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ORIGINAL ARTICLE

Platelet and monocyte activity markers and mediators of inflammation in Takotsubo cardiomyopathy

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Abstract Patients with Takotsubo cardiomyopathy (TC) often present with symptoms similar to those of myocardial infarction (MI). We analyzed blood concentrations of mediators of inflammation and platelet- and monocyte-activity markers in patients with TC and MI for significant differences. Clinical data of patients with TC ($n = 16$) and acute MI ($n = 16$) were obtained. Serial blood samples were taken at the time of hospital admission (t_0), after 2–4 days (t_1) and after 4–7 weeks (t_2), respectively. Plasma concentrations of interleukin (IL)-6, IL-7, soluble CD40 ligand (sCD40L), and monocyte chemotactic protein 1 (MCP-1) were determined with an ELISA. Tissue factor binding on monocytes**,** platelet-activation marker CD62P, platelet CD40-ligand (CD40L), and platelet-monocyte aggregates were measured using flow cytometry. Expression of CD62P on platelets and IL-6 plasma levels were significantly lower in patients with TC compared to MI at the time of hospital admission. IL-7 plasma levels were significantly elevated in patients with TC compared to patients with MI at 2–4 days after hospital admission. No significant differences were observed concerning sCD40L and MCP-1 plasma levels, tissue factor binding on monocytes, CD40L expression on platelets, and platelet-monocyte aggregates at any point in time. Our results indicate that inflammatory mediators and platelet-activity markers contribute to the differences in the pathogenesis of MI and TC.

Keywords Platelets · Inflammation · Takotsubo cardiomyopathy · Stress

Introduction

Takotsubo cardiomyopathy (TC) is characterized by reversible regional ventricular contractile dysfunction, typically precipitated by severe emotional or physical stress. It sometimes mimics acute myocardial infarction (MI) with respect to its clinical symptoms, electrocardiographic findings, and elevated troponin or creatine kinase indicative of myocardial damage. In contrast to MI, however, there is a lack of occlusive atherosclerotic disease and typically multiple coronary territories are involved. The pathophysiology has not been fully elucidated, but an exaggerated sympathetic activation with catecholamine excess seems to play an essential role [1]. Activation of α1-adrenoceptor in the blood vessels and activation of β1-adrenoceptors in the heart are mainly responsible for stress-induced alteration of cardiac and vascular gene profiles [2].

The pathogenesis of atherosclerosis is well established. In the initiation and progression of atherosclerosis under a chronic inflammatory condition, activated platelets and monocytes play a pivotal role [3]. In this respect, the CD40 receptor and its ligand (CD40L) on activated platelets are of particular interest. They are known to modulate both inflammation and thrombosis, two processes important for the development and clinical expression of atherosclerosis [4]. CD40L can also be found in plasma as a soluble protein (sCD40L), which is commonly elevated in patients

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with acute coronary syndrome [5]. Thus, elevated plasma levels of sCD40L are considered as a new and independent cardiovascular risk factor [6]. In addition, sCD40L is able to activate platelet aggregation [7] and enhance monocyte tissue factor expression [8]. Binding of CD40L to its CD40-receptor on endothelial cell membranes induces an enhanced release of potent proinflammatory and atherosclerosis promoting cytokines and chemokines (e.g., IL-6 and MCP-1) [9]. Upon platelet activation, like CD40L, the P-selectin CD62P is expressed on the surface of platelets and is directly involved in the interaction of platelets with endothelial cells and leukocytes [10].

Elevated levels of circulating cytokines have been demonstrated in patients with heart failure and coronary heart disease. In particular, interleukin 6 (IL-6) concentrations were related to the severity of left ventricular dysfunction and to the degree of activation of the sympathetic and renin-angiotensin systems [11]. Interleukin 7 (IL-7)-driven inflammation plays a role in atherogenesis and the promotion of clinical instability in coronary artery disease involving interactions between platelets, monocytes, and chemokines [12].

There is still little known about the underlying pathogenic mechanisms in TC. At present, no study has assessed the differences between TC and MI regarding inflammatory mediators and platelet-activity markers. Therefore, the aim of the present study was to determine whether the different pathogenesis of both diseases is reflected by these markers and if both entities can be distinguished by them.

