bjh short report

Delayed-phase thrombocytopenia in patients with coronavirus disease 2019 (COVID-19)

Wanxin Chen,[1] Ziping Li,[1] Bohan Yang,[2] Ping Wang,[3] Qiong Zhou,[2] Zhiguo Zhang,[4] Jianhua Zhu,[5] Xuexing Chen,[1] Peng Yang[6] and Hao Zhou[1]

[1]Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, [2]Department of Respiratory and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, [3]Department of Clinical Laboratory, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, [4]School of Medicine and Health Management, Tongji Medical College, Huazhong University of Science and Technology, [5]Laboratory of Clinical Immunology, Wuhan No. 1 Hospital, Tongji Medical College, Huazhong University of Science and Technology, and [6]Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China

Received 7 April 2020; revised 21 May 2020; accepted for publication 25 May 2020

Correspondence
Hao Zhou, Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
Email: zhouhao@hust.edu.cn
Peng Yang, Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
Email: yangpenguh@hust.edu.cn

*Wanxin Chen and Ziping Li contributed equally to the work.

Summary

Coronavirus disease 2019 (COVID-19) can affect the haematopoietic system. Thrombocytopenia at admission was prevalent, while late-phase or delayed-phase thrombocytopenia (occurred 14 days after symptom onset) is rare. This retrospective, single-centre study screened 450 COVID-19 patients and enrolled 271 patients at the Union Hospital, Wuhan, China, from January 25 to March 9, 2020. COVID-19-associated delayed-phase thrombocytopenia occurred in 11·8% of enrolling patients. The delayed-phase thrombocytopenia in COVID-19 is prone to develop in elderly patients or patients with low lymphocyte count on admission. The delayed-phase thrombocytopenia is significantly associated with increased length of hospital stay and higher mortality rate. Delayed-phase nadir platelet counts demonstrated a significantly negative correlation with B cell percentages. We also provided and described bone marrow aspiration pathology of three patients with delayed-phase thrombocytopenia, showing impaired maturation of megakaryocytes. We speculated that immune-mediated platelet destruction might account for the delayed-phase thrombocytopenia in a group of patients. In addition, clinicians need to pay attention to the delayed-phase thrombocytopenia especially at 3–4 weeks after symptom onset.

Keywords: clinical features, COVID-19, cytokine, lymphocyte, SARS-CoV-2, thrombocytopenia.

First published online 18 June 2020
doi: 10.1111/bjh.16885

Introduction

In December 2019, the outbreak of coronavirus disease 2019 (COVID-19) was initially reported in Wuhan, China.[1] Common symptoms of COVID-19 include fever, cough and shortness of breath, since the lung is the major target of SARS-CoV-2. Cardiac, digestive and neurologic complications were also found in COVID-19 patients. These extrapulmonary manifestations imply diverse target organs in addition to the lung. The haematopoietic system can also be affected by COVID-19. A multicentre study by our hospital and others demonstrated that, on admission, lymphocytopenia was present in 83·2% of the patients and thrombocytopenia in 36·2%.[2]

With increased hospitalisation capacity and prolonged isolation period, we are now able to study the disease longitudinally apart from cross-sectionally on admission. In particular, our initial observations showed there were sudden dramatic declines in platelet count in several COVID-19 patients without evidence of other coagulation abnormalities, which happened 3 weeks or more after symptoms' onset. COVID-19-related, early-phase thrombocytopenia was prevalent,[3] while late-phase or delayed-phase thrombocytopenia was rare.

In the current study, we report the incidence, characteristics and outcomes of patients with delayed-phase thrombocytopenia. We also present the bone marrow aspiration pathology of three patients with delayed-phase thrombocytopenia.

Methods

Study design and participants

This was a retrospective, descriptive, longitudinal study, conducted from January 25 to March 9, 2020. All patients were recruited from the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. As a routine, electronic medical data have been archived onto a local server, from which we can retrieve the data. The study was approved by the Research Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. 2020-0079-1). Written informed consent was obtained from the patients in our study.

