels are highly variable among men, with lower testosterone levels seen in men of older age, as well as men with other

Table 2 Current literature on hormone therapy and coronavirus disease-2019 clinical trials

Ref.	Focus	Predictors or conditions	Sample Population	Outcomes/Findings
Ghandehari <i>et al</i> [36]	Los Angeles, California; Effect of progesterone therapy in men with moderate to severe COVID-19	Randomized control trial	42 hospitalized men with confirmed moderate to severe COVID-19 Experimental Cohort: re received 100 mg of progesterone subcutaneously twice a day for 5 d while hospitalized Control Cohort: Standard of care	There was a 1.5 point overall improvement in median clinical status score on a seven-point ordinal scale from baseline to day 7 in the progesterone group ($n = 18$) compared with the control group ($n = 22$) This study shows that the use of progesterone may help to lower the length of hospital stay, use of supplemental O2 and need for mechanical ventilation
Dhindsa <i>et al</i> [12]	Association of concentration of serum sex hormones with COVID-19 Severity	Prospective cohort study	152 consecutive patients (59% men and 40.8% women) presenting with COVID-19 to the hospital were recruited. Of the participants, 143 (94.1%) were hospitalized. The mean age of participants was 63 yr	Lower testosterone concentrations and increased estradiol to testosterone ratios during hospitalization are associated with disease severity, inflammation, and mortality in men with COVID-19. Men with severe COVID-19 had 65%-85% lower testosterone concentrations compared with men with milder disease course, and was independent of other known risk factors associated with COVID-19 severity
van Zeggeren <i>et al</i> [25]	Assess the association between androgen levels and mortality in patients with severe COVID-19	Observational Case-control study	16 postmenopausal women (age > 55), and 24 age matched men	Total and free testosterone were lower in deceased men than in survivors. Significantly lower SHBG levels were associated with in both deceased men and women compared with survivors Low SHBG levels were associated with mortality rate in patients with COVID-19 and low total and free testosterone levels were associated with mortality in men. However, whether these hormone levels influence the disease severity, or are a marker of disease severity needs elucidation
Seeland <i>et al</i> [31]	Evidence for treatment with estradiol for women with SARS-COV2 infection	Retrospective cohort study	Electronic health record for a large, 68,466 case international COVID-19 cohort	Incidence of SARS-CoV-2 infection is $\geq 15\%$ higher in women than men, but fatality rate is higher is 50% higher in men. Age stratification showed, that while preadolescent men and women had same risk of infection and fatality rate, compared with men of the same age, premenopausal women had a higher risk of infection, but peri and post-menopausal infection rates were similar to men of the same age; -fatality risk for women > 50 yr receiving hormone therapy with estradiol was reduced by > 50% (OR 0.33, HR 0.29) compared with women not receiving HRT. For younger women, (15-49 yr of age) risk of COVID-19 fatality was the same irrespective of estradiol treatment
Infante <i>et al</i> [24]	Asses testosterone levels at time of admission with inflammatory state and in-hospital mortality rate	Retrospective cohort study	40 symptomatic men with confirmed COVID-19 infections admitted to hospital. Patients were divided into two groups, survivors ($n = 20$), and non-survivors ($n = 39$)	Low total testosterone levels and elevated E2/T ratios (a marker of aromatase activity) were associated with a hyperinflammatory state. Low testosterone was an independent risk factor for in-hospital mortality
Rambhatla <i>et al</i> [27]	Assessed the outcomes of COVID-19 infection in men on testosterone replacement therapy	Retrospective case control study	32 men diagnosed with COVID-19 on testosterone replacement therapy (TRT) were matched to 63 men with COVID-19 diagnosis but not on TRT	No statistically significant difference in outcome endpoints (hospitalization, ICU admission, ventilator utilizations, thrombotic event, death) between two groups. Results suggest that no statistically significant difference in outcomes for men treated with TRT than men not on TRT.
Salonia <i>et al</i> [26]	Evaluated testosterone levels in men with COVID-19 compared with healthy men	Retrospective case control study	286 symptomatic men with COVID-19 requiring hospital admission Control group: 281 healthy men	Men with COVID-19 had significantly lower serum testosterone levels than healthy men. Lower testosterone levels were independently associated with COVID-19 infection status, and lower levels of testosterone predicted more severe clinical outcomes
Ding <i>et al</i> [30]	Examined how menstrual status and sex hormones affect the progression and outcomes of	Retrospective cohort study	All confirmed hospitalized COVID-19 patients from three hospitals ($n = 1902$). Cohort 1: Sex differences and disease severity ($n = 1902$); Cohort 2: Women with menstrual status	Non-menopausal (NM) women had milder severity and better outcomes compared with age match males. Menopausal(M) patients had longer hospitalization times compared with NM patients. -Anti Mullerian hormone (AMH) and estradiol (E2) negatively correlated with infection severity. Menopause is an independent risk factor for female COVID-19 patients, AMH and

	COVID-19		(<i>n</i> = 509) Cohort 3: Serum hormone levels (<i>n</i> = 78), Cytokines levels (<i>n</i> = 263)	E2 inversely correlated with COVID-19 severity. Thought to offer protective benefits, E2 specifically through regulation of cytokines related to immune inflammatory response
Lee <i>et al</i> [43]	Assessed the effects of female sex hormones on clinical outcomes of COVID-19 using national claims data	Retrospective cohort study	Adult patients with COVID-19 infection (<i>n</i> = 5061). Subgroup analyses using aged matched case-control data	There was no significant difference in mortality rate between males and females, and HRT was not associated with improved clinical outcomes

Table 3 Transgender care and coronavirus disease 2019

Ref.	Study type	Findings
Masterson <i>et al</i> [38]	Prospective Case study	TW patients treated with E+P as part of feminizing GAHT showed reduced testicular ACE-2 R expression in testicular tissue. In comparison to control group (cis-gender males with no hormone therapy) and the TW cohort treated with E only, O+E cohort also had higher degree of tissue fibrosis. Significance: Support the possibility that short course of E+P or P alone could help protect men against COVID-19 infection through downregulation of ACE-2 Receptor
Durcan <i>et al</i> [39]	Single center, cross-sectional web-based survey	Of 238 participants (179 FTM, 59 FTM) with GD receiving hormone therapy, the risk of contracting COVID-19 was 3.46x higher in FTM receiving testosterone therapy, compared with FTM patients receiving estrogen and anti-androgen therapies. Furthermore, among the FTM cohort, longer treatment periods with testosterone was associated with increased risk of contracting COVID-19; Significance: TM receiving Testosterone as part of GAHT are at an increased risk for contracting COVID-19

comorbidities that concurrently increase the risk of COVID-19 severity and morbidity, *i.e.* type 2 diabetes, chronic lung disease, obesity, and renal insufficiency[20-22]. While the above-mentioned arguments consider endogenous testosterone as a potential factor impacting the risk of SARS-CoV-2 infection, severity, and morbidity associated with COVID-19, whether exogenous hormone consumption in the setting of GAHT in transgender individuals would confer the same risks is mostly a matter of speculation.