Methods

Study population

For this prospective comparative study, patients presenting with TC ($n = 16$) or MI ($n = 16$) were included consecutively. All patients were admitted to the hospital within 6 h after onset of symptoms. Both patients with TC and MI received 500 mg aspirin intravenously before coronary angiography either by the emergency physician or in the chest pain unit. Coronary angiography was performed immediately after admission. Diagnosis of TC was based on the Mayo Clinic criteria [13]: (1) acute onset of mid-LV wall-motion abnormalities with or without apical involvement and not confined to the vascular territory of a single major coronary artery, (2) absence of obstructive coronary sleeves or angiographic evidence of plaque rupture, (3) new ECG abnormalities (either ST-segment elevation and/or T-wave inversion) or elevated cardiac troponin in the absence of pheochromocytoma or myocarditis. Sixteen patients with acute ST-segment elevation myocardial infarction (STEMI) and angiographically documented coronary artery occlusion served as controls. Reperfusion therapy was performed in all patients with MI. Periprocedurally, no patient required intra-aortic balloon pump (IABP) or inotropic agents. During further hospitalization, no patient developed complications such as aggravation of heart failure or sustained ventricular arrhythmias. The investigation conforms with the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee and all patients gave informed consent to the use of their medical record for research purposes.

Enzyme-linked immunosorbent assay (ELISA)

Plasma levels of MCP-1 (Human MCP-1/CCL2 Immunoassay, R&D Systems GmbH Wiesbaden, Germany), Interleukin 6 (Human Interleukin 6 Immunoassay, R&D Systems) and Interleukin 7 (Human Interleukin 7 Immunoassay, R&D Systems) and serum levels of soluble CD40 ligand (Human sCD40L Immunoassay, R&D Systems) were measured according to the manufacturer's instructions.

All concentration analysis was performed on an ELISA-Reader-Lab Systems Multiskan RC (Lab systems, Finland). Genesis Lite Software, ELISA Multiskan RC was used for data acquisition and evaluation.

Flow cytometric analysis

Blood samples of heparinized blood (15 IE heparin per ml blood) (Sarstedt AG & Co/Nuembrecht, Germany) were obtained. To avoid aggregation and activation of platelets, the blood samples were shaken over the time. All whole-blood samples were subsequently investigated on activation of monocytes and platelets as well as platelets binding on monocytes. Surface expressions of CD62P and CD40L on platelets were measured by flow cytometry. Platelet-monocyte aggregates were measured by CD41 (GPIIb/IIIa receptor) surface expression on platelets adherent to monocytes. Optilyse C (Beckman Coulter/Krefeld, Germany) was used for a complete lysing of the red blood cells as well as for fixing of cells.

For the analysis of platelets, 100 µl of each whole-blood sample were stained for 30 min at room temperature with 10 µl aliquots of mouse anti-human CD62P-PE antibodies (CLB-Thromb/6) (Coulter Immunotech/Krefeld, Germany) and mouse anti-human CD40L-FITC antibodies (P2) (Calbiochem/Merck KGaA, Darmstadt, Germany). For the analysis of monocytes, 100 µl of each whole-blood sample were stained for 30 min at room temperature with 10 µl aliquots of PE-conjugated murine antibody against CD41 (Coulter Immunotech/Krefeld, Germany) and murine FITC-conjugated antibody against tissue factor (American Diagnostica/Pfungstadt, Germany). To identify monocytes,

the probes were additionally stained with mouse anti-human CD14-ECD (RM052) (Coulter Immunotech/Krefeld, Germany). Isotype-matched mouse anti-human IgG1 PE/FITC antibodies (Beckman Coulter/Marseille, France) were used as a control. After incubation, erythrocytes were lysed with 500 µl Optilyse C (Coulter Immunotech/Krefeld, Germany). After 15 min, cells were resuspended in 500 µl PBS and were then ready for flow cytometric analysis. For measurement of CD62P and CD40L on platelets, a gating for forward and sideward scatter was performed. For measurement of CD41 on platelets adherent to monocytes to determine platelet-monocyte-aggregates and for measurement of membrane-bound tissue factor a gating for the monocyte surface antigen CD14 and sideward scatter was performed. All flow cytometry analysis was performed on an EPICS XL-MCL machine (Coulter Immunotech/Krefeld, Germany) equipped with an argon laser tuned at 488 nm. System II version 3.0 software was used for data acquisition and evaluation. Compensation of the four-channel fluorescence was precisely adjusted using Cyto-Comp™ reagents and Cyto-Trol™ control cells (Coulter Immunotech/Krefeld, Germany).

