Androgen Drives the Expression of SARS-CoV-2 Entry Proteins in Sinonasal Tissue

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Abstract

Background and objectives: Men have higher morbidity and mortality from COVID-19 than women, possibly due to androgen receptor-regulated viral entry protein expression. This led to a clinical trial of androgen deprivation therapy (ADT), which has not shown a significant benefit in the outcomes among hospitalized male COVID-19 patients. The aim of this study was to explore biological explanations for the failure of ADT to mitigate clinical outcomes in men with severe COVID-19 by assessing the role of androgen in regulating viral entry protein expression in the upper and lower respiratory tract. Methods: Immunohistochemistry was used to assess the expression of transmembrane serine protease 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) and how it correlated to androgen receptor expression in the sinonasal epithelium, minor salivary glands of the sinus, lacrimal glands, and lungs from mice pretreated with and without castration and ADT as well as the sinonasal epithelium obtained from healthy human donors and hospitalized COVID-19 patients. Results: In murine models, castration and ADT treatment downregulated the expression of TMPRSS2 and ACE2 in the sinonasal epithelium, minor salivary glands of the sinus, lacrimal glands, and lungs from mice pretreated with and without castration and ADT as well as the sinonasal epithelium obtained from healthy human donors and hospitalized COVID-19 patients. Conclusions: Our study suggests a potential benefit of ADT in male patients with early COVID-19 when the virus enters the nasopharynx, but not in those with advanced disease. The downregulation of viral entry proteins in the upper respiratory system following androgen blockade may be a key mechanism for this effect.

Introduction

The morbidity and mortality of COVID-19 are higher in men than women, whereas the incidence is only slightly higher in women.1 The gender disparity indicates a potential role of androgen and/or estrogen in the regulation of viral infection in target cells and in the host immune response. SARS-CoV-2 viral entry into host cells is mediated by the interaction between the viral spike (S) protein and two host cell-surface molecules: receptor angiotensin-converting enzyme 2 (ACE2) and S protein primer transmembrane serine protease 2 (TMPRSS2). TMPRSS2 cleaves the S protein and allows the activated S protein to bind to its receptor ACE2. Furin, another cell-surface protease, is also involved in S protein priming by cleaving the S protein on a second proteolytic site.2 TMPRSS2 is known to be transcriptionally upregulated by androgen in the human prostate and in prostate cancer (PCAs). Approximately 40% of human PCAs harbors a translocation between the TMPRSS2 and ERG genes, leading to androgen-dependent overexpression of ERG oncoprotein. In early 2020, a study from Italy showed that PCAs patients on androgen dep-
rivation therapy (ADT) had a significantly lower incidence of COVID-19 compared to PCa patients not on ADT. Based on the above evidence, we hypothesized that ADT may be able to suppress SARS-CoV-2 viral entry into target cells through the downregulation of TMPRSS2 and perhaps ACE2 and furin. Two phase 2 randomized, double-blind, placebo-controlled clinical trials, including our “Hormonal Intervention for the Treatment in veterans with COVID-19 requiring Hospitalization” (HITCH) study (ClinicalTrials.gov Identifier: NCT04397718), failed to demonstrate that rapid suppression of serum androgen levels to a castrate range affected the clinical outcomes of men hospitalized for COVID-19. During the trial, several independent studies reported preclinical evidence in animal models and cell lines that androgen deprivation or androgen receptor (AR) antagonists reduce SARS-CoV-2 host cell entry. In this study, we aimed to critically evaluate the role of androgen in regulating TMPRSS2, ACE2, and furin protein expression in the upper and lower respiratory tract epithelium.