Multiple clinical studies have shown that low baseline testosterone levels in men with COVID-19 at the time of admission are associated with worsening outcomes. A recent prospective study by Dhidsa *et al*[12] found that lower testosterone concentrations and increased estradiol to testosterone (E2/T) ratios (a marker of aromatase inhibitor activity) during hospitalization are associated with disease severity, inflammation, and mortality in cis-gender men with COVID-19. The authors did not specify if there were transgender individuals in their studied population. Men with severe COVID-19 had 65%-85% lower testosterone concentrations compared with men with a milder disease course. Similarly, a retrospective cohort study by Infante *et al*[24] evaluated men who were admitted with COVID-19 and found that compared with the survivor cohort, non-survivors had a significantly lower testosterone level at time of admission, which was inversely correlated with E2/T ratios and inflammatory marker levels. The study found that low testosterone levels at time of admission were an independent risk factor for in-hospital mortality and may serve as a surrogate marker for disease severity in male patients [24]. In addition, an observational cohort study in the Netherlands found that lower sex hormone binding globulin (SHBG) levels were associated with a higher mortality rate in both men and women, but low testosterone levels were only associated with mortality in men and not women.

The association of low testosterone and worse outcomes in male patients in these studies supports the theory that low testosterone levels may lead to an increase in proinflammatory cytokine markers, facilitating the development of a cytokine storm and subsequent disease severity and morbidity in men with COVID-19. The findings are consistent with a larger case-control study that found lower serum testosterone in men infected with SARS-CoV-2 at time of admission compared with the unaffected controls, and that the level of testosterone on admission was associated with worse outcomes. Interestingly, this study found that in as many as 85% of cases, sex hormone levels were suggestive of secondary hypogonadism[26].

Despite the repeated observed association between low testosterone levels and COVID-19 disease severity in males, it is not clear if low testosterone in males predisposes individuals to COVID-19 infection and increases the chance of higher severity of the disease, or if low testosterone is simply a marker of illness severity. Further studies looking at testosterone levels prior to infection are required to clarify this relationship. Adding to the possible immune role of testosterone levels in COVID-19 infection and disease course, a retrospective case-control study examining the outcomes of COVID-19 infection in men on testosterone replacement therapy (TRT) (*n* = 32), found no statistically significant difference in outcomes compared with men not on TRT[27]. However, considering the limited number of cases evaluated and the considerable number of potential confounding factors, the study was not powered enough to draw strong and valid conclusions.

Another possible explanation for the dimorphism in outcomes between cis-gender males and females may be that regardless of testosterone levels in men, female sex hormones provide a much greater protection. Thus the higher levels of female sex hormones in cis-gender women may account for the disparity in outcomes between the two sexes.

ESTROGEN AND PROGESTERONE AND COVID-19

The role of female sex hormones, including estrogen and progesterone, have also been proposed as potential protective factors contributing to the dimorphism in COVID-19 infection between cis-gender men and cis-gender women. Earlier studies have shown that estrogen plays an important modulatory role in both cellular and humoral immune responses, including causing a reduction in T-cell exhaustion and suppression of inflammatory cytokines[29,30].

In line with the hypothesis of female sex hormones playing a significant protective role, a retrospective study from China by Ding *et al*[30], indicated that non-menopausal (NM) females presented with milder disease severity and had better outcomes compared with age-matched males, but these differences disappeared between menopausal (M) females and age-matched men. This supports the idea that female hormones of NM women (pre-menopausal cis-gender) may provide protection, and the authors further noted that estradiol (E2) and anti-Mullerian hormone (AMH), which serves as a marker for ovarian reserve and function, showed a negative correlation with severity of infection in women. The study also found that E2 Levels specifically were negatively correlated with cytokines related to immunity and inflammation[30]. Further illustrating the potential protective role of E2, a retrospective cohort study from Germany found that compared with PM women not taking hormone replacement therapy (HRT), PM women receiving HRT, containing E2, had a 50% lower risk of mortality following SARS-CoV-2 infections (Odds Ratio 0.33; Hazard Ratio 0.29)[31]. In addition to the immunoprotective role of E2, progesterone is also thought to play a significant immunomodulatory role, including the prevention of free radical formation and suppression of proinflammatory cytokines[32,33]. This inflammatory dampening facilitated by high endogenous progesterone levels is thought to be protective against cytokine storms and subsequent development of ARDS in COVID-19 patients[34,35]. Results from a recent randomized control trial found that subcutaneous progesterone administration was associated with significant clinical improvement in hypoxemic men hospitalized with COVID-19[37].

Researchers investigating the potential protective effects of estrogen on endothelial cells against oxidative stress induced by interleukin (IL)-6 and by SARS-COV-2 spike protein (S protein) demonstrated that in response to S protein or IL-6 exposure of endothelial cells, estrogen inhibits initial viral response and alleviates cytokine storm-induced endothelial dysfunction, a critical mediator in ARDS/multi-organ failure, ultimately attenuating disease progression, severity, and mortality. This lab based research supports the notion that estrogen provides significant protection against COVID-19 in cis-gender females and underlines the potential utility of estrogen administration as a treatment option for COVID-19 to reduce disease severity and improve survival. While not reviewed in this paper, several clinical studies are currently taking place to study the utility of estrogen treatment in infected cis-gender males and females[38].

