Low molecular weight heparin reduces arterial blood lactic acid content and increases estimated glomerular filtration rate in patients with moderate Covid-19 pneumonia

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Abstract

Background: Coronavirus disease 2019 (Covid-19) remains a serious health threat worldwide. We aimed to investigate whether low molecular weight heparin (LMWH) can promote organ function recovery in moderate Covid-19 pneumonia patients.

Methods: We initiated an LMWH protocol in Covid-19 patients with increased D-dimer, body mass index >30 kg/m^2 or a history of diabetes from January 18, 2020 at Shanghai Public Health Clinical Center. In this retrospective study, we assigned moderate Covid- 19 pneumonia patients admitted between January 18th and April 18, 2020 receiving the LMWH protocol to the LMWH group. Moderate patients who met the inclusion criteria but did not receive LMWH protocol were included in the control group by 1:2 propensity score matching. General clinical information, indicators for renal function, arterial blood gas analyses, arterial blood lactic acid content (mmol/L), and coagulation indexes at 0 day, 3 days, 7 days, and 11 days after admission were recorded and compared between the two groups.

Results: There were 41 patients in the LMWH group and 82 patients in the control group. General information in both groups were similar. Compared to the control group, the arterial blood lactic acid content (mmol/L) at day 11 (1.3 [1.1, 1.7] *vs.* 1.2 [0.9, 1.3], $P = 0.016$) was reduced in the LMWH group. The estimated glomerular filtration rate (eGFR) in the LMWH group was higher than that in the control group at day 7 (108.54 [89.11, 128.17] *vs.* 116.85 [103.39, 133.47], $P = 0.039$) and day 11 (113.74 [94.49, 126.34] *vs.* 128.31 [112.75, 144.12], $P = 0.003$). The serum creatinine levels (Scr) in the LMWH group were lower than that in the control group at day 7 (62.13 [51.47, 77.64] *vs.* 55.49 [49.50, 65.75], $P = 0.038$) and day 11 (63.35 [50.17, 75.73] *vs.* 51.62 [44.62, 61.24], $P = 0.005$).

Conclusions: LMWH treatment can reduce arterial blood lactic acid levels and improve eGFR in moderate Covid-19 pneumonia patients. Randomized controlled trials are warranted to further investigate this issue.

Trial registration: ChiCTR.org.cn, ChiCTR2000034796.

Keywords: Arterial blood lactic acid; Covid-19; Kidney function; LMWH

Introduction

The novel coronavirus designated Severe Acute Respiratory Syndrome-related coronavirus 2 (SARS-CoV-2) has caused a global outbreak of respiratory illness termed Coronavirus disease 2019 (Covid-19), starting in December 2019 and still spreading rapidly. By July 12, 2021, SARS-CoV-2 has affected more than 200 countries, resulting in >180 million confirmed cases, with 4 million confirmed deaths. The main clinical manifestation of Covid-19 pneumonia is respiratory function deterioration. Severe patients may have multiple organ injury, and it is reported that the mortality rate of these patients is as high as 66%.[1]

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Several therapeutic agents have been evaluated for the treatment of Covid-19, but thus far none have been shown to be effective. Coagulation dysfunction is one of the important causes of death in patients with Covid-19. Studies have shown that 71% of the patients who die meet the diagnostic criteria for disseminated intravascular coagulation (DIC) of the International Society of Thrombosis and Hemostasis (ISTH).[2] The potential of low molecular weight heparin (LMWH) for Covid-19 has already gained the attention of some scholars.[3,4] The

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ISTH recommends prophylactic anticoagulation for inpatients with Covid-19, based on a study of inpatients with moderate to severe Covid-19 disease.[5] However, these recommendations are based on general thromboprophylaxis. There is still no evidence of a protective effect of LMWH on organ function in Covid-19 pneumonia.

Shanghai Clinical Treatment expert Group for Corona virus Disease 2019 has been actively carrying out anticoagulation therapy for Covid-19 patients. LMWH was used for anticoagulation treatment in COVID-19 patients. In this retrospective study, we investigated the effects of LMWH on renal/lung function, arterial blood lactic acid levels, and coagulation indicators in patients diagnosed with a moderate type of Covid-19 pneumonia on admission. This study aims to report that LMWH can decrease blood lactic acid levels and improve estimated glomerular filtration rate (eGFR) in moderate cases of Covid-19 pneumonia.

