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The impact of COVID-19 on BNP, NT-proBNP and ANP in heart failure

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ABSTRACT

Extensive research has been conducted on biomarkers associated with coronavirus disease 2019 (COVID-19) in both healthy individuals and those with various conditions, particularly heart diseases. However, there is a limited investigation into the relationship between widely used cardiac biomarkers known as natriuretic peptides, including Brain natriuretic peptide (BNP), N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP), and Atrial natriuretic peptide (ANP), and COVID-19 infection specifically in patients with heart failure. These natriuretic peptides assess the hemodynamic stress on the heart wall and have the potential to serve as biomarkers for evaluating the severity of COVID-19 infection in heart failure patients. Therefore, this study aimed to assess the plasma concentration of BNP, NT-proBNP, and ANP in a medium-sized cross-sectional case-control study involving 360 heart failure patients, both infected and uninfected with COVID-19. The heart failure patients were categorized into subgroups based on their Ejection Fraction (EF) percentage, namely heart failure with reduced EF (HFrEF), heart failure with mid-range EF (HFmrEF), and heart failure with preserved EF (HFpEF). Our findings demonstrate a significant increase in plasma levels of BNP and NT-proBNP in all heart failure patients, as well as in each subgroup (HFrEF, HFmrEF, and HFpEF) when infected with COVID-19, compared to uninfected heart failure patients. These established cardiac biomarkers have the potential to be utilized as future indicators for assessing the severity of COVID-19 infection in heart failure patients, thereby enhancing heart failure management and reducing irreversible cardiac damage.

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Introduction

coronavirus disease 2019 (COVID-19), a life-threatening respiratory infection, was first reported in late 2019 and spread worldwide. To date, there are more than 760 million reported cases, and the infection has caused more than 6.8 million deaths according to World Health Organization (1, 2). One of the primary uses of biomarkers is for the detection of patients at risk of deterioration. This is especially useful in COVID-19 infection due to high morbidity and mortality rates. The use of cardiac prognostic biomarkers to detect patients at risk of developing severe COVID-19 infection has been widely accepted since the start of the disease breakout. Cardiac biomarkers are highly related to the worsening of COVID-19 infection due to the discovery of myocardial damage upon post-mortem examination of heart tissues (3-5). Troponin is one of the most investigated cardiac biomarkers and is routinely used to detect cardiac injury. Interestingly, this biomarker was found to be associated with COVID-19 infection (6). Moreover, studies such as in situ RNA labelling detected cardiac tropism in cardiomyocytes and interstitial and endothelial cells from autopsy samples of individuals infected with COVID-19 (7). Other biomarkers that are directly indicative of myocardial damage are B-Type Natriuretic Peptide (BNP) and N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) which are shown to markedly increase in patients with severe COVID-19 infection brought into Intensive Care Unit (ICU) (8). Signs of cardiac damage manifests in, arrhythmia, myocardial injury and mild to severe heart failure (9).

Natriuretic peptides (NPs) released from the atrium and the ventricles are called brain and atrial natriuretic peptides (BNP and ANP), respectively (10, 11). These NPs orchestrate vital functions in the cardiovascular and renal system such as maintaining electrolyte balance and normal blood pressure (12). BNP and ANP are released upon stress on myocytes from the ventricles and the atrium, respectively. The local synthesis of the NPs such as in the brain, kidney and the heart itself is important to maintain control over the mechanisms governing cardiovascular functions (13, 14). NPs act like endogenous ligands that bind to their specific receptors. COVID-19 is one of the conditions that put pressure on the right ventricle due to its direct link to the lungs which are primarily affected by the infection and increased pulmonary pressure as a result. Raised pulmonary pressure might also result in the distension of the atrium and the consequent release of the ANP.