The inclusion criteria for this study were (1) each patient was confirmed by real-time RT-PCR and diagnosed as having COVID-19 according to WHO interim guidance;[4] (2) all patients underwent chest CT and a complete panel of routine laboratory tests. The exclusion criteria were (1) monitoring period less than 21 days from symptom onset; (2) autoimmune or haematological disease history; (3) previous HIV, hepatitis B or hepatitis C infection; (4) dialysis patients.

Procedures

The demographic data, clinical characteristics, laboratory data and treatment data were obtained from patients' medical records. The clinical outcomes (i.e., discharges, mortality and hospital stay time) were monitored up to April 15, 2020, the final date of follow-up. Any uncertain information was clarified through direct communication with patients' families. We collected continuously monitored laboratory data, including blood routine, blood coagulation function, inflammatory cytokines, and lymphocytes subset analysis. For some patients, the SARS-CoV-2 IgG results were recorded when available. The date of disease onset was defined as the day when the symptom was noticed. The severity of COVID-19 was defined according to the diagnostic criteria of the "COVID-19 diagnosis and treatment plan (trial seventh edition)".[5] Throat swab samples were collected for viral detection. SARS-CoV-2 was confirmed with nucleic acid detection kit (Shanghai Bio-germ Medical Technology, Shanghai, China). The IgG antibody was detected with SARS-CoV-2 IgG antibody detection kit (YHLO biotechnology, Shenzhen, China).

Statistical analysis

Descriptive data were presented as means [± standard deviation (SD)] for normally distributed continuous variables, and as medians with interquartile range (IQR) for non-normally distributed data. Categorical variables were presented as percentages. Proportions for categorical variables were compared using the chi-squared test, and the Fisher exact test was used when data were limited. The quantised variables of parameters are tested by *t*-test. Nonparametric variables are tested by Mann–Whitney *U*-test. The Spearman rank correlation coefficient was used for correlation analysis. All statistical analysis was performed using SPSS v.19·0 (IBM Corp., Armonk, NY, USA). A two-tailed P value $< 0{\cdot}05$ was considered statistically significant.

Results

Patient flow and baseline characteristics

A total of 450 hospitalised COVID-19 patients were reviewed, and 271 patients were finally enrolled according to the inclusion and exclusion criteria. Their baseline characteristics are shown in Table I. The average time from symptom onset to hospital admission was 6·65 days (SD = 2·78). After admission, there were 246 (90·8%) patients receiving antiviral treatment, 176 (64·9%) on antibiotics, 115 (42·4%) on glucocorticoids, 117 (43·2%) on inhaled interferon-α and 65 (24·0%) on intravenous immunoglobulin. On the final day of follow-up, 48 patients were still in hospital (17·7%), 215 (79·3%) had been discharged and 11 (3·0%) had died. Moreover, 29 patients had been transferred to the ICU (10·7%).

Among the discharged patients, the average hospital isolation ward stay was 31·96 days (SD = 10·86).

Incidence and outcomes of patients with delayed-phase thrombocytopenia

Based on the dynamic of antibody response,[6] duration of the viremia phase after SARS-CoV-2 infection[7] and our preliminary clinical observations, we propose setting 14 days as the rough though reasonable and feasible cutoff value. Therefore, delayed-phase thrombocytopenia is defined as thrombocytopenia beginning after 14 days post-symptom appearance. We found 32 patients (11·8 %) developed delayed-phase thrombocytopenia (Table I). The mean time for delayed-phase thrombocytopenia nadir appeared at 28·3 days from illness onset. The mean duration time for

Table I. Baseline characteristics and clinical outcomes of COVID-19 patients.