Methods

Cell lines, xenografts, and patient-derived xenograft (PDX) models

The cell lines used in this study (LNCaP, A549, H441, H2170) were purchased from the American Type Culture Collection (Manassas, VA, USA) and cultured in the recommended media. 16D cells were obtained from Dr. Amina Zenovich (Vancouver Prostate Centre, BC, Canada) and maintained as previously described. The cells were grown on plates coated with 0.01% poly-L-lysine (Sigma; St. Louis, MO, USA) to enhance attachment. Enzalutamide (Selleck Chemicals; Houston, TX, USA; 10 μM) or apalutamide (Janssen Research & Development; Titusville, NJ, USA; 1 μM), was replaced every other day for the period specified in each figure. For the castration experiments, the cells were cultured in media supplemented with charcoal-stripped fetal bovine serum (Sigma). LNCaP cells were used for the subcutaneous xenograft injections within four passages. Six-week-old male ICR/scid mice were purchased from the American Type Culture Collection (PDX) models

Western blot and RNA sequencing

Cells were lysed in radioimmunoprecipitation assay buffer (50 mM Tris-HCl pH 8.0, 150 mM NaCl, 1% NP-40, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate; Fisher Scientific) containing a complete protease inhibitor cocktail tablet (Roche, Indianapolis, IN, USA) and Halt Phosphatase Inhibitor (Fisher Scientific). Each sample was sonicated for 40 s at 20 kHz with a sonic dismembrator (Fisher Scientific) to improve the membranous and nuclear protein yield. Samples were run on NuPAGE 4-12% Bis-Tris gels (Invitrogen, Carlsbad, CA, USA) and transferred onto 0.45-μm polyvinylidene fluoride membranes (Millipore Sigma, Burlington, MA, USA). Total protein was visualized using SYPRO RUBY protein blot stain (Fisher Scientific), and membranes were blocked in phosphate-buffered saline + 0.1% Tween-20 (Fisher Scientific) + 5% milk (Fisher Scientific) for 1 h. The membranes were probed overnight at 4°C with the following primary antibodies: prostate-specific antigen (PSA; Cell Signaling Technology, Danvers, MA, USA; 5877, 1:1,000), TMPRSS2 (Abcam; Waltham, MA, USA; 92323, 1:1,000), vinculin (Abcam; 129002, 1:6,000), AR (Cell Signaling Technology; 5153, 1:2,000), furin (Abcam; 183495, 1:1,000), glyceraldehyde 3-phosphate dehydrogenase (GAPDH; Cell Signaling Technology, Danvers, MA, USA; GT239, 1:10,000). The membranes were then incubated with chromophore-conjugated secondary antibodies (Fisher Scientific) or horseradish peroxidase-conjugated secondary antibodies (Fisher Scientific) for 1 h and detected via florescence or horseradish peroxidase chemiluminescence using an Amersham ECL Premiere Western Blotting Detection Reagent (Fisher Scientific, respectively). For RNA sequencing, RNA was extracted from 16D cells treated with dimethyl sulfoxide or 10 μM enzalutamide for 48 h using a RNeasy Mini Kit (Qiagen; Germantown, MD, USA). Library preparation was performed using the KAPA Stranded mRNA-Seq Kit.
(Roche). The workflow consists of mRNA enrichment, cDNA generation, and end repair to generate blunt ends, A-tailing, adaptor ligation, and polymerase chain reaction amplification. Different adaptors were used for multiplexing samples in one lane. The Illumina HiSeq 3000 was used to perform sequencing for 1 × 50 runs. The data have been deposited in NCBI’s Gene Expression Omnibus and are accessible through GEO Series accession number GSE202885.

IHC

Tissue sections (3 μm) were subjected to immunohistochemical staining. The sections were stained using anti-TMPRSS2 (clone EPR3861, rabbit, Abcam; 1:16,000), anti-TMPRSS2 (obtained from the Peter Nelson Lab, University of Washington, Seattle, WA, USA; mouse; 1:200), anti-AR (clone SP107, rabbit, Cell Marque, Rocklin, CA, USA; 1:100), anti-AR (441, mouse, Santa Cruz, 1:100), anti-ACE2 (clone MM0073-11A31, mouse, Abcam, 1:200), anti-ACTB (ab15348, rabbit, Abcam, 1:100), and anti-furin (EPR14674, rabbit, Abcam, 1:600). IHC was carried out on a Dako Link 48 autostainer (Agilent Technologies, Santa Clara, CA, USA), with antibody incubation for 60 min, amplification using Envision FLEX rabbit or mouse linkers, and visualization using the Envision Flex High-sensitivity visualization system (Agilent Technologies).