GENDER-AFFIRMING HORMONE THERAPY AND TRANSGENDER CARE

While several studies have looked at the interplay of hormone and innate hormone levels on cis-gender male and females, less is known about the impact of COVID-19 on individuals undergoing GAHT. Similar to studies that have looked at the protective effects of progesterone and estrogen in cis-gender females, the mechanism of estrogen and progesterone in relation to COVID-19 infection and susceptibility can also be readily studied in the transgender population. A recent study by Masterson and colleagues has been one of the first to examine the impact of feminizing GAHT in transgender individuals being treated for gender dysphoria GD[39]. Transgender women (TW) are routinely treated with estrogen (E) or estrogen plus progesterone (E+P) as part of feminization GAHT. Compared with orchiectomy samples of cis-gender men and TW on E alone, the TW cohort receiving E+P therapy prior to gender-affirming orchiectomy surgery had fewer Leydig cells and less ACE-2 expression when examined with immunohistochemistry. Their findings suggest that P appears to significantly diminish ACE-2 expression in the testes. This reduction in ACE-2 expression helps to support the hypothesis that a short course of exogenous P or E+P therapy may downregulate ACE-2 expression and help offer protection against COVID-19 infection and limit disease severity in cis-gender men and TW undergoing GAHT. While this study demonstrated the differences in ACE-2 expression in gonadal tissues when exposed to P+E therapy, it is unclear if the lower rate of expression in the studied group confers a lower risk of COVID-19 infection and severity, nor is it broadly applicable to the cis-gender population at large. The findings support prior work published by Montopoliet al[39], which showed that men undergoing prostate cancer treatment who received androgen deprivation therapy (ADT) were four times less likely to be diagnosed with COVID-19 compared with those who did not receive ADT. In

contrast, a more recent prospective cohort study consisting of 1779 men with prostate cancer found a higher rate of COVID infection in the ADT group (17.1% ADT group *vs* 5.7% no ADT group), but upon further multivariable analysis did not indicate a difference in infection rate for men treated with ADT compared with no ADT once confounding variables were accounted for (OR 0.93 95%CI: 0.54–1.61, $P = 0.8$)[40].

In addition to histochemical and laboratory studies on the mechanism of sex hormones, clinical studies looking at the infection rates and outcomes among transgender individuals treated with hormone therapy help to further deepen our understanding of the role of sex hormones. A recent web-based survey evaluation by Durcan *et al*[13] found that the risk of COVID-19 infection was 3.46 times higher in transgender men (TM), who were receiving testosterone therapy compared with TW, who received estrogen and anti-androgen therapy. In addition, the TM cohort who contracted COVID-19 had a longer androgen therapy treatment history compared with TM patients who did not contract the virus. While these findings suggest that TM individuals who receive androgen therapy as part of GAHT are at greater risk of COVID-19 infection, the study was limited by the small cohort size and retrospective design. Additionally, while the study stated that most patients who contracted COVID-19 did not require hospital admission, further studies looking at the severity of COVID-19 infection and need for ICU admission among transgender individuals undergoing GAHT would further help to demonstrate the risk of COVID-19 and its relationship with the COVID severity and morbidities in patients receiving supplemental androgen therapy (testosterone).

Despite the interest in the use of exogenous hormone therapies to help reduce COVID-19 infection and severity, still, very little research on the impact of COVID-19 on the transgender community and transgender individuals undergoing GAHT is available, as that cohort has been largely overlooked in demographic data, research studies and public health surveillance data collection[41]. While the currently available literature suggests that GAHT has a role in COVID-19 infected individuals, the current small sample sizes and limited understanding make generalizing to the overall transgender community (TM, TW, and non-binary individuals) or cis-gender individuals receiving sex hormone supplement difficult. As of now, the current hypothesis and available data on transgender-identifying individuals suggests that those undergoing MTF HRT (transgender women) may be more protected from becoming infected or suffering from severe COVID-19. In contrast, those who undergo FTM GAHT (transgender men), including androgens, may carry a higher risk. While the above current literature broadly supports this hypothesis, the impact of other biological and behavioral factors, including genetic differences in biological men and women, and higher rates of comorbidities, including smoking and other chronic illnesses in transgender individuals.

LIMITATIONS

Despite the unique opportunity to study hormone therapy and its impact on COVID-19 in this population, only two studies to date have reported on this subject. The studies are generally retrospective in nature and on a small number of individuals, thus are not powered adequately to draw valid and strong conclusions.

CONCLUSION

Transgender care and use of GAHT within this population represents a unique opportunity to study the implications of these treatments, as currently used, in relation to COVID-19 and biological sex. While several clinical trials looking at the use of E+P in COVID-19 infected cis-gender men, the understanding of their role in transgender care is limited. While clinical trials investigating the utility of hormone therapy in COVID-19 may prove useful, studying the effects of GAHT in transgender individuals already taking these medications may prove a more efficient route to understanding the role of hormone therapy in the treatment of COVID-19. Not only would studying transgender individuals in COVID-19 studies help to further broaden our understanding of the role of biologic sex and hormone treatment in disease susceptibility and course, but it would also serve to benefit those in the transgender community, who are often a vulnerable and underserved population within healthcare.

ARTICLE HIGHLIGHTS

Research background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can produce a wide range of clinical manifestations from asymptomatic to life-threatening. Differences in individual responses to systemic inflammation and coagulopathy appear to be modulated by several factors including sex steroid

hormones. Androgens may facilitate initial coronavirus disease 2019 (COVID-19) infection. However, once that occurs, testosterone may have a protective effect. Few studies have investigated the role of GAHT in COVID-19 infections. Additional research is necessary to enhance our understanding of this relationship and provide better care for transgender patients.

Research motivation

The role of estrogen and progesterone has also been proposed as potential protective factors in COVID-19 infection.

Research objectives

To investigate the potential role of GAHT in the development of COVID-19 infections and complications.

Research methods

The current systematic review implemented an algorithmic approach using PRISMA guidelines. PubMed, Scopus, Google Scholar top 100 results, and archives of *Plastic and Reconstructive Surgery* was on January 12, 2022 using the key words of “gender” AND “hormone” AND “therapy” AND “COVID-19” as well as associated terms.

Research results

The database search resulted in the final inclusion of 14 studies related to GAHT COVID-19. Of the included studies, only two studies directly involved and reported on COVID-19 in transgender patients. Several clinical trials looked at the relationship between testosterone, estrogen, and progesterone in COVID-19 infected cis-gender men and women. It has been proposed that androgens facilitate initial COVID-19 infection, however, once that occurs, testosterone may have a protective effect. A number of clinical studies have shown that low baseline testosterone levels in men with COVID-19 are associated with worsening outcomes. The role of female sex hormones, including estrogen and progesterone have also been proposed as potential protective factors in COVID-19 infection. This is exemplified in multiple studies investigating different outcomes in pre- and post-menopausal women as well as those taking hormone replacement therapy. Two studies related specifically to transgender patients and GAHT found that estrogen and progesterone could help protect men against COVID-19, and that testosterone hormone therapy may increase the risk of contracting COVID-19.