Characteristics	All patients (n = 271)	Patients without delayed-phase Thrombocytopenia (n = 239)	Patients with delayed-phase Thrombocytopenia (n = 32)	P value
Age (y)	57·74 ± 14·30	56·52 ± 13·93	67·00 ± 12·86	0·026
Age groups, *n* (%)				
<60 y	125 (46·1%)	116 (48·5%)	9 (28·1%)	0·030
≥ 60y	146 (53·8%)	123 (51·5%)	23 (71·9%)	
Gender (M/F), *n* (%)				
Male (M)	145 (53·5%)	124 (51·9%)	21 (65·6%)	0·143
Female (F)	126 (46·5%)	115 (48·1%)	11 (34·4%)	
Respiratory rate	22·08 ± 4·51	21·74 ± 3·99	23·03 ± 5·36	0·157
Smoking, *n* (%)	14 (5·2%)	12 (5·0%)	2 (6·3%)	0·896
Comorbidities, *n* (%)				
Cardio cerebrovascular disease	75 (27·7%)	66 (27·6%)	9 (3·3%)	0·952
Endocrine system disease	35 (12·9%)	29 (12·1%)	6 (18·8%)	0·295
Respiratory system disease	11 (4·1%)	9 (3·8%)	2 (6·3%)	0·848
Digestive system disease	10 (3·7%)	7 (2·9%)	3 (9·4%)	0·188
Nervous system disease	6 (2·2%)	5 (2·1%)	1 (3·1%)	0·790
Malignant tumor	9 (3·3%)	7 (2·9%)	2 (6·3%)	0·646
Symptoms on admission, *n* (%)				
Fever	220 (81·2%)	195 (81·6%)	25 (78·1%)	0·638
Cough	190 (70·1%)	169 (70·7%)	21 (65·6%)	0·555
Dyspnea	75 (27·7%)	65 (27·2%)	10 (31·3%)	0·630
Pharyngalgia	16 (5·9%)	15 (6·3%)	1 (3·1%)	0·756
Mucocutaneous hemorrhage	0 (0·0%)	0 (0·0%)	0 (0·0%)	–
Diarrhea	40 (14·8%)	37 (15·5%)	3 (9·4%)	0·516
Anorexia	51 (18·8%)	46 (19·2%)	5 (15·6%)	0·801
Abdominal pain	4 (1·5%)	4 (1·7%)	0 (0·0%)	0·957
Palpitation	17 (7·0%)	16 (6·7%)	1 (3·1%)	0·694
Hypodynamia	101 (37·3%)	89 (37·2%)	12 (37·5%)	0·977
Paresthesia	4 (1·5%)	4 (1·7%)	0 (0·0%)	0·960
Myalgia	47 (17·3%)	43 (18·0%)	4 (12·5%)	0·602
Dizziness	18 (6·6%)	15 (6·3%)	3 (9·4%)	0·777
Days from illness onset to admission	6·65 ± 2·78	6·64 ± 2·73	6·84 ± 3·06	0·701
Treatment before delayed-phase thrombocytopenia, *n* (%)				
Antibiotic treatment	176 (64·9%)	155 (64·9%)	21 (65·6%)	0·932
Antiviral treatment	246 (90·8%)	216 (90·4%)	30 (93·8%)	0·769
Glucocorticoids	115 (42·4%)	101 (42·3%)	14 (43·6%)	0·873
Inhaled Interferon-α	117 (43·2%)	103 (43·1%)	14 (43·8%)	0·944
Intravenous immunoglobulin	65 (24·0%)	57 (23·8%)	11 (34·4%)	0·197
Oxygen therapy	248 (91·5%)	218 (91·2%)	30 (93·8%)	0·884
Number of cases admitted to ICU	29 (10·7%)	21 (8·8%)	8 (25·0%)	0·005
Clinical outcome, *n* (%)				
Discharged	215 (79·3%)	196 (82·0%)	19 (59·4%)	0·003
Remained in hospital	48 (17·7%)	39 (16·3%)	9 (28·1%)	0·100
Died	8 (3·0%)	4 (1·7%)	4 (12·5%)	0·002
Hospital days	31·96 ± 10·86	31·07 ± 10·74	35·84 ± 11·20	0·021

Table II. Laboratory findings of patients with COVID-19 on admission.