Statistical analysis

Numerical data were expressed as mean ± standard deviation (SD). A Mann–Whitney test was applied as a non-parametric test. Categorical variables were analyzed using a Chi-square test and *t* test. Values are expressed as mean values ± SD. In the figures, data are presented as box plots with medians, 25th and 75th percentiles as boxes, and 10th and 90th percentiles as whiskers. A two-tailed probability <0.05 was considered significant. All calculations were performed using GraphPad InStat version 3.01 (GraphPad Software, San Diego, CA, USA) and SPSS Statistics version 17 (SPSS-Software GmbH, Munich, Germany).

Results

Clinical and angiographic findings

The clinical characteristics of patients with TC ($n = 16$) and MI ($n = 16$) are summarized in Table 1. Coronary angiography did not exhibit complex coronary lesions

Table 1 Clinical characteristics of the study groups

Characteristic	Group		*p*
	TC ($n = 16$)	MI ($n = 16$)	
Mean age (years)	67.1 ± 11.0	64.1 ± 11.7	0.453
Male sex (*n*)	4	10	0.073
Initial ejection fraction (%)	42 ± 13	52 ± 7	0.022
Preserved (%)	18.8	31.2	
Mildly reduced (%)	12.5	31.2	
Moderately reduced (%)	31.2	25.0	
Severely reduced (%)	37.5	0	
Past medical history			
Diabetes mellitus (*n*)	3	4	1.000
Hypertension (*n*)	10	9	1.000
Current smoking (*n*)	6	12	0.073
Hyperlipidemia (*n*)	5	10	0.156
Adipocytes (BMI > 30) (*n*)	2	5	0.394
Positive family history (*n*)	5	7	0.715
Long-term medication			
Platelet aggregation inhibitors (*n*)	2	5	0.391
Lipid-lowering drug (*n*)	0	6	0.018
β-Adrenergic inhibitor (*n*)	3	6	0.432
Angiotensin-converting enzyme inhibitor (*n*)	6	5	1.000
Peak values of laboratory tests			
CK (IU/l)	676 ± 1,648	1,163 ± 1,519	0.424
CK-MB (IU/l)	39 ± 48	76 ± 98	0.330
Troponin I (µg/l)	3.1 ± 2.8	16.3 ± 30.0	0.127
CRP (mg/l)	33.6 ± 42.0	16.5 ± 18.0	0.196
Leucocytes (10E9/l)	9.2 ± 3.8	10.5 ± 3.0	0.365

Values are mean ± SD

MI myocardial infarction, *TC* Takotsubo cardiomyopathy, *CK* creatine kinase, *CK-MB* creatine kinase MB sub-fraction, *TNI* troponin I

(defined as ulceration, intimal flap, lumen irregularities, thrombus, and aneurysm) in patients with TC. In the TC group, 13 patients (81%) had normal coronary arteries or atherosclerosis without significant stenosis (luminal narrowing <25% in all three coronary arteries). Three patients (19%) had >25% but less than 70% luminal narrowing in a branch vessel along with extensive regional wall motion abnormalities not confined to the vascular territory of a single major coronary artery. The initial mean ejection fraction (EF) in TC patients was significantly lower compared to MI patients [TC: 42 ± 13% (range 19–61%), MI: 52 ± 7% (range 40–60%); $p = 0.022$]. In the MI group, single, double, and triple vessel disease were present in 19, 44, and 38%, respectively.

Cardiac biomarkers and markers of inflammation

Levels of cardiac troponin I (reference range 0–0.5 µg/l), creatine kinase (CK; reference range 0–145 U/l) and CK-MB (reference range 2–6 U/l) were elevated in patients with both TC and MI but did not differ significantly between both patient groups. In addition, leukocyte cell count (reference range 4.2–10.2 × 10^9/l) and levels of C-reactive protein (CRP; reference range 0–5 mg/l) did not differ significantly between the study groups (Table 1).