Methods

Ethical approval

This study was approved by the Institutional Ethics Board of Ruijin Hospital (2020305) and has been retrospectively registered in ChiCTR (ChiCTR2000034796).

Study design

This retrospective clinical study was conducted at Shanghai Public Health Clinical Center. Since January 18, 2020, we began to use the LMWH protocol in the treatment of Covid-19 patients who met the criteria. The inclusion criteria were: (1) Age >18 years; (2) No other trial drug treatment used within the time frame of the study; (3) In accordance with any of the following: D-dimer increased on admission; Body mass index (BMI) >30 kg/m^2; History of diabetes. The exclusion criteria were: (1) Platelets $<30 \times 10^9$/L or fibrinogen <150 mg/dL; (2) Pregnancy and lactation; (3) Presence of blood system diseases; (4) Immunosuppression (patients having received organ transplantation, radiotherapy, or chemotherapy, patients with an immune system dysfunction including rheumatic diseases); (5) Serious brain injury, cerebrovascular malformation, bronchiectasis, peptic ulcer, liver cirrhosis, hemorrhoids, or other diseases with potential bleeding risk; (6) Receiving anticoagulant drugs or antiplatelet drugs during treatment; (7) <24 h since severe trauma or surgery. The diagnosis and severity classifications followed the guidelines of the National Health and Family Planning Commission of the People's Republic of China.[6] The specific diagnostic criteria for mild, moderate, severe, and critical types of disease are shown in Supplementary Table 1, http://links.lww.com/CM9/A867.

We retrospectively screened the patients admitted during the three previous months (between January 18 and April 18, 2020). We screened 552 patients with moderate Covid- 19 pneumonia admitted between January 18th and April 18, 2020, among which 213 patients met the inclusion criteria. Of these 213 patients, 41 patients who received LMWH were included in the LMWH group. We also screened 217 patients who did not receive LMWH treatment and 82 subjects met the inclusion criteria for the control group. Propensity score matching was conducted to minimize the impact of potential confounders and selection bias between the patients in the LMWH and control groups. A propensity score for each patient was calculated through logistic regression modeling and covariates of age and gender were matched. A 1:2 matching was used to select patients in the control group [Figure 1].

Treatment protocol

All patients were treated according to the guidelines of the National Health and Family Planning Commission of the People's Republic of China and the Shanghai Expert Consensus on the comprehensive treatment of Covid-19.[7] The main associated therapies within the first few weeks after admission included antiviral therapy, antibiotics, glucocorticoids, fluid resuscitation, and nutrition support. The two groups did not differ with respect to these treatments. The LMWH protocol consisted of a subcutaneous injection of 4100 U LMWH per day from admission until D-dimer returned to normal, or 5 to 7 days from the time of admission.

Data collection

The information and data from the two groups were collected from electronic medical records and reviewed by two trained physicians. Information about age, gender, coexisting diseases (diabetes, hypertension, chronic heart, lung, kidney disease, and other chronic diseases), BMI, and onset-to-admission time was obtained. Laboratory data at days 0, 3, 7, and 11 after admission were collected for the two groups. Indicators of kidney function included serum creatinine levels (Scr), blood urea nitrogen, and eGFR. Indicators of lung function included arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2), and arterial oxygen saturation (SaO_2). Coagulation parameters included D-dimer, fibrin degradation products (FDPs), and platelet enumeration. Arterial blood lactic acid levels were also measured.

Statistical analysis

Continuous variables were presented as medians and interquartile range (IQR, shown in square brackets) and compared using the Mann-Whitney *U* test, or reported as the mean with standard deviation and compared using the *t* test as per the distribution type. Categorical variables were presented as frequencies/percentages and compared using Fisher exact test. All statistical analyses were performed using SAS *v*. 9.2 (SAS Institute Inc., Cary, NC, USA). Two-sided *P* values of <0.05 were considered statistically significant.