Nasopharyngeal (NP) swabs

The NP swab specimens obtained from the HITCH subjects were placed in viral transport media and then centrifuged to remove the supernatant fluid. The cell pellets were transferred to a 1.5-mL Eppendorf tube. One drop of warmed Histogel heated at 42°C was added to each pellet. A clot formed within 3–5 min. The clot was then processed by routine formalin-fixation and paraffin-embedding for histology.

Statistical analysis

Prism v8.3.0 (GraphPad; San Diego, CA, USA) was used to generate graphs and perform statistical analyses. All t-tests conducted were two-sided t-tests with Welch’s correction. All error bars represent the standard error of the mean. A p-value of <0.01 was considered statistically significant.

Results

Androgen has a minimal effect on TMPRSS2 protein expression in murine or human PCa

Although TMPRSS2 is a canonical AR target in human PCa, it is still unknown whether TMPRSS2 expression is exclusively regulated by androgen in prostate tissue and PCa. To examine the dependency of androgen regulation in TMPRSS2 expression, we assessed the changes in TMPRSS2 protein expression in prostate glands of male mice after ADT. C57BL/6 (n = 9) mice were treated with vehicle or the AR antagonist enzalutamide (n = 3 each). Similarly, androgen deprivation by surgical castration did not reduce the staining intensity of any of these viral entry proteins in murine lungs (Fig. 2c). Next, we tested the effect of an androgen antagonist and androgen deprivation on the expression levels of TMPRSS2, ACE2, and furin in murine lungs. We observed no apparent reduction in TMPRSS2, ACE2, or furin staining in murine lungs following enzalutamide treatment for 1 week or 2 weeks (n = 3 each group), regardless of the age of the mouse (Fig. 2a). Similarly, androgen deprivation by surgical castration did not reduce the staining intensity of any of these viral entry proteins in murine lungs (n = 6 each) (Supplementary Fig. 3). In agreement with the IHC results in murine studies, immunoblot analysis from three different human lung cancer cell lines showed minimal AR expression as well as a low level of TMPRSS2 expression that was not altered by enzalutamide treatment (Fig. 2b).

Androgen regulates TMPRSS2, ACE2, and furin in murine sinonasal tissue

The injection of SARS-CoV-2 in humans first occurs in the nasal cavity and nasopharynx in the very early phase of COVID-19
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Fig. 1. TMPRSS2 protein expression in the prostate and prostate cancer is not primarily driven by androgen. (a) Representative images of TMPRSS2 IHC of murine prostate glands (n = 18; 9 young and 9 old) treated with vehicle, enzalutamide for 1 week, or enzalutamide for 2 weeks (n = 3 each), respectively. (b) Representative images of TMPRSS2 IHC of murine prostate glands (n = 8) treated with vehicle (n = 4), enzalutamide (n = 2), or abiraterone (n = 2), respectively. (c) Western blots of LNCaP and 16D cells treated with castration, enzalutamide (Enza), or Apalutamide (Apa), demonstrating the expression of TMPRSS2, PSA, and the loading control vinculin. (d) Quantification of RNA sequencing data (TPM) demonstrated reduced mRNA levels of KLK3 (PSA) and TMPRSS2 in 16D cells treated with vehicle or enzalutamide for 48 h. Data represent the unpaired t test with Welch’s correction. ***p < 0.001, **p < 0.01. (e, f) Representative images of TMPRSS2 IHC of LNCaP xenografts (e) (n = 2 each) and a patient-derived xenograft (f) at precastration, 7 days post castration, or 7 days post castration + enzalutamide treatment, respectively (n = 2 each). IHC, immunohistochemistry; KLK3, kallikrein 3; PSA, prostate-specific antigen; TMPRSS2, transmembrane serine protease 2.
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Fig. 2. Androgen signaling showed no effect on regulating the expression of viral entry proteins in murine lungs. (a) Representative images of lungs of mice (9 young and 9 old) treated with vehicle, enzalutamide for 1 week, or enzalutamide for 2 weeks (n = 3 in each group), stained with antibodies against TMPRSS2, ACE2, furin, and AR (all at 200× magnification). (b) Western blots of LNCaP and three different lung cell lines treated with 10 µM enzalutamide for 3.5 days, blotted for AR, PSA, TMPRSS2, and the loading control GAPDH. ACE2, angiotensin-converting enzyme 2; AR, androgen receptor; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; PSA, prostate-specific antigen; TMPRSS2, transmembrane serine protease 2.
Androgen regulates SARS-CoV-2 entry proteins in nasosinus disease. Subsequently, the virus spreads to the lower respiratory tract, including the bronchi and lungs, the main target organs. Accordingly, we sought to assess the potential role of androgen signaling in SARS-CoV-2 entry protein expression in the nasal cavities. First, we performed immunostaining using turbinate specimens from male patients who underwent sinus surgery. The respiratory epithelium showed a low level of AR protein expression. TMPRSS2 and ACE2 colocalized at the ciliated apical border of the respiratory epithelium (Fig. 3a). Co-expression of AR and TMPRSS2 as well as co-expression of AR and ACE2 were easily detected by dual immunostaining.