Since the start of the pandemic, research groups have put tremendous efforts into determining the effect of CO-

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VID-19 infection on the level of NT-proBNP as well as BNP in otherwise without heart failure (HF). However, the level of ANP has not been investigated with COVID-19 neither in healthy nor in HF patients. Therefore, in the current study, in order to harness the indicative effect of ANP in the detection of HF patients at higher risk of developing severe COVID-19 infection and deterioration of HF, we sought to seek out the change of ANP levels in COVID-19-infected individuals in comparison to non-infected individuals amongst HF patients. Moreover, to the best of our knowledge, the levels of BNP and NTproBNP have not been investigated in HF patients infected with COVID-19. Therefore, we compared the levels of BNP and NTproBNP in both COVID-19 and Non-COVID-19 infected patients suffering from heart failure. The current article could have an impact on using already established cardiac biomarkers such as BNP, NT-proBNP and ANP as new biomarkers to predict the severity of COVID-19 infection and associated deterioration of HF in HF patients.

Materials and Methods

Study design and patients

The study was designed as a cross-sectional case-control study. The total number of patients enrolled in this study was 360. Subjects were recruited from consecutive HF patients visiting two Heart Centres in Erbil and Baghdad during the period of 01/2021-09/2022. HF patients were Echocardiograph tested and further classified based on Ejection Fraction EF readings to HF reduced EF (HFrEF) where EF was less than 40%, HF mid-range EF (HFmrEF) where EF was 40 – 49% and HF preserved EF (HFpEF) where EF was equal and more than 50% (15). The COVID patients were determined as patients who recovered from COVID within the past 30 days and they were enrolled in the study consecutive while visiting the aforementioned centers. Non-COVID patients were determined as patients who never had COVID or not had COVID in the past six months. The study procedure was approved by Hawler Medical University/ College of Pharmacy's committee for ethics under the approval number HMU-PH-EC 25112020-120.

BNP and NT-proBNP measurement

BNP and NT-proBNP serum levels of each sample were measured quantitatively by either BNP (GP Getein Biotech, Inc.) or NT-proBNP (Hotgen) specified diagnostic assay kit, respectively. The kits were equilibrated to room temperature for half an hour before use. Plasma was immediately isolated from each sample and the level of each natriuretic peptide was measured in the lab within the cardiac centres on the day of the sample received and every time samples were acquired consecutively. 100 µl of the plasma was added to a 150 µl of BNP or NT-proBNP diluent buffer and mixed well. To transfer the sample, 100 µl of the mixed plasma solution was drawn and transferred to each well and timed immediately. The samples were incubated at room temperature for 15 minutes and read within one minute in a bench-top-sized immunoassay reader (Hotgen).

ANP measurement

Human Atrial Natriuretic peptide ANP levels were measured using an ELISA kit (Sunlong Biotech Co., Ltd). The kit was stored at $4C^0$ and brought to room temperature before use. In this procedure, standards and isolated serum from unknown samples were added to appropriate microwells where they bind to the pre-coated ANT-specific antibody. Standard curve samples were prepared in duplicates and concentrations were in the range of 15-180 pg/ml. The final volume in each microwell was 50 µl. After each incubation period, the wells were aspirated and washed with wash buffer for 30 seconds and repeated five times to remove the unbound components in each wash step. Care was taken not to disturb the walls of the wells during the process. The ANP level was measured with a colorimetric readout on a spectrophotometer at 450 nm wavelength within 15 minutes of the addition of the stop solution. The concertation of ANP of unknown samples was calculated against the standard curve.

Statistical Analysis

Baseline characteristics of all numbers were expressed as mean ± SEM. Multiple independent T-test was employed between COVID and Non-COVID HF group for each of the BNP, NT-proBNP and ANP measurements. Two-way ANOVA was carried out for the ratio of NT-proBNP/BNP between COVID and Non-COVID HF groups based on gender, age and reduced and non-reduced EF. Either a t-test or one-way ANOVA was carried out for significant parameters from the above. Statistical analysis was conducted using (SPSS 27.0 statistical package). Differences were considered significant if the P-value was less than 0.05.

Results

Patient characteristics

Data from a total of 360 HF patients were collected consecutively as they visited Heart Centres in Erbil and Baghdad for 20 months. 131 HF patients were recorded as COVID group while 229 HF patients fell under the Non-COVID group. The percentage of male, diabetic, hypertensive and smokers in COVID and Non-COVID HF are demonstrated in Table 1. In addition, age and weight are shown in Table 1. An echocardiograph was taken for all HF patients and they were divided based on EF parameters into HFrEF, HFmrEF and HFpEF. Surprisingly, the EF was significantly lower in the covid group compared to Non-COVID patients (P value = 0.001) in HFrEF. Levels of natriuretic peptides were compared between COVID and Non-COVID groups in all HF, HFrEF, HFmrEF and HFpEF.

