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Serum Testosterone Is Associated With the Severity of COVID-19

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Abstract. *Background/Aim: Coronavirus disease 2019 (COVID-19) is more likely to be severe in men than in women. Its association with sex hormones as an aggravating factor for male patients has been attracting attention. This study aimed to investigate whether serum testosterone is associated with the aggravation of COVID-19. Patients and Methods: Serum testosterone concentrations in 116 male patients with COVID-19 and residual serum were measured and examined upon their admission to Sapporo Medical University Hospital between February 1, 2020 and March 31, 2021. Results: Blood samples collected from these patients with COVID-19 were analyzed. The serum testosterone levels were 2.19±1.35, 1.29±0.88, and 0.75±0.58 ng/ml in mild, moderate, and severe groups, respectively. Patients with severe COVID-19 on admission had lower testosterone levels (p<0.001). At a cutoff level of 1.31 ng/ml, the area under the curve for the comparison of severe with non-severe cases was 0.825. Furthermore, serum testosterone levels negatively correlated with C-reactive protein and serum amyloid A levels but positively correlated with calcium, zinc, C3, and C4. Conclusion: In male patients with COVID-19, low serum testosterone levels correlated with disease severity, accompanied by a strong inflammatory reaction and proportion of complement consumption.*

A severe atypical pneumonia was identified in Wuhan, China, in late 2019, which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1).

Since its discovery, numerous studies have tried to understand the complex pathophysiology of the disease, its influences on the human body, and risk factors of severe clinical effects by analyzing epidemiologic trends. Even when known risk factors for coronavirus disease 2019 (COVID-19) such as age are considered, men have a higher disease burden, including worse outcomes (hospitalization and death), highlighting clear sex differences (2, 3). To better understand male predisposition to more severe disease, several studies have proposed hypotheses, one of which involves the possible role of androgens (4, 5). The SARS-CoV-2 S protein binds to angiotensin-converting enzyme 2 (ACE2). After binding to ACE2, the spike protein on the virus is cleaved by proteases such as the transmembrane protease serine 2 (TMPRSS2), a crucial step that allows host cell membrane fusion and viral uptake. In this process, TMPRSS2 interacts with ACE2 and stimulates ACE2, which is thought to be important for host cell infection. TMPRSS2 transcription is mainly regulated by the androgen receptor (AR), and ACE2 expression increases in an androgen-dependent manner (6).

Among patients, those who tend to have a more severe course have advanced age and underlying diseases such as chronic obstructive pulmonary disease, chronic kidney disease, diabetes, hypertension, cardiovascular disease, obesity, and smoking. Currently, interleukin-6 (IL-6), interferon-λ3 (IFN-λ3), thymus activation-regulated chemokine (TARC), *etc*., are used as predictive markers for aggravation. However, these are difficult to perform in many facilities because they require dedicated equipment and reagents. Contrastingly, various factors are speculated to be involved in disease aggravation, such as the

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Table I. *Participant characteristics*.

	Mild	Moderate	Severe	*p*-Value
Number of patients	53	27	36	
Age (median) [IQR]	53.0 [44.0-65.75]	59.0 [51.0-73.0]	57.0 [48.25-61.75]	–
Testosterone (ng/ml)	2.19±1.35	1.29±0.88	0.75±0.58	<0.0001***
AST (GOT) (IU/l)	41.1±19.5	50.7±27.4	60.9±31.2	0.0035**
ALT (GPT) (IU/l)	29.9±18.5	29.2±17.3	44.3±30.9	0.0156*
K (mEq/l)	4.43±3.16	3.90±0.36	4.47±0.73	0.0007***
Ca (mEq/l)	8.81±1.27	8.55±0.49	7.67±0.72	<0.0001***
T-bil (mg/dl)	0.46±0.18	0.53±0.21	0.63±0.45	0.1304
CRP (mg/dl)	3.66±3.79	7.19±3.45	10.3±8.75	<0.0001***
SAA (μg/ml)	561±741	906±736	1543±1291	<0.0001***
C3 (mg/dl)	159.4±26.3	152.8±33.1	123.4±36.7	<0.0001***
C4 (mg/dl)	42.0±10.3	41.2±9.0	27.1±11.4	<0.0001***
IL-6 (pg/ml)	37.2±42.4	61.8±61.8	507.4±1651	<0.0001***
HP (mg/dl)	259.5±121.4	304.4±123.8	232.0±110.8	0.1510
Zn (μg/dl)	70.8±13.5	62.8±9.65	56.6±18.5	<0.0001**
TARC (pg/ml)	148.6±153.9	157.7±301.0	86.3±68.8	0.0037**
IFN-λ3 (pg/ml)	17.9±22.0	26.5±21.4	15.8±15.8	0.0348*