Characteristics	Reference range	All patients (n = 271)	Patients without delayed-phase thrombocytopenia (n = 239)	Patients with delayed-phase thrombocytopenia (n = 32)	P value
Blood routine					
White blood cell count, $\times10^9$/l	3·50–9·50	6·88 ± 4·03	6·94 ± 4·14	6·10 ± 3·60	0·275
Hemoglobin, g/l	130·00–175·00	127·52 ± 17·50	128·31 ± 16·58	129·92 ± 19·67	0·612
Platelet count, $\times10^9$/l	125·00–350·00	228·86 ± 87·34	233·75 ± 93·49	212·08 ± 67·79	0·103
Neutrophil count, $\times10^9$/l	1·80–6·30	3·58 (2·48–5·84)	3·64 (2·60–5·83)	2·92 (2·05–7·31)	0·905
Lymphocyte count, $\times10^9$/l	1·10–3·20	1·10 (0·77–1·58)	1·20 (0·87–1·61)	0·745 (0·62–1·03)	0·001
Platelet-to-lymphocyte ratio (PLR)		160·05 (125·91–291·07)	169·06 (125·91–297·27)	151·95 (126·82–234·55)	0·346
Hemorrhage and coagulation indicators					
D–dimer, mg/l FE	<0·50	0·40 (0·22–1·27)	0·395 (0·22–1·22)	0·50 (0·22–1·09)	0·270
Fibrinogen degradation products, ug/ml	<5·00	5·47 (5·14–6·53)	5·28 (5·10–6·44)	5·75 (5·17–6·93)	0·382
Prothrombin time, s	11·00–16·00	14·05 ± 3·56	14·17 ± 3·32	13·59 ± 2·04	0·150
Activated partial thromboplastin time, s	28·00–43·50	38·78 ± 11·30	38·69 ± 11·69	37·60 ± 5·98	0·362
Fibrinogen, g/l	2·00–4·00	4·34 ± 1·18	4·45 ± 1·11	4·20 ± 1·40	0·343
Blood biochemistry					
Alanine aminotransferase, U/l	21·00–72·00	30·50 (19·75–43·00)	29·50 (19·25–42·75	32·50 (20·75–43·00)	0·582
Aspartate aminotransferase, U/l	17·00–59·00	26·00 (20·00–37·25)	24·00 (19·25–33·75)	34·00 (26·00–44·75)	0·041
Blood urea nitrogen, mmol/l	3·20–7·10	4·81 (3·49–6·16)	4·78 (3·41–5·87)	5·27 (4·03–7·17)	0·273
Creatinine, μmol/l	58·00–110·00	71·45 (60·58–87·15)	70·75 (59·15–84·50)	78·15 (21·15–49·00)	0·269
Albumin, g/l	35·00–50·00	34·23 ± 7·65	35·40 ± 7·69	32·96 ± 6·75	0·067
Immunoglobulins, g/l	23·00–32·00	30·66 ± 6·94	30·21 ± 6·90	31·29 ± 7·86	0·414
Lactate dehydrogenase, U/l	109·00–245·00	228·00 (188·75–308·00)	211·50 (186·50–290·50)	283·50 (243·75–383·00)	0·022
Infection-related biomarkers					
C-reactive protein, mg/l	0·00–5·00	38·93 ± 37·69	35·18 ± 36·80	40·86 ± 35·08	0·411
Inflammatory cytokines					
Interleukin-2, pg/ml	0·10–4·10	3·01 ± 0·87	3·08 ± 0·93	2·77 ± 0·77	0·072
Interleukin-4, pg/ml	0·10–3·20	2·65 ± 1·17	2·74 ± 1·07	2·26 ± 1·21	0·019
Interleukin-6, pg/ml	0·10–2·90	17·64 ± 40·62	9·11 ± 17·30	40·73 ± 71·84	0·020
Interleukin-10, pg/ml	0·10–5·00	4·63 ± 2·11	4·82 ± 2·29	4·37 ± 1·87	0·288
Tumor necrosis factor-α, pg/ml	0·10–23·00	2·56 ± 1·41	2·66 ± 1·62	2·20 ± 0·80	0·005
Interferon-γ, pg/ml	0·10–18·00	2·64 ± 1·00	2·71 ± 0·84	2·42 ± 1·42	0·274
Lymphocyte Subsets					
CD3 + T Lymphocytes, %	58·17–84·22	72·40 ± 9·06	74·53 ± 7·46	69·43 ± 10·33	0·012
CD4 + T Lymphocytes, %	25·34–51·37	42·76 ± 10·30	44·34 ± 9·14	38·79 ± 12·45	0·021
CD8 + T Lymphocytes, %	14·23–38·95	25·14 ± 9·88	26·45 ± 9·07	24·07 ± 12·57	0·313
B Lymphocytes, %	4·10–18·31	13·95 ± 9·43	11·24 ± 4·97	17·28 ± 12·22	0·010
NK Lymphocytes, %	4·10–18·31	9·05 ± 7·09	8·50 ± 6·03	11·00 ± 8·63	0·126