BNP and NT-proBNP measurement

The level of BNP and NT-proBNP were measured for COVID and Non-COVID patients in all HF, HFrEF, HFmrEF and HFpEF classes. Our results showed a normal pattern of highest BNP and NT-proBNP levels in HFrEF which was 563 ± 91 pg/ml and 3658 ± 711 pg/ml respectively compared to all HF, HFmrEF and HFpEF group in the non-covid group (16). When comparing the plasma concertation of BNP and NT-proBNP between COVID and Non-COVID groups, all four groups recorded significantly higher BNP and NT-proBNP levels in COVID patients than in Non-COVID patients (Figures 1 and 2) which was again the highest in HFrEF in comparison to HFmrEF and HFpEF group. The p values in BNP between COVID and Non-COVID groups were $p < 0.001$, $p < 0.001$, $p = 0.006$

Table 1. Mean ± SEM values of baseline characteristics of HF patients classified to covid and non-covid groups.

	HF		HFrEF		HFmrEF		HFpEF	
	Covid	Noncovid	Covid	Noncovid	Covid	Noncovid	Covid	Noncovid
No. of HF cases	131	229	60	80	19	77	52	72
Age (years)	65.06 ± 0.86	63.55 ± 0.86	62.38 ± 1.36	63.89 ± 1.21	68.63 ± 1.8	64.19 ± 1.1	65.79 ± 1.2	62.49 ± 1.23
Weight (Kg)	76.65 ± 0.77	77.07 ± 0.64	77.27 ± 1.26	77.21 ± 1.24	73 ± 1.66	77.22 ± 1.26	77.27 ± 1.12	76.75 ± 0.67
Male (%)	73	70	78	70	47	71	77	79
DM (%)	58	44	63	45	68	45	48	42
HTN (%)	47	40	37	64	68	57	50	46
Smoker (%)	41	37	42	44	37	21	44	46
EF (%)	42.06 ± 1.07	43.29 ± 0.7	30.18 ± 0.51	32.53 ± 0.39	42.63 ± 0.5	42.2 ± 0.3	55.5 ± 0.58	56.42 ± 0.63
LVSD (mm)	43.94 ± 0.8	42.22 ± 0.59	50.3 ± 0.99	49.86 ± 0.6	44.05 ± 1.44	42.61 ± 0.78	36.56 ± 0.81	33.32 ± 0.63
LVDD (mm)	56.66 ± 0.69	55.07 ± 0.52	61.28 ± 0.86	60.85 ± 0.59	57.63 ± 1.44	55.49 ± 0.8	51.15 ± 0.84	48.18 ± 0.64

Where, HF: Heart failure, DM: Diabetes mellitus, HTN: Hypertension, EF: Ejection fraction, LVSD: Left ventricular systolic diameter, LVDD: Left ventricular diastolic diameter, DM: diabetes mellitus. HFrEF: Heart failure reduced ejection fraction, HFmrEF: Heart failure mid-range ejection fraction, HFpEF: Heart failure preserved ejection fraction.