Age is presented as the median [interquartile]. Other data are presented as the mean±standard deviation. The three groups were compared using the Kruskal–Wallis test. Differences between the groups regarding sex were assessed using the chi-squared test. *$p<0.05$; **$p<0.01$, ***$p<0.001$. ALT (GPT): Alanine aminotransferase; AST (GOT): aspartate aminotransferase; C3: complement 3; C4: complement 4; CRP: C-reactive protein; HP: haptoglobin; IFN-λ3: interferon; IL-6: interleukin-6; SAA: serum amyloid A; TARC: thymus activation-regulated chemokine; T-bil, total bilirubin.

association between a decrease in blood testosterone level and disease severity in male patients with COVID-19.

Although the incidence, severity, and mortality rates of COVID-19 are greater in men than those in women, the underlying factors contributing to this sex difference are still being explored. Thus, in this study, we aimed to investigate whether serum testosterone levels are associated with the aggravation of COVID-19. Moreover, we tried to understand the relationship between the severity of various markers reported as COVID-19 severity predictors, testosterone-containing hormones, and commonly used inflammation markers and evaluate markers currently in use.

Patients and Methods

Patient selection. The study enrolled 116 male patients with COVID-19 who had been admitted to Sapporo Medical University Hospital before March 31, 2021. According to World Health Organization (WHO) guidelines, a confirmed COVID-19 case was defined as being positive to the antigen test and/or real-time reverse-transcriptase polymerase chain reaction assay of nasal swab specimens.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the hospital's ethics board (Approval no. 332-114). Informed consent was obtained in an opt-out form on the website.

Data collection and COVID-19 clinical classification. Data were collected from patients' medical records, including demographics, medical history, symptoms, vital signs, laboratory findings, and radiological images. Patients with COVID-19 were classified into three groups according to the COVID-19 severity categorization by WHO.

Measurement of serum protein concentration. Aspartate aminotransferase (AST), alanine aminotransferase (7), potassium (K), calcium (Ca), total bilirubin (T-BIL), C-reactive protein (CRP), serum amyloid A (8), complement 3 (C3), complement 4 (C4), testosterone, IL-6, IFN-λ3, TARC, zinc (Zn), and haptoglobin (HP) using residual specimens (serum or He-Li-added plasma) were measured upon admission. AST, ALT, K, Ca, T-BIL, CRP, SAA, C3, and C4 levels were determined using LABOSPECT008 (Hitachi High-Technologies Corporation, Tokyo, Japan). Testosterone and IL-6 levels were determined by cobas e801 (Roche Diagnostics GmbH, Mannheim, Germany). IFN-λ3 and TARC levels were determined using HISCL-800 (Sysmex Corporation, Kobe, Japan). Zn and HP were measured by BioMajesty ZERO JCA-ZS050 (JEOL Ltd., Tokyo, Japan).