delayed-phase thrombocytopenia was 4·32 days (SD = 2·15). We also found the mean platelet count at nadir to be $86·0 \times 10^9$/l (SD = 37·48). Delayed-phase thrombocytopenia is more prevalent in elderly persons (71·9% in >60-years-old patients). The clinical outcomes for these 32 patients with delayed-phase thrombocytopenia were: nine patients remained in hospital, 19 were discharged and four died. Additionally, there were eight cases that were admitted to ICU (delayed-phase thrombocytopenia patients). Notably, mortality was markedly higher in patients with delayed-phase thrombocytopenia than in patients without delayed-phase thrombocytopenia (four [12·5%] *versus* four [1·7%]) (Table I). The representative platelet count curves are shown in Supplemental Data.

Laboratory findings of patients with delayed-phase thrombocytopenia

On admission, the delayed-phase thrombocytopenia cases demonstrated lower lymphocyte count (0·745 [0·62–1·03],

$P = 0{\cdot}001$), compared to the group without delayed-phase thrombocytopenia (Table II). The level of the lymphocyte subsets ($CD3^+$ T, $CD4^+$ T and B cells) and inflammatory cytokines (IL-4, IL-6 and TNF-α) showed significant alterations from their counterpart. Furthermore, we conducted time-correlated data analysis of the cytokines and lymphocyte subset results at around the time delayed-phase thrombocytopenia occurred. Delayed-phase nadir platelet counts demonstrated a significantly negative correlation with B cell percentages ($r_s = 0{\cdot}509$, $P < 0{\cdot}001$) and serum IL-6 levels ($r_s = 0{\cdot}443$, $P < 0{\cdot}001$).

Bone marrow aspiration analysis of three cases

We specifically studied three patients who underwent bone marrow aspiration in the Union Hospital. All three patients developed rapid and dramatic decline in platelet count at delayed phase, without evidence of other coagulation abnormalities. The pathology results from each of the three patients shared common features: (1) bone marrow showed no obvious abnormities in the myeloid or the erythroid cells; (2) number of atypical or reactive lymphocytes increased; (3) maturation of megakaryocyte was impaired, the mature platelet-producing megakaryocytes were rare and most megakaryocytes were immature granular megakaryocytes. Two patients' bone marrow smear images are presented in Supplemental Data.

Discussion

The present study was conducted by reviewing the medical records of patients with COVID-19 from January 25 to March 9, 2020, in a heavily-affected hospital during the initial outbreak in China. We found that COVID-19-associated delayed-phase thrombocytopenia occurred in 11·8% of enrolling patients. Delayed-phase thrombocytopenia in COVID-19 is prone to develop in elderly patients or patients with low lymphocyte count on admission. Delayed-phase thrombocytopenia is significantly associated with increased length of hospital stay and higher mortality rate.

Previous cross-sectional studies have shown that, at admission time, thrombocytopenia was prevalent in acute COVID-19-infected patients.[3,8,9] Besides, patients infected by other coronaviruses, severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), also frequently suffered thrombocytopenia at admission.[10,11] However, the acute viral infection associated with delayed-phase thrombocytopenia has only been reported as rare case reports without enough patients for statistical analysis.[12,13] Our retrospective study showed that thrombocytopenia might occur at delayed phase in COVID-19 patients and at a significant percentage in the enrolled patients.

To clarify the pathogenesis of the delayed-phase thrombocytopenia cases, we longitudinally reviewed the results of cytokines and lymphocyte subsets. Our results suggest that IL-6 might be an active player in the delayed-phase platelet decline. Since antibody production by B cells is crucial in virus protection, our results imply, but do not confirm, that antibodies might play an important role in the delayed-phase platelet decrease. We also found most of the delayed-phase thrombocytopenia lasted less than 7 days, implying the delayed-phase thrombocytopenia is transient.