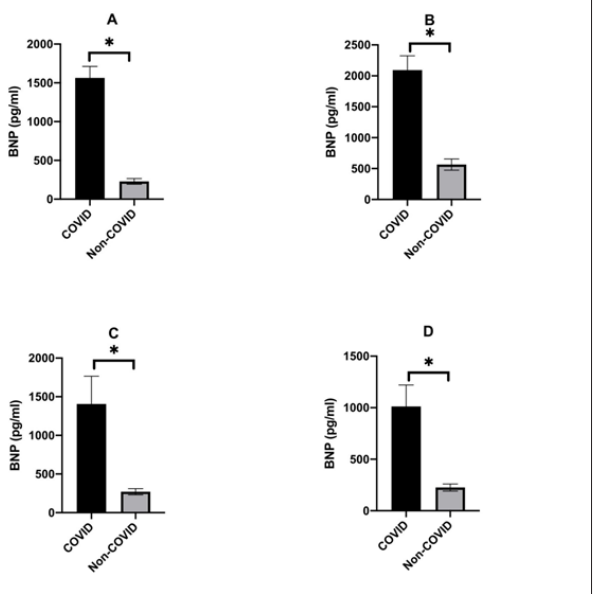

Figure 1. BNP measurement in COVID and Non-COVID patients in all HF (A), HFrEF (B), HFmrEF (C) and HFpEF (D) classes. The BNP is significantly higher in the COVID group in all four classes of HF. HF: Heart failure, HFrEF: Heart failure reduced ejection fraction, HFmrEF: Heart failure mid-range ejection fraction, HFpEF: Heart failure preserved ejection fraction.

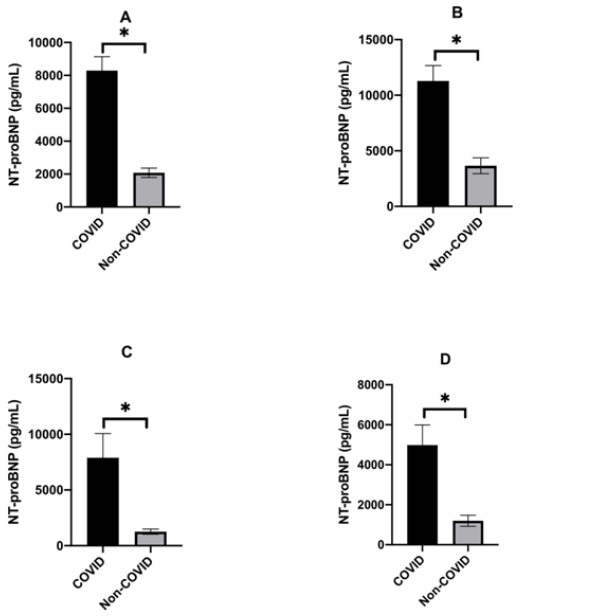

Figure 2. NT-proBNP measurement in Covid and Non-COVID patients in all HF (A), HFrEF (B), HFmrEF (C) and HFpEF (D) classes. The NT-proBNP is significantly higher in the covid group in all four classes of HF. HF: Heart failure, HFrEF: Heart failure reduced ejection fraction, HFmrEF: Heart failure mid-range ejection fraction, HFpEF: Heart failure preserved ejection fraction.

and $p < 0.001$ for all HF, HFrEF, HFmrEF and HFpEF groups respectively. Moreover, the p values in NT-proBNP between COVID and Non-COVID groups were $p < 0.001$, $p < 0.001$, $p = 0.007$ and $p = 0.001$ for all HF, HFrEF, HFmrEF and HFpEF groups respectively.

ANP measurement

Levels of ANP natriuretic peptides were also compared between COVID and Non-COVID groups in all HF, HFrEF, HFmrEF and HFpEF classes. There was no significant difference in ANP concentration between COVID and Non-COVID groups in all classes of HF (Figure 3).

Association between NT-proBNP/BNP ratio and HF classes or basic patient characteristics

The ratio of NT-proBNP/BNP was compared between COVID and Non-COVID groups in all HF and classes of HF. There was no significant difference between these values in all HF patients and each EF class. In addition, the NT-proBNP/BNP ratio was measured for both COVID and Non-COVID groups of sex and age-classified HF patients. Among the various classed patients based on age, there was a significantly higher ratio of NT-proBNP/BNP in the age group of more than 75 years between the COVID