Statistical analysis. All statistical analyses were performed using JMP 13.0 (SAS Institute, Cary, NC, USA) and GraphPad Prism version 9 (GraphPad, Inc., San Diego, CA, USA). Between-group differences were analyzed by the Mann–Whitney *U*-test. The three groups were compared using the Kruskal–Wallis test. Categorical variables were analyzed using the chi-squared test. To determine the appropriate cutoff level using JMP 13.0, serum testosterone levels were further analyzed using the receiver operating characteristic (ROC) curve, allowing for optimal diagnostic accuracy. To identify correlations between two datasets, simple regression analysis (r) was conducted using JMP 13.0. For all analyses, $p<0.05$ was considered statistically significant.

Results

Patient selection and serum testosterone. The study cohort included 116 male patients with COVID-19 who were admitted to Sapporo Medical University Hospital between February 1,

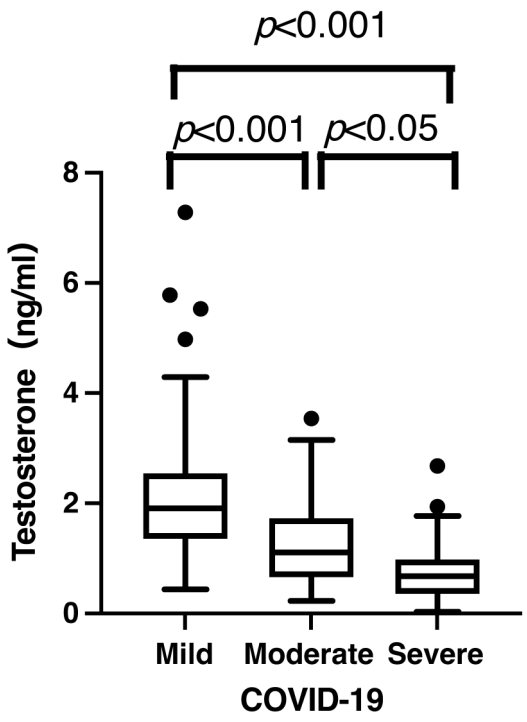

Figure 1. *COVID-19 severity and serum testosterone. Between-group differences were analyzed by the Mann–Whitney U-test.*

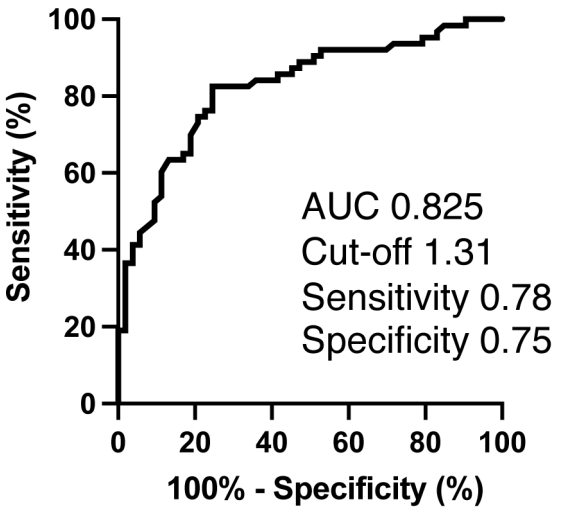

Figure 2. *Receiver operating characteristic (ROC) curves of the serum testosterone with respect to COVID-19 severity. AUC: Area under the curve.*

2020, and March 31, 2021. Blood samples collected from these patients were analyzed. The median age values of the patients with mild, moderate, and severe COVID-19 were 53.0 (IQR=44.0-65.75), 59.0 (IQR=51.0-73.0), and 57.0 (IQR=48.25-61.75) years, respectively (Table I). The serum testosterone levels were 2.19±1.35, 1.29±0.88, and 0.75±0.58 ng/ml in the mild, moderate, and severe groups, respectively. Patients with severe COVID-19 on admission had lower testosterone levels ($p<0.001$) (Figure 1). At a cutoff level of 1.31 ng/ml, the area under the curve (AUC) when comparing severe with non-severe cases was 0.825 (Figure 2).