In addition, we sought to obtain evidence from bone marrow. All bone marrow aspiration pathology showed common features, such as impeded megakaryocyte maturation, and mature platelet-producing megakaryocytes were rare (less than five in the bone marrow smear). These bone marrow features were similar to those in immune thrombocytopenia. Based on the antibody curve after SARS-CoV-2 infection,[6,14] we speculate that the delayed-phase platelet decrease in these three patients might be immune-mediated.

Virus-associated immune thrombocytopenia may include several mechanisms:[15] first, a virus-induced change in the host's immune system by polyclonal B cell activation or release of cytokines; second, the production of autoantibodies against platelet glycoproteins induced by the modification of platelet surface proteins by virus infection; third, cross-reaction of the virus protein-directed antibodies with platelet glycoproteins; fourth, virus-infected megakaryocyte sheds platelets that present viral antigens, so antiviral antibodies attack against platelets. Animal models with Rauscher virus infection developed delayed-phase immune thrombocytopenia.[16]

This study has several limitations. First, our retrospective study was based on a relatively small sample. Second, our hospital-based study no doubt missed patients who were mild cases. Third, regression and survival analysis are recommended. Fourth, the relationship between prognosis and thrombocytopenia remains to be investigated, since a few patients were still hospitalised.

Acknowledgements

We acknowledge all health care workers involved in the diagnosis and treatment of patients at Union Hospital.

Authors' contributions

W.C. and Z.L.: drafting or revision of the submitted article. Q.Z. and B.Y.: health care providers of the patients. P.W. and Z.Z.: constructive suggestions and data analysis. J.Z. and X.C.: data collection and analysis. H.Z. and P.Y.: design of the study and revision of the submitted article.

Written informed consent was obtained from the patients in our study.

Funding

This work was supported by the Clinical Innovation Funds of Union Hospital (No. 2019-125).

Conflict of interest

All authors declare that they have no conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Dynamic changes of platelet count in COVID-19 patients.

Data S2. Wright's stained bone marrow aspirate smears from two patients.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China. *New England J Med*. 2019;**382**:727–33.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;**382**:1708–20.
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2020;**323**:1061.
4. WHO. Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected: interim guidance. January, 2020. (https://www.who.int/internal-publications-detail/clinical-management-of-severeacute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected) (accessed February 5, 2020).
5. Health N.Commission of People's Republic of China. Diagnosis and treatment of pneumonia caused by novel coronavirus (trial seventh edition). (http://www.nhc.gov.cn/yzygj/s7653p/202003/46c929.4a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf).
6. Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med*. 2020. [Epub ahead of print].
7. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. *Emerging Microbes & infections*. 2020;**9**:727–32.
8. Simon AY, Sutherland MR, Pryzdial EL. Dengue virus binding and replication by platelets. *Blood*. 2015;**126**:378–85.
9. Maan R, van der Meer AJ, Hansen BE, Feld JJ, Wedemeyer H, Dufour JF, et al. Effect of thrombocytopenia on treatment tolerability and outcome in patients with chronic HCV infection and advanced hepatic fibrosis. *J Hepatol*. 2014;**61**:482–91.
10. Wong RS, Wu A, To KF, Lee N, Lam CW, Wong CK, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. *BMJ (Clinical research ed)*. 2003;**326**:1358–62.
11. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *Lancet Infect Dis*. 2013;**13**:752–61.
12. Sharp TM, Muñoz-Jordán J, Perez-Padilla J, Bello-Pagán MI, Rivera A, Pastula DM, et al. Zika virus infection associated with severe thrombocytopenia. *Clin Infect Dis*. 2016;**63**:1198–201.
13. Karimi O, Goorhuis A, Schinkel J, Codrington J, Vreden SGS, Vermaat JS, et al. Thrombocytopenia and subcutaneous bleedings in a patient with Zika virus infection. *Lancet (London, England)*. 2016;**387**:939–40.
14. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis*. 2020;**20**(5):565–74.
15. Audia S, Mahévas M, Samson M, Godeau B, Bonnotte B. Pathogenesis of immune thrombocytopenia. *Autoimmun Rev*. 2017;**16**(6):620–32.
16. Grau GE, Morrow D, Izui S, Lambert PH. Pathogenesis of the delayed phase of Rauscher virus-induced thrombocytopenia. *J Immunol* (Baltimore, Md : 1950) 1986;**136**(2):686–91.