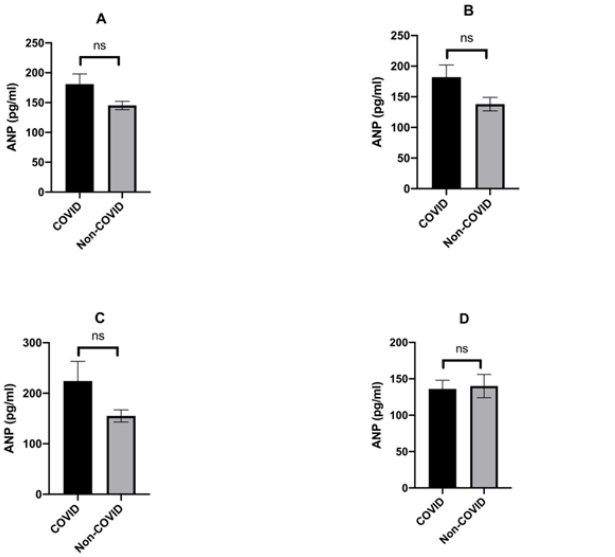

Figure 3. ANP measurement in COVID and Non-COVID patients in all HF (A), HFrEF (B), HFmrEF (C) and HFpEF (D) classes. There is no significant difference between ANP levels in COVID and Non-COVID patients in any of the HF classes. Where, HF: Heart failure, HFrEF: Heart failure reduced ejection fraction, HFmrEF: Heart failure mid-range ejection fraction, HFpEF: Heart failure preserved ejection fraction.

and Non-COVID groups. Moreover, this ratio was significantly higher in the male sex compared to the female sex (Figure 4).

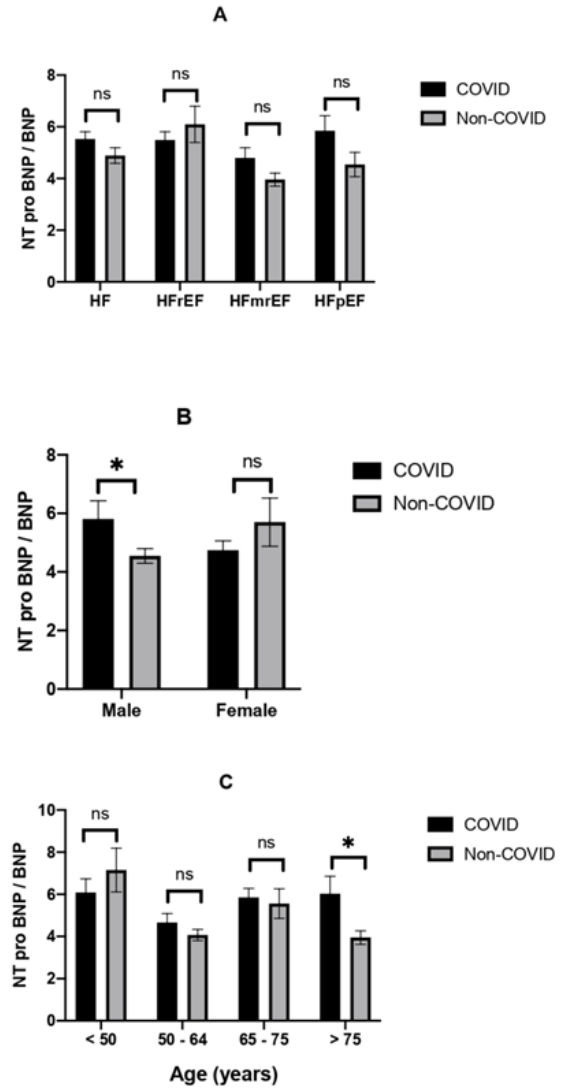

Figure 4. The NT-proBNP/BNP ratio was compared between COVID and Non-COVID groups among heart failure (HF) classified patients based on ejection fraction (EF) (A), gender in all HF patients (B), and age in all HF cases (C). The analysis revealed a significant difference in the male group (as per gender) and in the age group older than 75 years (as per age). It is worth noting that HF stands for heart failure, where HFrEF denotes heart failure with reduced ejection fraction, HFmrEF represents heart failure with mid-range ejection fraction, and HFpEF signifies heart failure with preserved ejection fraction.

Discussion

The current study aimed to investigate the potential use of natriuretic peptides, specifically B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and atrial natriuretic peptide (ANP), as biomarkers to detect the severity of COVID-19 infection and its impact on heart failure (HF) patients. To achieve this, we measured the plasma concentrations of these biomarkers in two groups: HF patients who recently recovered (less than one month) from COVID-19 (COVID group) and HF patients who have not contracted the infection for at least six months (Non-COVID group). The patients were enrolled during their routine visit for regular HF check-ups at the two cardiac centers.