Correlation of serum testosterone with inflammatory biomarkers, Ca, Zn, and complements. Among the three groups of COVID-19 severity, the severe group had significantly higher serum AST (41.1±19.5, 50.7±27.4, and 60.9±31.2 IU/l), CRP (3.66±3.79, 7.19±3.45, and 10.3±8.75 mg/dl), SAA (561±741, 906±736, and 1,543±1,291 μg/ml), and IL-6 (37.2±42.4, 61.8±61.8, and 507.4±1,651 pg/ml) levels on admission than the mild and moderate groups (Table I). Compared with the mild and moderate groups, the severe group had significantly lower serum Ca (8.81±1.27, 8.55±0.49, and 7.67±0.72 mEq/l), Zn (70.8±13.5, 62.8±9.65, and 56.6±18.5 μg/dl), C3 (159.4±26.3, 152.8±33.1, and 123.4±36.7 mg/dl), and C4 (42.0±10.3, 41.2±9.0, and 27.1±11.4 mg/dl) levels on admission. TARC and IFN-λ3 levels, which are COVID-19-specific biomarkers, did not clearly correlate with COVID-19 severity.

Moreover, CRP and SAA positively correlated with serum testosterone (Figure 3A and B), whereas Ca and Zn (Figure 3C and D) and C3 and C4 (Figure 3E and F) negatively correlated with serum testosterone.

Discussion

In this study, we investigated the relationship between severity and factors reported as COVID-19 severity markers, testosterone-containing hormones, and commonly used inflammation markers and evaluated the markers currently in use. Serum testosterone levels in male patients with COVID-19 correlated with disease severity.

Epidemiological studies have shown higher incidence, severity, and mortality of COVID-19 in men compared to women. However, the underlying factors contributing to this sex difference are still under investigation. SARS-CoV-2 infection is initiated by the binding of the virus to ACE2 on the cell membrane. A targeted analysis approach revealed androgen signaling to be a key regulator of ACE2 levels (9). Treatment with antiandrogenic drugs reduced ACE2 expression against SARS-CoV-2 infection, suggesting a link between male sex hormone signaling and regulation of the SARS-CoV-2 receptor ACE2 and co-receptor TMPRSS2. Inhibitors of 5α-reductase, which dampens androgen signaling, may reduce the infectivity of SARS-CoV-2 by reducing ACE2 levels in target cells. ACE2 expression levels are lower in Asian men and older adults, who tend to have poorer outcomes. At the population level, a