Next, we assessed AR expression in the nasal mucosa of male mice by examining coronal sections of the mouse skull. In the murine nasal cavities, the dorsal portion was lined by the olfactory epithelium, and the ventral portion was lined by the respiratory epithelium. AR was weakly expressed in both the olfactory and respiratory epithelia (Fig. 3b). TMPRSS2, ACE2, and furin were all expressed at the apical border of the respiratory epithelium. TMPRSS2 was expressed in the respiratory epithelium but not in the olfactory epithelium. Co-expression of AR and TMPRSS2 was detected in the respiratory epithelium, as shown in Figure 3b, with the inset showing...
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Colocalization of AR and TMPRSS2 in the same ciliated columnar cells. ACE2 was expressed in both the respiratory and olfactory epithelium, with a stronger expression in the olfactory epithelium (Fig. 3b, 4a). Furin was diffusely expressed in the mucosa of the entire nasal cavity. Interestingly, murine lacrimal glands showed a strong expression of AR, TMPRSS2, ACE2, and furin; whereas the minor salivary glands surrounding the respiratory sinus strongly expressed AR, TMPRSS2, and furin (Fig. 4). Next, we evaluated the effects of ADT on the abundance of these proteins in the sinonasal tissue by treating mice with mock castration or surgical castration (n = 6 in each group). In the castrated mice, the staining intensity of AR, TMPRSS2, ACE2, and furin was markedly reduced in the lacrimal glands, and it was mildly reduced in the nasal epithelium and minor salivary glands compared with that of the control mice (Fig. 4a). Immunoblots of mouse nasal mucosa from the same set of mice demonstrated a mild reduction of TMPRSS2 expression in the castrated mice (Fig. 4b). Additionally, we treated mice with the androgen antagonist enzalutamide or bicalutamide (n = 3 each) for 1 week. AR blockade was associated with a mild reduction of TMPRSS2, ACE2, and furin expression in the mouse nasal mucosa, as detected by western blot and IHC (Fig. 4c, Fig. 4). Table 1 summarizes all experiments that were conducted in this study to assess the role of androgen in modulating the expression of viral entry proteins.

Sample inadequacy prohibited IHC evaluation for NP epithelium collected from HITCH patients

Next, we sought to examine the potential antiviral effect of ADT in male COVID-19 patients. First, we established the
protocol of NP cell block preparation and subsequent IHC staining using NP swabs obtained from healthy male donors (Supplementary Fig. 5a). The NP swab generated abundant respiratory epithelial cells, with most cells strongly positive for TMPRSS2 and a small subset of cells weakly positive for AR and ACE2. Subsequently, we collected paired NP swabs from HITCH trial patients at hospital day 1 (just prior to medical castration) and day 8 (one week after medical castration). Unexpectedly, most of the NP samples obtained from the HITCH patients generated few epithelial cells; therefore, there were insufficient cells for IHC evaluation. In rare NP samples with good cellularity, we were able to detect the co-expression of viral guide RNA and TMPRSS2 in ciliated epithelial cells (Supplementary Fig. 5b). Paired day 1/day 8 samples from two trial patients showed no apparent changes in the TMPRSS2 staining intensity in rare NP cells (Supplementary Fig. 5c). Further optimization of the methodology was not able to increase the cellularity of the patient samples. Thus, we discontinued NP swab collection, given the risk of disease contraction during the sample collection and handling.