Research conclusions

Few studies were found related to the role of GAHT in COVID-19 infections. Additional research is necessary to enhance our understanding of this relationship and provide better care for transgender patients.

Research perspectives

SARS-CoV-2 can produce a wide range of clinical manifestations from asymptomatic to life-threatening. Differences in individual responses to systemic inflammation and coagulopathy appear to be modulated by several factors, including sex steroid hormones. Androgens may facilitate initial COVID-19 infection, however, once that occurs, testosterone may have a protective effect. The role of estrogen and progesterone has also been proposed as potential protective factors in COVID-19 infection. Few studies have investigated the role of GAHT in COVID-19 infections. Additional research is necessary to enhance our understanding of this relationship and provide better care for transgender patients.

FOOTNOTES

Author contributions: Hamidian Jahromi A contributed to conceptualization and manuscript editing; Ferraro JJ, Reynolds A, Edoigiawerie S, Seu MY, Horen SR, Aminzada A contributed to writing, statistical analysis, and manuscript editing; All authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflicting interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Ma YJ

L-Editor: Filipodia

P-Editor: Ma YJ

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Associations between SARS-CoV-2 infections and thrombotic complications necessitating surgical intervention: A systematic review

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Specialty type: Medical laboratory technology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Al-Ani RM, Iraq; Du BB, China

Received: April 15, 2022

Peer-review started: April 15, 2022

First decision: August 1, 2022

Revised: September 1, 2022

Accepted: November 4, 2022

Article in press: November 4, 2022

Published online: November 20, 2022



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Abstract

BACKGROUND

Several unique clinical features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19) infection, have been identified and characterized. One such feature, mostly among patients with severe COVID-19 infection, has become known as COVID-19-induced coagulopathy. Surgical patients with a history of or active COVID-19 infection bear a significantly higher risk for postoperative thrombotic complications. These patients may require surgical intervention to treat severe thrombotic complications. Few studies have been carried out to better characterize this association. The purpose of this study was to perform a systematic review and meta-analysis of the literature on COVID-19 infections that led to thrombotic complications necessitating surgical intervention. We hypothesized that patients with recent or active COVID-19 infection would have high rates of thromboembolic complications both arterial and venous in origin.

AIM

To perform a systematic review and meta-analysis of the literature on COVID-19 infections that led to thrombotic complications necessitating surgical intervention.

METHODS

The current systematic review implemented an algorithmic approach to review all

the currently available English medical literature on surgical interventions necessitated by COVID-19 thrombotic complications using the preferred reporting items for systematic reviews and meta-analysis principles. A comprehensive search of the medical literature in the “PubMed”, “Scopus”, “Google Scholar” top 100 results, and archives of *Plastic and Reconstructive Surgery* was performed using the key words “COVID-19” AND “surgery” AND “thromboembolism” AND “complication”. The search string was generated and the records which were not specific about surgical interventions or thrombotic complications due to COVID-19 infection were excluded. Titles and abstracts were screened by two authors and full-text articles were assessed for eligibility and inclusion. Finally, results were further refined to focus on articles that focused on surgical interventions that were necessitated by COVID-19 thrombotic complications.

RESULTS

The database search resulted in the final inclusion of 22 retrospective studies, after application of the inclusion/exclusion criteria. Of the included studies, 17 were single case reports, 3 were case series and 2 were cross sectional cohort studies. All studies were retrospective in nature. Twelve of the reported studies were conducted in the United States of America, with the remaining studies originating from Italy, Turkey, Pakistan, France, Serbia, and Germany. All cases reported in our study were laboratory confirmed SARS-CoV-2 positive. A total of 70 cases involving surgical intervention were isolated from the 22 studies included in this review.

CONCLUSION

There is paucity of data describing the relationship between COVID-19 infection and thrombotic complications necessitating the need for surgical intervention. Intestinal ischemia and acute limb ischemia are amongst the most common thrombotic events due to COVID-19 that required operative management. An overall postoperative mortality of 30% was found in those who underwent operative procedures for thrombotic complications, with most deaths occurring in those with bowel ischemia. Physicians should be aware that despite thromboprophylaxis, severe thrombotic complications can still occur in this patient population, however, surgical intervention results in relatively low mortality apart from cases of ischemic bowel resection.

Key Words: Thromboembolic; COVID-19; SARS-CoV-2; Surgical intervention; Complications; Surgery

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Core Tip: Surgical patient with a history of or current active infection with severe acute respiratory syndrome coronavirus 2 bear a significantly high risk for postoperative thrombotic complications. These patients may require surgical intervention to treat severe thrombotic complications. In total, 70 cases of thromboembolic complications necessitating surgical intervention have been documented. These patients have an overall mortality rate of 30%. Intestinal ischemia and acute limb ischemia are the most common thrombotic complications that required operative management. Physicians should be aware that severe thrombotic complications can occur in this patient population, however, surgical intervention results in relatively low mortality apart from cases of ischemic bowel resection.

Citation: Ferraro JJ, Reynolds A, Edoigiawerie S, Seu MY, Horen SR, Aminzada A, Hamidian Jahromi A. Associations between SARS-CoV-2 infections and thrombotic complications necessitating surgical intervention: A systematic review. *World J Methodol* 2022; 12(6): 476-487

URL: <https://www.wjgnet.com/2222-0682/full/v12/i6/476.htm>

DOI: <https://dx.doi.org/10.5662/wjm.v12.i6.476>

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. Since December 2019, COVID-19 has spread throughout the world and changed the landscape of biomedical research and healthcare in a myriad of ways. Several unique clinical features of the virus have been identified and extensively characterized. One such feature, mostly among patients with severe COVID-19 infection and to some extent in less severe cases, is known as COVID-19-induced coagulopathy (CIC), which manifests as considerable elevation in D-dimer and fibrin split products, with little to no associated change in activated partial thromboplastin time and prothrombin time[2].

A large proportion of patients with CIC have been reported to develop venous and arterial thromboembolic complications[3]. Critically ill patients and patients undergoing surgeries are generally predisposed to thromboembolism due to a combined immobility, systemic inflammation, endothelial dysfunction, and circulatory stasis[4,5]. The progression of CIC can be insidious, with some cases of pulmonary embolism (PE) identified as the first sign of SARS-CoV-2 infection in patients with no early evidence of virus upon testing with nasopharyngeal swab[6]. Thrombotic risks posed by CIC cannot be underestimated, as it is not limited to patients within intensive care or other high-dependency settings [7].