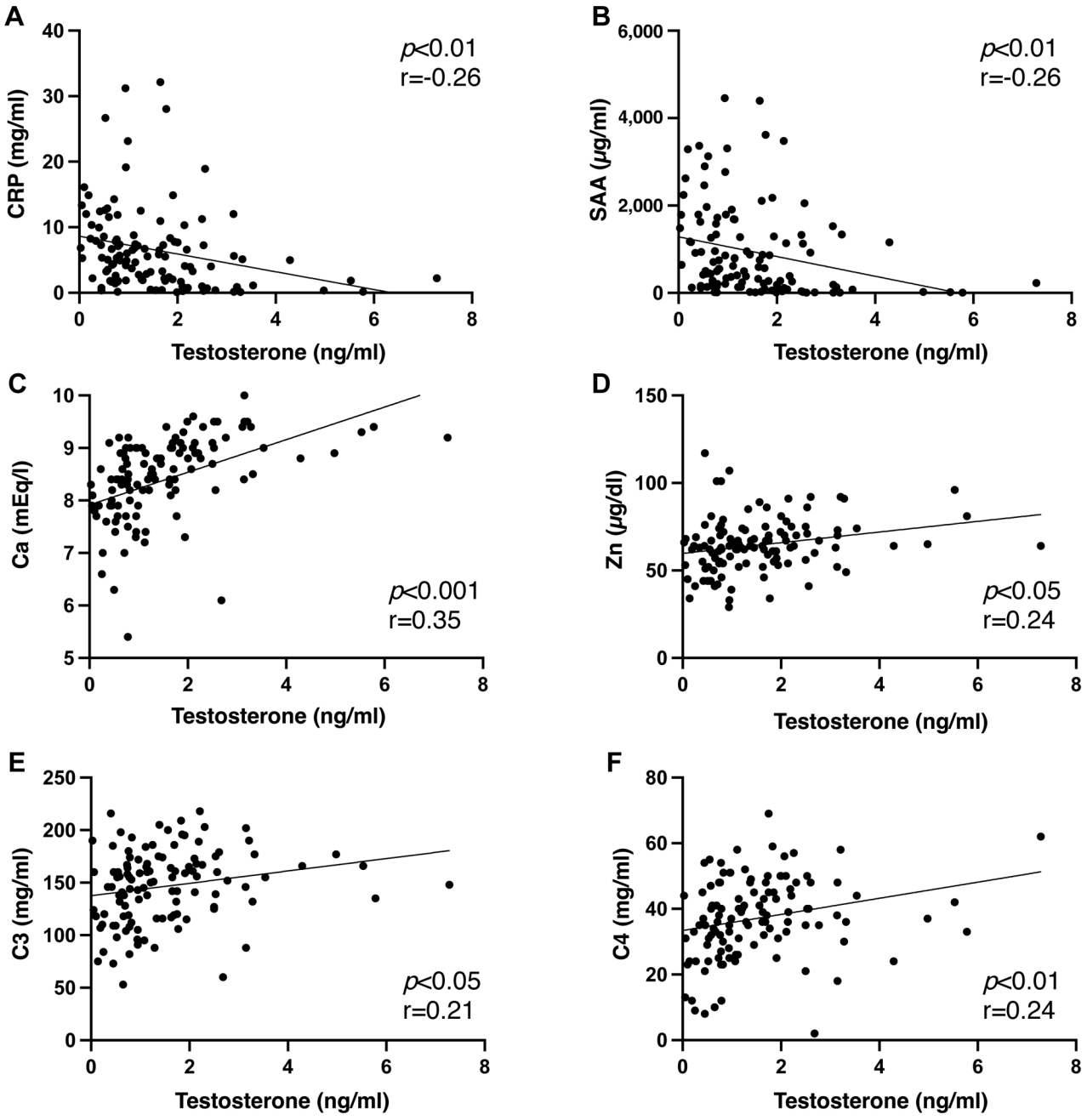

Figure 3. *Correlation of serum testosterone to serum (A) CRP, (B) SAA, (C) Ca, (D) Zn, (E) C3, and (F) C4 levels as determined by the simple regression analysis (r).*

negative correlation was found between ACE2 expression and COVID-19 severity and mortality (10).

A study using primary isolated human airway smooth muscle (ASM) cells showed that ACE2 is expressed on human ASM, and testosterone regulates ACE2 expression (11). Western blot analysis of ASM cell lysates showed significantly lower baseline ACE2 expression in women than in men. Furthermore, in ASM cells exposed to estrogen and testosterone for 24 h, testosterone significantly up-regulated ACE2 expression in men and women, whereas estrogen down-regulated ACE2. These sex hormone-induced differences may help explain sex differences in COVID-19 (11). Thus, serum testosterone may augment the immunological reaction against COVID-19.

SARS-CoV-2 attacks various organs, with the lung being the most damaged, and requires two host cell surface proteins, ACE2 and TMPRSS2, for cell entry. Therefore, the down-regulation of ACE2 and/or TMPRSS2 may be a potential therapeutic approach for COVID-19 (12). TMPRSS2 targets AR, a ligand-activated transcription factor, and AR activation increases TMPRSS2 levels in various tissues. Importantly, in studies of COVID-19, anti-androgens significantly reduced the entry of SARS-CoV-2 and infection into lung cells. Anti-androgen therapy has shown potential to reduce COVID-19 severity.