Results

Patient characteristics

As shown in Figure 1, 552 moderate Covid-19 pneumonia patients admitted to Shanghai Public Health Clinical

Center between January 18 and April 18, 2020 were screened. Forty-one patients meeting the inclusion criteria received the LMWH protocol and were included in the LMWH group. The control group consisted of 82 patients diagnosed with moderate Covid-19 pneumonia but not receiving the LMWH protocol. The controls were selected to match patients in the LMWH group in a 2:1 ratio according to age and gender [Figure 1].

Characteristics of patients in the LMWH and control groups are described in Table 1. Patients in the LMWH group showed no significant difference in age and gender composition compared to the controls. When basic diseases were considered, the results showed no significant differences between the two groups in the prevalence of diabetes, hypertension, chronic heart disease, lung disease, kidney disease, and others. The BMI and onset to admission time in the LMWH group showed no significant difference compared with the control group.

Results of arterial blood lactic acid levels, kidney, and lung function

Results of arterial blood lactic acid levels, kidney, and lung function are described in Table 2. The arterial blood lactic acid levels at day 0 were similar between the control group and LMWH group. However, when compared with the

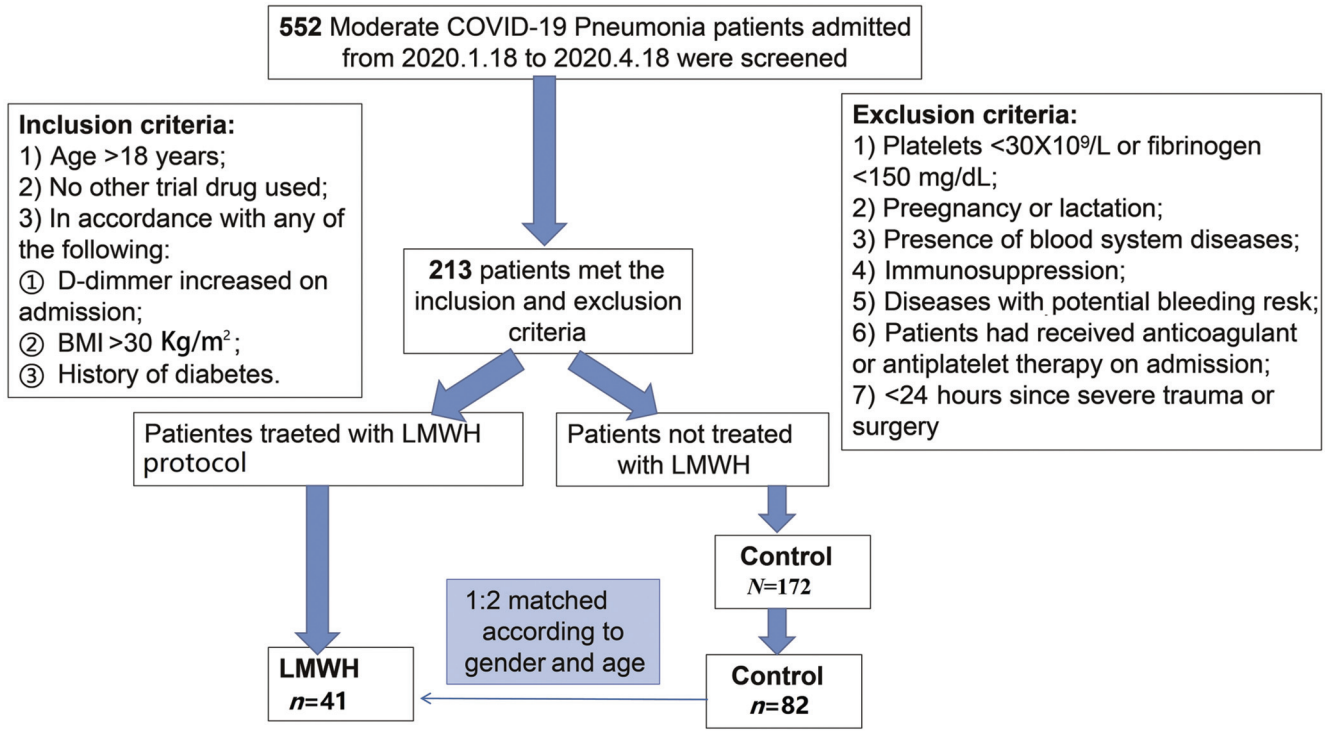

Figure 1: Study flowchart. BMI: Body mass index; Covid-19: Coronavirus disease 2019; LMWH: Low molecular weight heparin.