Postoperative thrombotic complications such as venous thromboembolism (VTE) and PE are responsible for significant morbidity and mortality among patients undergoing invasive procedures and surgeries[8,9]. Approximately 50% of all reported VTEs are provoked by prolonged immobilization, trauma, surgery, or hospitalization within the last 3 mo[10,11]. Therefore, a surgical patient with a history of or active COVID-19 infection would be at a significantly higher risk for postoperative thrombotic complications than the general population[12,13]. Traditionally cases of VTE are treated with systemic anticoagulation (*i.e.*, heparin, low molecular weight heparins, direct oral anticoagulants, and vitamin-K antagonists) following a careful evaluation of the risks and benefits. The thrombolysis is reserved for clinically serious and massive PE conditions in an attempt to dissolve the clot more rapidly than with anticoagulation options and reduce the mortality[14]. Severe cases of thromboembolic complications may require surgical intervention (*i.e.*, mechanical thrombectomy, catheter direct thrombolysis) to reduce the risk of post thrombotic syndrome and venous insufficiencies [in case of deep venous thrombosis (DVT)][15] or the risk of pulmonary insufficiencies, hemodynamic instability and or death (in cases of PE)[14]. Therefore, a patient with previous or active COVID-19 infection may require surgical intervention to treat severe thrombotic complications. Few studies have characterized this association. The purpose of this study was to perform a systematic review and meta-analysis of the literature on COVID-19 infections that led to thrombotic complications necessitating surgical intervention.

MATERIALS AND METHODS

The current systematic review implemented an algorithmic approach to review all the currently available English medical literature on surgical interventions necessitated by COVID-19 thrombotic complications using the preferred reporting items for systematic reviews and meta-analysis principles (Figure 1). A comprehensive search of the medical literature in the “PubMed”, “Scopus”, “Google Scholar” top 100 results, and archives of *Plastic and Reconstructive Surgery* was performed by two authors (Reynolds A and Edoigiawerie S) on January 4, 2022, using the key words “COVID-19” AND “surgery” AND “thromboembolism” AND “complication” as well as associated terms.

The search string was generated and the records which were not specific about surgical interventions or thrombotic complications due to COVID-19 infection were excluded. Foreign language articles were not eligible for inclusion. Articles published prior to 2019 were excluded as being prior to the COVID-19 pandemic and therefore not relevant to complications associated with COVID-19 infection. Titles and abstracts were screened by two authors (Reynolds A and Edoigiawerie S) after which full-text articles were assessed for eligibility and inclusion. On initial and secondary search, papers in review, commentary, or letter format or those without accessible full-text articles were excluded.

Finally, results were further refined to focus on articles that featured surgical interventions that were necessitated by COVID-19 thrombotic complications. For completion of the search, the references of the selected publications were additionally screened with the priorly mentioned inclusion criteria. We also cited high-quality articles in *Reference Citation Analysis* (<https://www.referencecitationanalysis.com>).

RESULTS

The database search resulted in the final inclusion of 22 retrospective studies, after application of the inclusion/exclusion criteria. Of the included studies, 17 were single case reports, 3 were case series and 2 were cross sectional cohort studies. All studies were retrospective in nature. Twelve of the reported studies were conducted in the United States of America, with the remaining studies originating from Italy, Turkey, Pakistan, France, Serbia, and Germany. All cases reported in our study were laboratory confirmed SARS-CoV-2 positive. A total of 70 cases involving surgical intervention were isolated from the 22 studies included in this review. The 22 studies which were included in the review are listed in detail in (Table 1).

Table 1 Synopsis of reviewed studies on coronavirus disease 2019 thromboembolisms necessitating surgical intervention

Ref.	Location	Study design	No. of patients	Age (yr)	Sex: Males, females (%)	Comorbidities	Thromboprophylaxis	Thromboembolic complication(s)	Surgical intervention(s)	Outcome
Adekiigbe <i>et al</i> [43], 2020	NY, United States	Case report	1	47	Male	DM	Yes	Cutaneous vasculitic lesions and gangrene of all toes, bilateral DVT	Bilateral transmetatarsal amputations of all 10 toes	Discharged home
Ali Nasir <i>et al</i> [20], 2021	Pakistan	Case report	1	64	Male	T2DM, HTN	No	Acute LLI	Above knee amputation	Discharged home
Balanescu <i>et al</i> [33], 2021	MI, United States	Case series	4	20-77 (median 52)	Male (50)	Obesity (50%)	Unknown	PE	Mechanical thrombectomy (100%)	Discharged home (100%)
Bilge <i>et al</i> [21], 2021	Turkey	Case report	1	73	Male	HTN	No	Upper extremity arterial thromboembolism	Left upper extremity arteriotomy and arterial thrombectomy. Repeat thrombectomy 12 h later. Amputation at the level of the forearm 13 d later. Stump revision with amputation 22 d later	Discharged home
Bozzani <i>et al</i> [22], 2020	Italy	Case series	6	71 (49-83)	4 males (66)	3 PAD, other unknown	Unknown	Acute LLI	Urgent revascularization procedures (embolectomy in 3 cases, and hybrid open/endo procedures in other 3)	1 rethrombosed day 5, died 30 d later of MOF. 1 rethrombosed day 5, repeat embolectomy, above knee amputation. 4 discharged home. 23 discharged home in good condition
Cheung <i>et al</i> [55], 2020	NY, United States	Case report	1	55	Male	HTN	No	SMA thrombosis, bowel ischemia	Emergency exploratory laparotomy and SMA thrombectomy, necrotic small bowel resection	Discharged home
Dao <i>et al</i> [56], 2021	CA, United States	Case report	1	61	Male	HTN	Yes	Free floating descending aortic thrombus	Percutaneous vacuum assisted aortic thrombectomy	Discharged home
Dinoto <i>et al</i> [23], 2021	Italy	Case report	1	78	Male	DM, obesity, prior remote endovascular surgery for large popliteal aneurysm	No	Acute LLI. Thrombosis of left femoral-popliteal stent	Mechanical thrombectomy	Discharged home
Galastrri <i>et al</i> [34], 2020	Brazil	Case report	1	57	Male	DM, obesity, HTN	Yes	Massive PE	Catheter directed thrombolysis	Discharged home
Gutierrez <i>et al</i> [39], 2022	NY, United States	Case report	1	53	Male	HTN, remote smoking, DM	Yes	Due to phlegmasia cerulea dolens	Fasciotomy and mechanical thrombectomy	Discharged PAD 70
Hwabejire <i>et</i>	MA,	Case series	20	58 ± 7	13 males	Obesity (60%)	85% (17) received	Acute bowel ischemia	Laparotomy with resection of bowel	50% overall mortality rate: (1)