Mediators of inflammation and platelet and monocyte activity markers

IL-6 was significantly lower in patients with TC at the time of hospital admission (2.1 ± 2.6 vs. 5.2 ± 5.0 pg/ml; $p = 0.021$) but this difference disappeared at t_1 and t_2 (Fig. 1). IL-7 was significantly elevated in TC patients at t_1 (5.0 ± 2.7 vs. 2.4 ± 1.4 pg/ml; $p = 0.006$) (Fig. 2). MCP-1 and sCD40L did not differ significantly at any time between both groups (Table 2).

Patients suffering from TC had significantly lower CD62P expression on platelets at the time of hospital admission (0.7 ± 0.2 vs. 0.9 ± 0.5; $p = 0.039$) but not at t_1 and t_2 (Fig. 3). There was no significant difference between both patient groups regarding platelet surface expression of CD40L, the amount of platelet-monocyte aggregates and tissue factor binding on monocytes at any time (Table 2). There were no significant differences between male and female patients included in the study regarding all markers at all analyzed points in time.

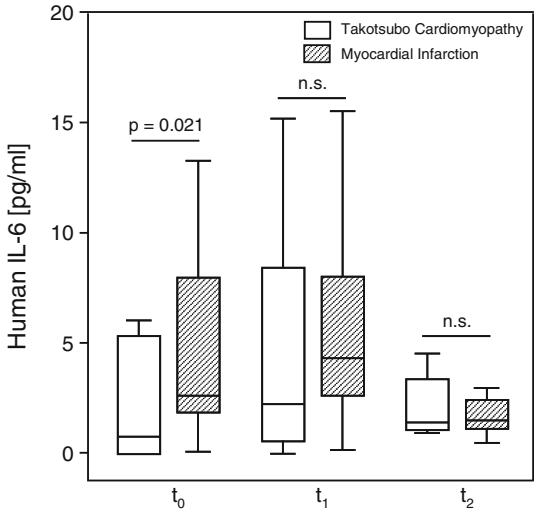

Fig. 1 Plasma levels of IL-6 were measured using ELISA at time of hospital admission (t_0), after 2–4 days (t_1) and after 4–7 weeks (t_2). IL-6 was significantly lower in patients with TC compared to patients with MI at the time of hospital admission ($p = 0.021$). Data are presented as medians, 25th and 75th percentiles (*boxes*) and 10th and 90th percentiles (*whiskers*); *n.s.* not significant, $p > 0.05$

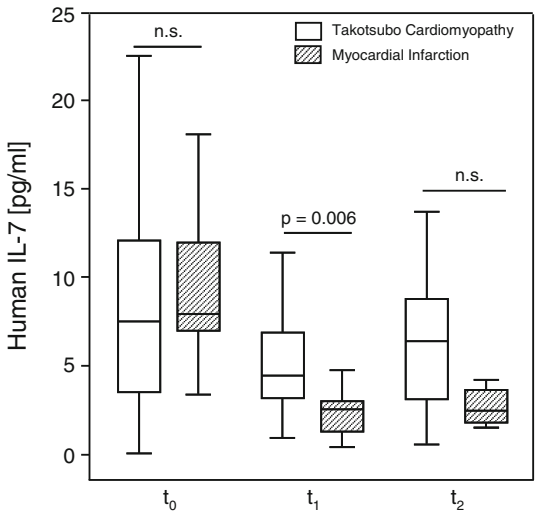

Fig. 2 Plasma levels of IL-7 were measured using ELISA at time of hospital admission (t_0), after 2–4 days (t_1) and after 4–7 weeks (t_2). IL-7 was significantly higher in patients with TC compared to patients with MI at t_1 ($p = 0.006$). Data are presented as medians, 25th and 75th percentiles (*boxes*) and 10th and 90th percentiles (*whiskers*); *n.s.* not significant, $p > 0.05$

Discussion

Takotsubo cardiomyopathy (TC) has been increasingly diagnosed in patients presenting with chest pain and ST-segment elevation within the last years. Since symptoms and ECG diagnostic criteria in TC mimic acute MI, in clinical practice a reliable discrimination between TC and MI can only be achieved by coronary angiography.