Table 1: Baseline characteristics of COVID-19 patients.

Variables	Control group ($n=82$)	LMWH Group ($n=41$)	*P* value
Gender			
Male	46 (56.1)	23 (56.1)	1.000
Female	36 (43.9)	18 (43.9)	
Age (years)	55.7 ± 11.7	57.6 ± 13.6	0.443
Basic diseases			
Diabetes	8 (9.76)	7 (17.07)	0.189
Hypertension	25 (30.49)	11 (26.83)	0.404
Heart disease	8 (9.76)	4 (9.76)	0.615
Lung disease	2 (2.44)	0 (0)	0.450
Kidney disease	1 (1.22)	0 (0)	0.664
Others	7 (8.54)	3 (7.32)	0.559
BMI > 30 kg/m^2	7 (8.54)	4 (9.76)	0.532
Onset admission time (days)	3.94 ± 2.57	4.73 ± 3.17	0.139

Data are presented as n (%) or mean ± standard deviation. Remark: Onset admission time: Interval from onset to admission. BMI: Body mass index; Covid-19: Coronavirus disease 2019; LMWH: Low molecular weight heparin.

Table 2: Effect of LMWH on organ functions.

Variable	Time points	Control group		LMWH group		*P* value
		n	Median (IQR)	*n*	Median (IQR)	
eGFR (mL/min)	Day 0	82	101.46 (87.65, 115.06)	40	102.58 (84.73, 115.44)	0.974
	Day 3	78	102.73 (83.30, 124.8)	39	110.26 (94.41, 125.68)	0.238
	Day 7	80	108.54 (89.11, 128.17)	39	116.85 (103.39, 133.47)	0.039*
	Day 11	78	113.74 (94.49, 126.34)	35	128.31 (112.75, 144.12)	0.003*
Scr (μmoI/L)	Day 0	82	67.66 (53.17, 79.72)	41	68.23 (59.85, 81.88)	0.592
	Day 3	78	66.50 (54.66, 77.59)	39	64.02 (55.01, 77.67)	0.349
	Day 7	80	62.13 (51.47, 77.64)	39	55.49 (49.50, 65.75)	0.038*
	Day 11	78	63.35 (50.17, 75.73)	35	51.62 (44.62, 61.24)	0.005*
BUN (mmol/L)	Day 0	80	4.86 (3.83, 5.89)	41	4.75 (3.73, 5.52)	0.691
	Day 3	78	4.57 (3.68, 5.76)	39	4.57 (3.51, 5.89)	0.731
	Day 7	80	4.73 (3.69, 5.60)	39	4.95 (3.62, 6.15)	0.921
	Day 11	78	4.61 (3.62, 5.75)	35	5.16 (3.83, 6.05)	0.252
Lactic acid (mmol/L)	Day 0	75	3.4 (2.9, 3.8)	35	3.2 (2.9, 3.8)	0.855
	Day 3	72	2.8 (2.2, 3.2)	37	2.6 (2.2, 3.1)	0.429
	Day 7	76	2.0 (1.5, 2.3)	41	1.9 (1.6, 2.2)	0.448
	Day 11	80	1.3 (1.1, 1.7)	40	1.2 (0.9, 1.3)	0.016*
$PaCO_2$ (kPa)	Day 0	73	6.37 (5.73, 6.74)	41	6.25 (5.70, 6.73)	0.692
	Day 3	74	6.07 (5.49, 6.40)	41	5.79 (5.20, 6.37)	0.223
	Day 7	70	5.55 (5.09, 5.92)	38	5.41 (4.71, 5.78)	0.120
	Day 11	76	5.09 (4.64, 5.35)	36	4.96 (4.36, 5.19)	0.087
PaO_2 (kPa)	Day 0	73	9.97 (9.75, 10.77)	41	9.97 (9.87, 10.44)	0.834
	Day 3	74	10.80 (10.04, 11.57)	38	10.55 (9.91, 11.60)	0.417
	Day 7	70	11.69 (10.85, 12.61)	38	11.45 (10.58, 12.44)	0.298
	Day 11	74	13.00 (11.69, 13.76)	35	12.54 (11.76, 13.60)	0.687
SaO_2 (%)	Day 0	73	95.90 (95.05, 97.45)	41	96.00 (94.80, 97.05)	0.603
	Day 3	74	97.05 (95.97, 98.20)	40	96.75 (95.70, 98.08)	0.255
	Day 7	71	97.80 (96.80, 98.50)	38	97.10 (96.30, 98.13)	0.068
	Day 11	75	98.60 (97.70, 99.10)	36	98.25 (97.23, 99.18)	0.273
D-dimer (mg/L)	Day 0	76	0.88 (0.62, 1.34)	37	1.03 (0.65, 1.35)	0.723
	Day 3	74	0.67 (0.48, 1.00)	37	0.71 (0.52, 0.86)	0.432
	Day 7	72	0.43 (0.33, 0.66)	35	0.44 (0.31, 0.52)	0.354
	Day 11	75	0.32 (0.24, 0.45)	33	0.33 (0.26, 0.45)	0.898
FDP (mg/L)	Day 0	76	3.68 (2.55, 5.26)	37	4.18 (2.80, 5.23)	0.517
	Day 3	75	2.57 (2.01, 4.01)	37	3.27 (2.04, 3.56)	0.696
	Day 7	72	2.03 (1.33, 2.77)	34	2.0 (1.47, 2.28)	0.421
	Day 11	76	1.34 (0.98, 1.90)	33	1.31 (1.09, 1.56)	0.510
PLT (10^9/L)	Day 0	82	167 (140, 201)	41	159 (128, 195)	0.449
	Day 3	74	182 (151, 234)	36	179 (138, 226)	0.539
	Day 7	77	237 (187, 286)	41	247 (170, 290)	0.810
	Day 11	74	279 (218, 344)	38	311 (188, 357)	0.636