<i>al</i> [19], 2021	United States				(65)			preoperative anticoagulation		100% mortality in patients ≥ 65 yr; (2) 33% mortality < 65 yr; and (3) 40% (8) developed
Jamshidi <i>et al</i> [40], 2021	CA, United States	Case report	1	51	Male	Tricuspid atresia status post Fontan and extracardiac Shunt	Yes	Bilateral lower extremity DVT, phlegmasia cerulea dolens of the left lower extremity	Catheter directed mechanical thrombectomy (PAD 13), left below knee amputation (PAD 41)	Discharged to rehabilitation facility PAD 50
Khanna <i>et al</i> [32], 2021	PA, United States	Case report	1	67	Female	HTN	No	Acute stroke from bilateral anterior circulation large vessel occlusion	Bilateral simultaneous mechanical thrombectomy	Full neurologic recovery
Nascimbene <i>et al</i> [35], 2021	TX, United States	Case report	1	44	Male	Patent foramen ovale, T2DM, HTN, dyslipidemia, obesity	No	Massive PE with a large right atrial thrombus	Percutaneous right and left atrium embolectomy	Discharged home
Naudin <i>et al</i> [24], 2021	France	Case report	1	56	Male	T2DM, HTN, obesity	No	Acute aortoiliac thrombus and LLI	Aortoiliac and lower limb artery mechanical thrombectomy and left lower limb fasciotomies, subsequent left below knee amputation	Extubated but still in ICU 6 wk post operatively
Szeles <i>et al</i> [25], 2021	NY, United States	Case report	1	67	Male	DM, hyperlipidemia, HTN	No	Acute LLI and aortic mural thrombosis	Emergency bilateral aortiliac and distal embolectomies, followed by transmetatarsal amputation of the right foot and below knee amputation of the left limb	
Topcu <i>et al</i> [26], 2021	Turkey	Single center cross sectional study	3	62 (58-70)	3 (100)	1 ex-smoker	Yes (100%)	Acute LLI	3 emergency surgical thrombectomy	1 minor amputation (33.3%); 1 death (33.3%); 1 bilateral major amputation (33.3%)
Traina <i>et al</i> [18], 2021	Italy	Case report	1	80	Male	CVD, prior endovascular aortic repair in 2019 for abdominal aneurysm repair, and dyslipidemia	No	Bowel ischemia with aorto-enteric fistula formation	Laparotomy with resection of necrotic small bowel (occult COVID-19, diagnosed on histologic examination of resected small bowel)	Discharged home
Vyas <i>et al</i> [36], 2020	NY, United States	Case report	1	32	Male	None	No	Large saddle pulmonary embolus	Bilateral percutaneous pulmonary artery mechanical thrombectomy	Discharged home 3 d post procedure
Yang <i>et al</i> [17], 2021	Germany	Cohort study	20	69 (62-72)	15 males (75)	65% (13) obese	25% (5)	Colonic ischemia	12 (60%) underwent (sub)total colectomy, 7 (35%) right hemicolectomy, 1 (5%) ileocecal resection	9 (45%) surgical complications, 10 (50%) required revision surgery, 9 (45%) mortality
Zivkovic <i>et al</i> [57], 2021	Serbia	Case report	1	44	Female	None	No	Ascending aorta floating thrombus with acute right arm ischemia	Surgical thrombus extraction through open sternotomy and bypass surgery	Discharged POD 6

Madani <i>et al</i> [27], 2021	CA, United States	Cases report	1	40	Male	HTN, T2DM	Yes	Acute LLI	Right lower extremity above knee amputation	Discharged 41 d after admission
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DM: Diabetes mellitus; DVT: Deep venous thrombosis; HTN: Hypertension; LLI: Lower limb ischemia; PE: Pulmonary emboli; MOF: Multi organ failure; SMA: Superior mesenteric artery; PAD: Peripheral artery disease; ICU: Intensive care unit; CVD: Cardiovascular disease; COVID-19: Coronavirus disease 2019; POD: Post op day.

DISCUSSION

Thromboembolic complications are a well-known sequela of COVID-19 infection, and their incidence has been the subject of many recent studies. The predisposition to the development of both venous and arterial thromboembolic complications by COVID-19 has also been well established, with incidences of thromboembolic complications in COVID-19 patients ranging from 7.2% to 40.8%[16]. The high complication rate poses a public health concern due to the increased morbidity, mortality and high costs associated with their development[16]. Such complications also pose a significant challenge to physicians treating them, as the need for a surgical intervention must be weighed against the risk of operation in an unstable and high-risk individual while the patient is in an already prothrombotic state. There is a significant gap in the literature describing the relationship between COVID-19 infections and thrombotic events requiring surgical intervention.

Of the 70 COVID-19 patients with thromboembolic complications necessitating surgical intervention found in our study, 85% ($n = 60$) had thrombotic complications considered to be arterial in origin. The most common complication reported was intestinal ischemia at 60% ($n = 42$)[17-19]. The second most common complication was acute limb ischemia (ALI) at 23% ($n = 16$), which included 14 cases of lower limb ischemia and 2 cases of upper limb ischemia[20-27]. ALI is defined as a sudden decrease in arterial perfusion of an extremity that compromises the viability of a limb[28]. Prior to the COVID-19 pandemic, the incidence of ALI in the general population was found to be 10 to 15 per 100000 cases each year (0.0001%-0.00015%)[20]. However, one study performed in a New York City hospital found the rate of ALI in the COVID-19 population to be as high as 0.38%[29]. Treatment of ALI includes endovascular or open surgical revascularization, however 10% to 15% of patients end up undergoing amputation during their hospitalization[30,31]. Of the 16 cases of ALI in the population being investigated, 8 (50%) of these patients eventually underwent some form of amputation of the affected extremity. In addition to the above cases, our cohort had 1 case of stroke due to bilateral arterial thrombosis of the anterior circulating vessels, which was treated with bilateral simultaneous mechanical thrombectomy[32].