Natriuretic peptides are reliable quantitative biomarkers used to assess cardiac stress and are valuable in the diagnosis and management of HF (17, 18). In HF patients, these peptides are released either from the ventricles (BNP and NT-proBNP) or the atrium (ANP) in response to increased pressure on the respective cardiac chambers (18, 19). While COVID-19 is a relatively new infection and limited research has explored its impact on heart conditions, various mechanisms have been suggested to be involved. These mechanisms include elevated levels of Angiotensin Converting Enzyme 2 (ACE2) in the plasma (20-22), hypoxia (22-24) and myocardial injury (6, 25, 26), thrombosis (22) and inflammation (27). However, the specific relationship between COVID-19 infection and natriuretic peptide levels in HF patients has not been established.

Studies conducted on COVID-19-infected individuals without HF have shown a significant increase in NT-proBNP plasma concentration (28-30). Therefore, in our study, we aimed to determine the association between COVID-19 infection and natriuretic peptides in HF patients due to the utmost relevance of COVID-19's effect on these biomarkers. Our findings indicate a relationship between COVID-19 infection and increased levels of BNP and NT-proBNP in all HF patients and across different HF patient classes based on ejection fraction (EF) measurements. Furthermore, the ratio of NT-proBNP to BNP is significantly higher in male HF patients and those aged above 75 who were infected with COVID-19, compared to those not infected. This suggests a greater increase in NT-proBNP levels relative to BNP in HF patients. Higher NT-proBNP levels have been associated with increased mortality risk in severe COVID-19 cases (28, 30, 31). Thus, the significant ratios of NT-proBNP to BNP in males and individuals aged more than 75 indicate greater severity of COVID-19 in these populations. However, the levels of ANP were not

affected by COVID-19 infection in HF patients, potentially due to the infection's limited impact on the atria or the short half-life of ANP, making it challenging to capture changes within the narrow window of its activity (32). These limitations should be taken into account, and alternative approaches such as using NT-proANP, which has greater stability and a longer half-life, could be explored.

The utilization of established biomarkers to assess the development of cardiac injuries associated with COVID-19 infection in HF patients is crucial for HF management and minimizing the risk of further cardiac complications during the infection period. Additionally, establishing an association between these markers and COVID-19 infection would facilitate the development of routine practices for monitoring the cardiac condition of HF patients during the infection, rather than relying on the appearance of symptoms, which could indicate irreversible damage. To the best of our knowledge, this is the first study to evaluate the connection between natriuretic peptide plasma concentrations and COVID-19 infection in HF patients.

Conclusion: In this study, we have demonstrated a significant elevation of natriuretic peptides, specifically BNP and NT-proBNP, in HF patients infected with COVID-19 compared to HF patients without COVID-19 infection. This indicates a clear impact of COVID-19 infection on heart function. The increase in NT-proBNP compared to BNP is more pronounced in male patients and those aged 75 or above. These findings provide a basis for further research to confirm the association between COVID-19 and natriuretic peptides, as well as their use as vital biomarkers for monitoring the severity of COVID-19 infection and assessing the cardiac status of HF patients. Moreover, since natriuretic peptide biomarkers are already established for clinical use in HF management, they can be readily incorporated into the management of COVID-19 infection in patients with heart-related conditions, particularly HF.

Declarations

Ethics approval and consent to participate

All methods were carried out in accordance with guidelines and regulations ruled out by the ethical committee of Hawler Medical University/Pharmacy College which approved the study on 25th November 2020 under the number of HMU-PH-EC 25112020-120. Informed consent was obtained from all subjects and/or their legal guardian(s).

Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. The request for data should be forwarded to the corresponding author.

Competing interests

The authors declare that the research was conducted in the absence of any financial or non-financial interests that could be considered as potential conflicts of interest.

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Authors' contributions

Rawaz Tawfeeq (RT), Mohammed Alwan (MA), Ava Ismael (AI) and Badraldin K. Hamad (BH) contributed to the conception and initiation of the research. RT and BH designed the experiments. MA and AI supervised the study. RT, MA, AI and BH conducted the experiments. MA, RT and BH collected and analysed the data. RT and BH wrote the first manuscript. All authors reviewed and approved the submitted version of the manuscript.

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