* $P < 0.05$. BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; FDP: Fibrin degradation products; IQR: Interquartile range; LMWH: Low molecular weight heparin; $PaCO_2$: Arterial partial pressure of carbon dioxide; PaO_2: Arterial partial pressure of oxygen; PLT: Platelet; SaO_2: Arterial Oxygen Saturation; Scr: Serum creatinine.

control group, patients in the LMWH group had significantly lower arterial blood lactic acid levels at day 11 (1.3 [1.1, 1.7] *vs.* 1.2 [0.9, 1.3], $P = 0.016$). Further analysis of the data showed that eGFR values increased in the LMWH group at day 7 (108.54 [89.11, 128.17] *vs.* 116.85 [103.39, 133.47], $P = 0.039$) and day 11 (113.74 [94.49, 126.34] *vs.* 128.31 [112.75, 144.12], $P = 0.003$). The value of Scr decreased (estimate = 0.1500, $P = 0.6189$) in the LMWH group at day 7 (62.13 [51.47, 77.64] *vs.* 55.49 [49.50, 65.75], $P = 0.038$) and day 11 (63.35 [50.17, 75.73] *vs.* 51.62 [44.62, 61.24], $P = 0.005$). We also analyzed the effect of LMWH on lung function. Results from blood gas analysis showed that LMWH anticoagulant therapy showed a trend to reduce $PaCO_2$, but the differences were not statistically significant. Moreover, analyses of the coagulation indexes showed that D-dimer and FDP levels also showed a decreasing trend in the LMWH group at Day 7 and Day 11, but again the differences were not statistically significant.

Discussion

Covid-19 is an illness caused by infection with the new coronavirus SARS-CoV-2 that is associated with a systemic inflammatory response and activation of coagu-

lation. The virus accesses host cells via the protein angiotensin-converting enzyme 2.[8] Many studies have shown that the virus mainly targets vascular endothelial cells, leading to endothelial dysfunction and hypercoagulability.[9] Increased fibrinogen and factor VIII, activated coagulation, direct viral endothelial infection, increased platelet-vessel wall interaction, and hypoxia play roles in the development of thrombotic complications. Coagulation disorders, including DIC, are prominent problems in Covid-19 patients and a frequent cause of death.