In contrast to arterial thrombotic events, venous thrombotic events are a more common sequela of COVID-19, with the PE and DVT at an estimated incidence of 13.5% and 11.8% respectively[16]. In our study, PE accounted for 10% ($n = 7$) of thrombotic events necessitating surgical intervention[33-36], notably higher than both the reported incidence of PE amongst non-intensive care unit (ICU) hospitalized patients and ICU patients with COVID-19 (1.3% and 6.2%, respectively)[37,38]. Interestingly, our study included two cases of phlegmasia cerulea dolens (PCD)[39,40], a rare and life-threatening form of DVT that results in arterial occlusion secondary to compartment syndrome caused by total venous occlusion[41]. PCD has been reported to have an amputation rate close to 50%, as well as a mortality of up to 40%[42]. Of the two patients in our study with PCD, only one required amputation. Also included

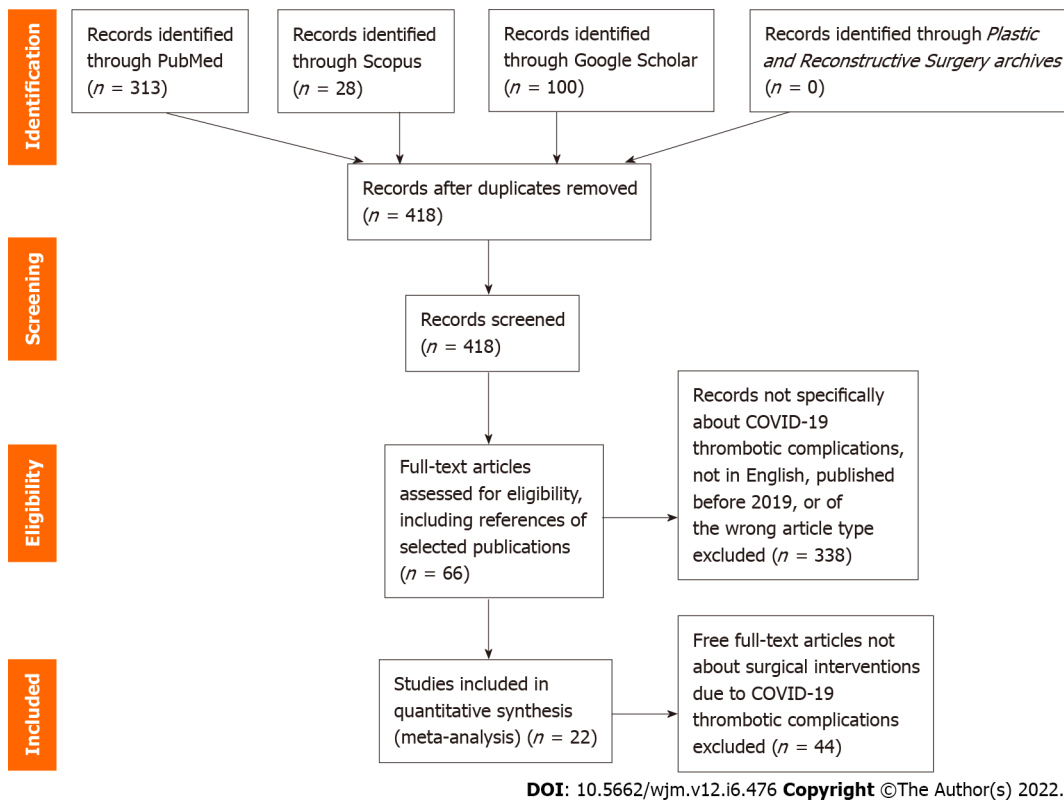


Figure 1 Search strategy for our systematic review to find the currently published medical literature describing surgical interventions necessitated by coronavirus disease 2019 thrombotic complications. COVID-19: Coronavirus disease 2019.

in our cohort was one patient who required bilateral transmetatarsal amputations due to the development of “COVID toes”, thought to be due to either microvascular thrombosis or related to a rare complication of venous thrombosis manifesting as venous gangrene[43].

Mortality

Several studies have attempted to quantify mortality related to thromboembolic events in COVID-19 patients. One study found that COVID-19 patients with a thromboembolic event had a 40% mortality rate, over twice that of COVID patients without a thrombotic event[44]. Another study, a meta-analysis of 8271 patients, found that patients with COVID-19 who had thromboembolic events had a pooled mortality rate of 23%, with thromboembolism significantly increasing the odds of mortality by as high as 74%[45]. Similarly, Gonzalez-Fajardo *et al*[46] found a mortality rate of 23.58% in their retrospective review of COVID-19 patients with thrombotic events, with a higher mortality seen in patients with peripheral arterial thrombosis and ischemic stroke compared to those with DVT and PE. Our study of COVID-19 patients with thrombotic events needing surgical intervention produced an overall mortality rate of 30% ($n = 21$). Notably, the highest mortality rate was seen in patients with acute intestinal ischemia who underwent bowel resection (45%, $n = 19$ of 42), followed by patients treated for ALI (13%, $n = 2$ of 15). It is unclear at this time if COVID-19 infection significantly complicated the cases of bowel resection, as acute intestinal ischemia has been noted to have a mortality rate as high as 80%, even without the added complexity of COVID-19 infection[47]. This is partly due to difficulty in diagnosis, importance of early diagnosis, and the rapid deteriorating nature of ischemic intestinal tissue and the patient’s condition. It is possible that severe COVID-19 infection delayed the diagnosis of intestinal ischemia in several of the patients included in this study, leading to higher mortality rates. Difficulties in accessing medical and surgical care due the widespread impact of the current COVID-19 pandemic in every aspect of the health care could also be influential although the true nature and depth of such an impact is a matter of speculation.

Comorbidities

In total, 17 of the 70 patients in this review had specific comorbidity data readily available. The most common comorbidities amongst our cohort of patients were hypertension (64%, $n = 11$), diabetes mellitus (53%, $n = 9$), and obesity (35%, $n = 6$), all of which have previously been associated with a prothrombotic state[48,49]. Hypertension has been noted to be an independent risk factor for the development of deep vein thrombosis in a large study of over 18000 patients[50], so it is not surprising that patients with hypertension and COVID-19 infection were at an increased risk of thrombotic

complications necessitating surgical intervention. However, a recent study by Xiong *et al*[51] demonstrated no increase in thrombotic events among COVID-19 patients who were obese or had hypertension. Interestingly, their meta-analysis also found a previous diagnosis of diabetes mellitus to have a protective rather than potentiating effect on thrombotic events in this population. These results have been attributed to the use of medications such as statins and metformin, which have some degree of anti-inflammatory effects. While concomitant medication use was not a variable under investigation in our study, future studies may look at the relationship between medications with anti-inflammatory effects and reduced thrombotic complications of COVID-19.