**Discussion**

Randomized clinical trials have failed to show that ADT improves the clinical outcomes of hospitalized male COVID-19 patients. Murine studies have reported conflicting data on androgen-mediated regulation of the expression of viral entry proteins in the lungs. In our IHC survey of mouse and human tissues, we detected the co-expression of AR and viral entry proteins in sinonasal tissues and the bronchial epithelium, while the co-expression was rarely detected in the pulmonary alveolar tissue. In the mouse studies, castration and AR antagonist treatment were associated with the reduced expression of viral entry proteins in the sinonasal tissue but failed to do so in the lungs.

Our observations in the murine experiments do not align with prior studies that demonstrated androgen-mediated TMPRSS2 and ACE2 expression in the lungs. The discrepancy is likely due to the difference in detection methods. Qiao et al. measured TMPRSS2 expression using RNA sequencing and RNA in-situ hybridization. The authors did not measure TMPRSS2 protein expression in murine or human lungs due to the lack of a suitable IHC antibody. Likewise, they showed co-expression of AR and viral RNA in murine and human lungs using in-situ hybridization dual staining. Importantly, the transcript and protein levels of many genes are poorly correlated, including for AR-regulated genes. In support of this notion, enzalutamide reduced TMPRSS2 mRNA expression but did not reduce the TMPRSS2 protein levels in PCA cell lines (Fig. 1c–d). In our dual IHC staining experiments, the co-expression of AR and ACE2 was rare in the human alveolar epithelium (Supplementary Fig. 2b). In line with our findings, Baratchian et al. found that treatment with enzalutamide did not decrease pulmonary TMPRSS2 or ACE2 protein expression in male mice. Similarly, Li et al. have reported that enzalutamide treatment failed to downregulate TMPRSS2 expression in mouse lungs and human lung organoids. Moreover, they observed that enzalutamide treatment did not inhibit SARS-CoV-2-driven entry into lung cells in mouse models. Similarly, a recent study has shown that enzalutamide treatment did not suppress TMPRSS2 mRNA expression and had no impact on SARS-CoV-2 infection in differentiated human bronchial epithelial cells.

**Table 1. Summary of results by tissue type and treatment modality**

<table>
<thead>
<tr>
<th>Tissue/Cell Type</th>
<th>Treatment</th>
<th>Reduced Expression Detected by IHC (or WB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TMPRSS2</td>
</tr>
<tr>
<td><strong>Mouse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>Enzalutamide or abiraterone</td>
<td>No</td>
</tr>
<tr>
<td>Lungs</td>
<td>Castration or enzalutamide</td>
<td>No</td>
</tr>
<tr>
<td>Sinonasal mucosa</td>
<td>Castration or enzalutamide</td>
<td>Yes (IHC&amp;WB)</td>
</tr>
<tr>
<td>Lacrimal glands</td>
<td>Castration or enzalutamide</td>
<td>Yes</td>
</tr>
<tr>
<td>Minor salivary glands of sinus</td>
<td>Castration or enzalutamide</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Human</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer cell lines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNCaP</td>
<td>Castration ± enzalutamide</td>
<td>No (WB)</td>
</tr>
<tr>
<td>16D</td>
<td>Enzalutamide or apalutamide</td>
<td>No (WB)</td>
</tr>
<tr>
<td>HSPC xenografts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNCaP xenograft</td>
<td>Castration ± enzalutamide</td>
<td>No</td>
</tr>
<tr>
<td>Patient PDX</td>
<td>Castration ± enzalutamide</td>
<td>No</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td></td>
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<tr>
<td>Lung cancer cell lines</td>
<td></td>
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</tr>
<tr>
<td>A549</td>
<td>Enzalutamide</td>
<td>No (WB)</td>
</tr>
<tr>
<td>H441</td>
<td>Enzalutamide</td>
<td>No (WB)</td>
</tr>
<tr>
<td>H2170</td>
<td>Enzalutamide</td>
<td>No (WB)</td>
</tr>
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</table>