Low testosterone levels (*i.e.*, age and body mass index) and high IL-6 levels (IL-6 normally rises with the cytokine storm that occurs following a viral infection) may aggravate SARS-CoV-2 infection to follow a severe course. Moreover, testosterone levels were associated with the clinical severity of COVID-19 upon hospital admission, with testosterone levels being significantly lower in men with the greatest need for intensive care unit (ICU) admission and highest risk of mortality (13). Our results of the analysis of patients with moderate disease showed that low testosterone levels tended to associate with high IL-6 levels. Current results show that testosterone levels are significantly lower in male patients with symptomatic COVID-19 upon hospital admission, with testosterone levels suggestive of hypogonadism, observed in most of the patients with moderate and severe COVID-19. A previous study identified that low testosterone levels are associated with an increased metabolic risk and systematic inflammation (14). Since adipose tissue is a source of inflammatory cytokines, testosterone may regulate inflammation by acting on adipose tissues. Inflammation was suppressed by testosterone in patients with coronary artery diseases, prostate cancer, and diabetes mellitus through increased levels of anti-inflammatory cytokines (IL-10) and decreased levels of pro-inflammatory cytokines (IL-1β, IL-6, and tumor necrosis factor-α). Low testosterone levels in patients with COVID-19 may reflect these systemic inflammations.

Low testosterone levels in middle-aged and older men diagnosed with or hospitalized with COVID-19 may reflect the inhibition of the hypothalamic–pituitary–testicular axis function during acute illness. Although it is difficult, knowing whether premorbid testosterone levels measured long before exposure to SARS-CoV-2 are independent predictors of COVID-19-related mortality risk in men is important. Middle-aged and older men with the highest premorbid serum total testosterone levels are at higher risk of COVID-19-related mortality (15). Even if men have relatively high serum testosterone levels, the risk of severe COVID-19 is not low, and this is a topic for future investigation.

Iron and Zn, which perform many physiological functions in nearly all living organisms, are also necessary for viral growth. The decline in their levels is thought to starve invading pathogens of these essential elements, limiting disease progression and severity (8). Low Zn levels upon admission were reported to be associated with poor clinical outcomes of COVID-19 (7). According to structural data, SARS-CoV-2 proteins contain several Zn-binding sites (16). Zn may contribute to the tuning of the structural features of polyproteins, which might ultimately affect the viral replication process. Increasing COVID-19 severity was also associated with a significant gradual decrease in serum Ca, Fe, Se, and Zn levels compared with controls (17). Metal metabolism significantly interferes with the pathogenesis of COVID-19, although the causal relations and precise mechanisms are yet to be elucidated. In this study, serum testosterone positively correlated with serum Ca and Zn. These results present that the development of severe COVID-19 with low testosterone levels was associated with metal metabolism.

C3 and C4 levels were increased in both mild and moderate groups but not in the severe group, where their levels remained within the normal range or were even lower (18, 19). In a systematic review and meta-analysis, serum concentrations of C3 and C4 were significantly lower in patients in severe COVID-19 or those who died during follow-up compared to those with milder disease or survivor status (20).

This study has two limitations. First, the study population was small, and the study design was retrospective. Second, as residual clinical specimens were used, the association between additional complement systems and various inflammatory cytokines was not examined.

Conclusion

Testosterone may possess anti-inflammatory properties in male patients with COVID-19. More data are needed to validate the use of testosterone as a marker of COVID-19 severity and in the management of chronic inflammatory conditions.

Conflicts of Interest

The Authors declare the following that may be considered potential competing interests: Satoshi Takahashi received speaker honoraria from MSD K.K. and Fujirebio Inc. and research grants from Shino-Test Corporation, Roche Diagnostics Japan Corporation, Fujirebio Inc., and Abbott Japan Corporation, Ltd. All other Authors declare no conflict of interest in relation to this study.

Authors' Contributions

All Authors met the ICMJE authorship criteria. ES, RM, KK, and ST were responsible for trial organization and coordination. KK was the chief investigator and was responsible for the data analysis. ES and HY developed the trial design and conducted the investigation. KK wrote the manuscript. All Authors developed the trial design, conducted the investigation, and contributed to the writing of the final manuscript.

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