Thrombotic prophylaxis

Since it became apparent that COVID-19 produces a prothrombotic state, much of the focus on thrombotic complication management has been shifted towards prevention. In May of 2020, the International Society on Thrombosis and Hemostasis published a statement regarding hospitalized COVID-19 patients in the ICU, recommending routine thromboprophylaxis with standard-dose low molecular-weight heparin or unfractionated heparin, unless contraindicated[52]. Yet our study found that 44% ($n = 31$) of patients who developed thrombotic complications requiring surgical intervention received some type of prophylactic anticoagulant therapy. This finding is consistent with the current literature, as studies have shown a high rate of thromboembolic complications in COVID-19 patients despite the use of prophylactic anticoagulation[53], with one study estimating this phenomenon to occur in almost one-third of all critically ill COVID-19 patients[54]. As previously stated, CIC has been reported to be the presenting symptom of some severe COVID-19 infections, making it possible for some patients in our study to have had thrombotic events prior to their presentation or COVID-19 diagnosis. Additionally, in several of the studies analyzed by this systematic review, dosage information and duration of thromboprophylaxis was not described, therefore it is unclear if some patients were subtherapeutic with their thromboprophylaxis regimen. Further studies to look at the dose and choice of anticoagulant in relation to severe thromboembolic events in the setting of COVID-19 infection is warranted.

Limitations

Our study is one of the first to analyze the relationship between COVID-19 infection and thrombotic complications that required surgical intervention, but there were several limitations. As all the included studies in this review were retrospective in nature, bias cannot be eliminated. Additionally, differences between the studies included in this review may lead to an additional bias, including the reporting of and variation of type and dosage of thromboprophylaxis. The reporting of outcomes and mortality, location of thrombotic events, and the method of surgical management also varied between many of the studies. Finally, our review drew a relatively small sample size, and our search criteria included only those studies in which patients were reported to have surgical intervention for their thrombotic events, and therefore incidence data could not be calculated.

CONCLUSION

There is paucity of data describing the relationship between COVID-19 infection and thrombotic complications necessitating the need for surgical intervention. Intestinal ischemia and ALI are amongst the most common thrombotic events due to COVID-19 that required operative management. An overall postoperative mortality of 30% was found in those who underwent operative procedures for thrombotic complications, with most deaths occurring in those with bowel ischemia. Physicians should be aware that despite thromboprophylaxis, severe thrombotic complications can still occur in this patient population, however, surgical intervention results in relatively low mortality apart from cases of ischemic bowel resection.

ARTICLE HIGHLIGHTS

Research background

It is well-known that coronavirus disease 2019 (COVID-19) infection is associated with hypercoagulability among affected patients. This has become known as COVID-19 induced coagulopathy (CIC). This study investigated CIC-related thrombotic complications through a systematic review and meta-analysis of the existing literature.

Research motivation

There is paucity of data describing the relationship between COVID-19 infection and thrombotic complications necessitating the need for surgical intervention. Intestinal ischemia and acute limb ischemia (ALI) are amongst the most common thrombotic events due to COVID-19 that required

operative management. An overall postoperative mortality of 30% was found in those who underwent operative procedures for thrombotic complications, with most deaths occurring in those with bowel ischemia. Physicians should be aware that despite thromboprophylaxis, severe thrombotic complications can still occur in this patient population, however, surgical intervention results in relatively low mortality apart from cases of ischemic bowel resection.

Research objectives

Main, overarching objective was to conduct a systematic review to find the currently published medical literature describing surgical interventions necessitated by COVID-19 thrombotic complications. We achieved this objective and identified intestinal ischemia and ALI as the most common thrombotic events necessitating surgical intervention.

Research methods

The current systematic review was performed using an algorithmic approach to review all the currently available articles in the English medical literature on surgical interventions necessitated by COVID-19 thrombotic complications using the preferred reporting items for systematic reviews and meta-analysis principles. A comprehensive literature search in the "PubMed", "Scopus", "Google Scholar" top 100 results, and archives of *Plastic and Reconstructive Surgery* was performed by two authors (Reynolds A and Edoigiawerie S) on January 4, 2022, using the key words "COVID-19" AND "surgery" AND "thromboembolism" AND "complication" as well as associated terms. The search string was generated and the records which were not relevant were excluded. Articles published prior to 2019 were excluded as being prior to the COVID-19 pandemic and therefore not relevant to complications associated with COVID-19 infection. Titles, abstracts, and full-text articles were assessed for eligibility and inclusion. On initial and secondary search, papers in review, commentary, or letter format or those without accessible full-text articles were excluded. Finally, results were further reviewed and refined to focus on articles that featured surgical interventions that were necessitated by COVID-19 thrombotic complications. For completion of the search, the references of the selected publications were additionally screened with the previously mentioned inclusion criteria.

Research results

The database search resulted in the final inclusion of 22 retrospective studies, after application of the inclusion/exclusion criteria. Of the included studies, 17 were single case reports, 3 were case series and 2 were cross sectional cohort studies. All studies were retrospective in nature. Twelve of the reported studies were conducted in the United States of America, with the remaining studies originating from Italy, Turkey, Pakistan, France, Serbia, and Germany. All cases reported in our study were laboratory confirmed severe acute respiratory syndrome coronavirus 2 positive. A total of 70 cases involving surgical intervention were isolated from the 22 studies included in this review.

Research conclusions

Physicians should be aware that despite thromboprophylaxis, severe thrombotic complications can still occur in this patient population, however, surgical intervention results in relatively low mortality apart from cases of ischemic bowel resection.

Research perspectives

Future directions could focus on how to prevent thrombotic complications and mitigate mortality among patients at risk for ALI and bowel ischemia in particular.

FOOTNOTES

Author contributions: Hamidian Jahromi A contributed to conceptualization and manuscript editing; Ferraro JJ, Reynolds A, Edoigiawerie S, Seu MY, Horen SR, and Aminzada A contributed to writing, statistical analysis, and manuscript editing.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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L-Editor: A

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