The results of a multicenter retrospective study involving 1099 patients with Covid-19 showed that the incidence of DIC in critically ill patients was significantly higher than that in non-critical patients.[10] A retrospective analysis of 99 patients with Covid-19 in Jinyintan Hospital showed that 36% of the patients had increased D-dimer levels.[11] Prof. Bijie Hu of Renmin Hospital of Wuhan University performed a retrospective analysis of 248 patients with Covid-19 and confirmed that D-dimer levels are a reliable prognostic marker for in-hospital mortality.[12] Tang *et al*[2] published a retrospective analysis of the conventional coagulation indices of 183 patients with Covid-19. They found that plasma FDP and D-dimer levels in dying patients were significantly higher than those of surviving patients. Preliminary evidence suggests that LMWH has both anticoagulant and anti-inflammatory effects.[13] Recent findings that heparin interacts with the receptor-binding domain of the SARS-CoV-2 spike protein S1 suggest that it has the potential to prevent viral adhesion.[14] A retrospective study including 449 patients with severe Covid-19 infection showed lower mortality in patients with Covid-19-associated coagulopathy who received prophylactic heparin than in patients not receiving anticoagulant treatment. Of particular note, in patients with increased concentrations of D-dimer (six times the upper limit of normal), mortality was lower in those receiving heparin.[3] However, the protective effect of LWMH on microcirculation and multiple organs in patients with Covid-19 is still not appreciated.

Studies in many countries have shown that >20% of critically ill or dying Covid-19 patients have acute kidney injury (AKI).[15-17] AKI is considered a negative prognostic factor regarding the survival of Covid-19 patients. The pathophysiologic mechanisms leading to AKI in Covid-19 may include organ interactions, endothelial dysfunction, hypercoagulability, rhabdomyolysis, and sepsis.[18] Segmental fibrin thrombus formation was found in the glomerular capillary loops in a recent postmortem histopathologic analysis of patients with Covid-19.[17] Researchers also reported that two Covid-19 patients developed renal dysfunction due to renal infarction.[19] Another study showed the possibility of proximal tubular injury in patients with COVID-19.[20] It has not been clear whether LMWH can protect kidney function in patients with Covid-19. In our study, improvements in eGFR in the LMWH anticoagulant group were higher than that for the control group, which may be related to the reduction of glomerular microthrombosis.

Endothelial dysfunction with vascular microthrombosis and capillary occlusion lead to damage of capillary blood flow, but microvascular evaluation remains a problematic issue in Covid-19 patients. In a clinical observation study of Covid-19 patients in Wuhan, Yang *et al*[21] found that non-survivors had higher lactic acid concentrations (1.9 [1.4–3.2] mmol/L) compared to survivors (1.6 [1.3–1.6] mmol/L). Our study, for the first time, shows that LMWH can reduce the plasma lactic acid concentration in patients with Covid-19. This may be related to a reduction in microthrombosis and is consistent with the previous results reported by Tang *et al*[3] that LMWH can reduce the Covid-19-related mortality.

Pulmonary microvascular coagulation in Covid-19 results in pulmonary embolism (PE) with occlusion and microthrombosis in pulmonary small vessels. A review of ten autopsies of Covid-19 patients (five men, five women) found evidence of microthrombi in lung tissue.[8] A case series of postmortem autopsies found that PE was the direct cause of death (33%).[22] Treatment with LMWH within the initial 7-day onset of acute respiratory distress syndrome significantly improved the PaO_2/FiO_2 ratio and reduced the risk of 7-day mortality by 48% and the risk of 28-day mortality by 37%, particularly in the subgroup receiving high-dose LMWH (≥5000 U/day).[23] However, the largest available study to date evaluating anticoagulation was an analysis of 2773 patients with Covid-19 in the Mount Sinai Health System. Here, the authors found that patients who received anticoagulation were significantly more likely to require invasive mechanical ventilation.[24] Our study did not show the improvement effect of LWMH on $PaCO_2$, PaO_2, and SaO_2, but it may be that the lung injury in patients with moderate Covid-19 pneumonia is not as severe.

This preliminary retrospective study showed that LMWH anticoagulant therapy in the early stage of Covid-19 pneumonia improves eGFR and reduces arterial blood lactic acid levels in moderate-type patients. The results of this study may provide supportive evidence for the application of LMWH in the treatment of Covid-19 patients.

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Conflicts of interest

The authors declare no conflict of interest regarding the publication of the article.

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