IHC, Immunohistochemistry; WB, Western Blot; HSPC, Hormone sensitive prostate cancer.
In our study, the co-expression of AR with TMPRSS2 or ACE2 was detected in human and murine sinonasal mucosa (Fig. 3–4). Castration or AR antagonist treatment downregulated the expression of TMPRSS2, ACE2, and furin in murine sinonasal tissue. Notably, the AR expression in the lacrimal glands and minor salivary glands of the sinus was much stronger compared with that in the sinonasal epithelium, indicating that those adjacent exocrine glands are more sensitive to ADT. While the nasal epithelium is a putative primary target for SARS-CoV-2 replication in the early stage of COVID-19,9–11,15 recent studies have shown that the salivary glands and lacrimal glands are potential primary targets in early COVID-19.16–20 The lacrimal glands and ducts may serve as a part of the ocular route of viral infection.16,21 The salivary glands are potential viral reservoirs for COVID-19 asymptomatic infection.15,22,23 Based on these findings, we speculate that ADT is potentially effective in men with early COVID-19, when the virus infects and replicates in the sinonasal tissue and adjacent organs. Nevertheless, our study has several limitations that must be addressed. We did not perform a SARS-CoV-2 viral infection experiment in mice, which would require transduction of humanized ACE2. Further, such experiments would require Biosafety Level 3 laboratories, which was not feasible during the execution of our study. In addition, we were not able to obtain evidence of AD-mediated TMPRSS2 expression in human NP mucosa due to inadequate NP swab samples obtained from patients in the HITCH study. The findings from our study implied a role of ADT in the early NP stage of COVID-19 but not in the pneumonia stage. This observation partially explains the failure of ADT in hospitalized men with COVID-19 in clinical trials, including the HITCH trial. The negative results of ADT in hospitalized patients may be traced to multiple factors. For instance, the HITCH trial reported reduced serum testosterone levels in the placebo group at day 8 and day 15, leading to a smaller difference in the serum testosterone levels between the d-garelix group and the placebo group.4 Men with critical illness frequently have decreased serum testosterone levels, through a decrease in adrenal and gonadal androgen synthesis.24–26 This observation further argues against the utility of ADT in late COVID-19. As such, there may be a limited window for ADT to be beneficial, i.e., when the viral infection mainly involves the nasopharynx and when the patients have normal testosterone levels. To test the benefit of ADT in early COVID-19, Cadegiani et al. treated male COVID-19 outpatients with a short course of androgen blockade (ClinicalTrials.gov Identifier: NCT04446429; EAT-DUTA AndroCoV trial).27–29 However, the benefit of ADT in early COVID-19 remains inconclusive, and we are awaiting results from independent trials.

Conclusions

We detected androgen-dependent regulation of TMPRSS2 and ACE2 in mouse sinonasal tissue but not in the mouse lungs. Our findings indicate a potential protective role of ADT in men with early-stage COVID-19.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study design, performance of experiments, analysis and interpretation of data, critical revision (RRH); performance of experiments, analysis and interpretation of data, statistical analysis (JMG, TH); study design, analysis and interpretation of data, critical funding, administration, technical and material support (LYZ); performance of experiments (WBY); technical support, administration (JYR); performance of experiments, analysis and interpretation of data (JWR); technical and material support (SPB); technical and material support, administration (NGN); study design, analysis and interpretation of data, critical revision, administration, material support (MBR); Study design, analysis and interpretation of data, technical and material support (AG); study design, analysis and interpretation of data, manuscript writing, critical revision, administration, technical and material support (HY). All authors have made a significant contribution to this study and have approved the final manuscript.

Data sharing statement

Additional data (figures) are included within the supplementary materials accompanying this publication.

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