Previous studies comparing TC with MI have focused on neurohormonal and neurohumoral factors. Compared to MI, TC exhibits a greater elevation in B-type natriuretic peptide, despite less myonecrosis [14]. There are inconsistent results concerning levels of catecholamines in MI

Table 2 Mediators of inflammation and platelet and monocyte activity markers

Characteristic	Group			*p*
	Point in time	TC ($n = 16$)	MI ($n = 16$)	
IL-6 (pg/ml)	t_0	2.1 ± 2.6	5.2 ± 5.0	0.021
	t_1	4.9 ± 5.8	5.6 ± 4.4	0.232
	t_2	3.8 ± 6.0	1.6 ± 0.9	1.000
IL-7 (pg/ml)	t_0	8.3 ± 6.0	9.3 ± 3.7	0.446
	t_1	5.0 ± 2.7	2.4 ± 1.4	0.006
	t_2	6.4 ± 4.2	2.7 ± 1.1	0.065
CD62P (MFI)	t_0	0.7 ± 0.2	0.9 ± 0.5	0.039
	t_1	0.7 ± 0.2	0.8 ± 0.4	0.171
	t_2	0.6 ± 0.1	0.7 ± 0.2	0.878
CD41 (MFI)	t_0	9.3 ± 4.4	11.1 ± 8.7	0.780
	t_1	11.0 ± 7.3	8.8 ± 3.6	0.539
	t_2	9.4 ± 4.7	6.9 ± 2.4	0.328
sCD40L (pg/ml)	t_0	1,147 ± 1,520	609 ± 911	0.151
	t_1	1,742 ± 1,929	2,126 ± 1,745	0.323
	t_2	1,655 ± 1,340	1,037 ± 334	0.955
Tissue factor binding on monocytes (MFI)	t_0	3.3 ± 2.3	2.4 ± 0.9	0.809
	t_1	2.4 ± 1.3	2.1 ± 0.4	0.423
	t_2	1.7 ± 0.4	2.2 ± 1.0	0.442
MCP1 (pg/ml)	t_0	323 ± 479	173 ± 76	0.696
	t_1	202 ± 98	161 ± 50	0.254
	t_2	154 ± 55	164 ± 61	0.505
CD40L (MFI)	t_0	5.0 ± 1.3	4.8 ± 0.9	0.724
	t_1	5.0 ± 1.6	4.8 ± 0.8	1.000
	t_2	4.5 ± 1.0	4.9 ± 0.9	0.382

Values are mean ± SD

t_0 = day of hospital admission, t_1 = day 2–4 after hospital admission, t_2 = week 4–7 after hospital admission

MI myocardial infarction, *TC* Takotsubo cardiomyopathy, *MFI* mean fluorescence intensity

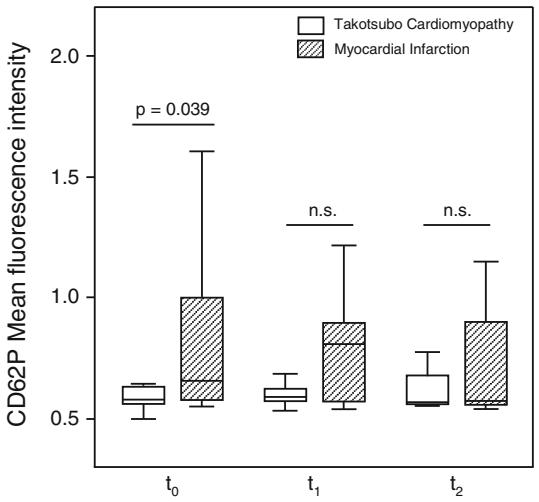

Fig. 3 Surface expression of CD62P on platelets was measured using FACS analysis at time of hospital admission (t_0), after 2–4 days (t_1) and after 4–7 weeks (t_2). CD62P on platelets was significantly lower in patients with TC compared to patients with MI at the time of hospital admission ($p = 0.039$). Data are presented as medians, 25th and 75th percentiles (*boxes*) and 10th and 90th percentiles (*whiskers*); *n.s.* not significant, $p > 0.05$

and TC. While Wittstein and colleagues demonstrated elevated plasma catecholamines and metanephrines in patients with TC compared to patients with MI, other groups had contrary findings [1, 14]. Routine measurement of these stress hormones is unlikely to be of diagnostic value in practice.

In the present study, we were able to show that concentrations of mediators of inflammation and markers of platelet and monocyte activity might be useful to discriminate between TC and MI. Surface expression of CD62P on platelets was significantly lower in patients with TC compared to MI patients at the time of hospital admission. CD62P is expressed on activated platelets and directly involved in the interaction of platelets with endothelial cells and leukocytes [15]. Previous studies demonstrated increased platelet activation in the setting of acute coronary syndromes [16, 17] and it is known that platelet CD62P surface expression in MI patients is significantly higher than in control individuals [18]. Our results confirm an elevated CD62P expression on platelets in MI patients and suggest that platelet activation and cellular coagulation play a minor role in TC.

Noteworthy, at the time of hospital admission, plasma levels of IL-6 were significantly elevated in MI patients compared to patients with TC. IL-6 is a key inflammatory factor that has been implicated in the pathogenesis and clinical course of both coronary heart disease [19] and heart failure [11]. Elevated IL-6 plasma concentrations have been shown to be associated with both the severity of unstable angina and an unfavorable clinical outcome in those patients [20]. It is known that IL-6 levels are significantly increased in patients with myocardial infarction compared to healthy individuals [21]. In our study patients, the differences in IL-6 levels between both study groups disappeared during the hospital course. This is mainly caused by rising IL-6 levels in TC patients over the course of time and might be explained by the known association of elevated IL-6 levels with the severity of left ventricular dysfunction [11]. In our study, patients with TC exhibited reduced left ventricular ejection fraction (LVEF) at an average of 42 ± 13%. This result is consistent with previous studies that reported reduced overall systolic function with left ventricular ejection fraction ranging from 20 to 49% [1, 22, 23]. Raised plasma levels of IL-6 have been shown to correlate with lowered LVEF and cardiac functional class [24], and increased myocardial IL-6 expression is associated with the progression of heart failure [25]. In vitro and in vivo investigations suggest that the proinflammatory cytokines might depress myocardial contractility [26].

In the present study we additionally measured IL-7 levels in TC patients for the very first time and compared them to MI patients. IL-7 is a regulator of T-cell homeostasis but may also be involved in inflammation [27, 28]. Damås and colleagues [12] have shown that plasma levels of IL-7 are significantly increased in patients with angina compared to healthy control subjects and proposed that IL-7 could represent a mediator of inflammation in these patients. It is an interesting finding that 2–4 days after hospital admission, IL-7 levels are significantly higher in patients with TC than in patients with MI while IL-7 levels decrease over time in both study groups. The study by Damås and colleagues also shows that aspirin administration significantly reduced the release of IL-7 from platelets. In our current study, all patients with suspected MI have been administered aspirin as emergency therapy. Following hospital admission, only the patients with MI further received a standard daily low-dose aspirin [29]. The platelet function of patients with TC could have been partially restored within days following admission. Accordingly, the relative increase in plasma levels of IL-7 in TC patients 2–4 days after admission may reflect a more pronounced suppressive effect of aspirin on platelets and, in consequence, decreased secretion and systemic levels of IL-7 in MI patients [12]. Between both groups studied, there were no significant differences regarding plasma levels of MCP-1 and sCD40L, platelet surface expression of CD40L, the amount of platelet-monocyte aggregates, and tissue-factor binding on monocytes at any point in time.

Hypercholesterolemia is associated with inflammation and the prothrombotic state and is a risk factor for cardiovascular diseases. Statin therapy significantly reduces CD62P and IL-6 [30, 31]. In our study, six MI patients but no TC patient presented with statins as a part of the long-term medication. In the remaining MI patients, statin therapy was started immediately after diagnosis according to current guidelines for the treatment of acute coronary syndrome. Our results show an enhanced inflammatory and thrombotic response in patients with MI compared to TC. In spite of the expected attenuation by statin therapy that was mentioned above, MI patients still exhibited significantly higher CD62P and IL-6 levels at admission (t_0).

Our results provide evidence of enhanced inflammatory and thrombotic response in MI compared to TC for the first time. Especially CD62P and IL-6, which are elevated in MI patients at the time of hospital admission, could support the differential diagnosis of MI and TC. As these differences had dissolved at the next reading point, further studies are required to measure these parameters at closer intervals within the first 2 days after the onset of symptoms and/or hospital admission.

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Conflict of interest The authors declare that they have no conflict of interest.

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