Review Article

Hematology, immunology and clinical chemistry profiles of COVID-19 patients: Systematic review

Mistire Wolde

Abstract

Background: COVID-19 is an emerging novel viral infection that first emerged in December 2019 and was officially pronounced as a 'pandemic' by March 2020. One of the strategies to control the spread of COVID-19 disease is expanding laboratory diagnosis services. So far, the molecular biology-based real-time polymerase chain reaction (RT-PCR) method is the only recommended laboratory test to diagnose the disease. However, during COVID-19 infection, hematology, immunology, and clinical chemistry test profile changes might also assist in diagnosing the disease.

Objective: The objective of this systematic review was "assessment of routine hematology, immunology, and clinical chemistry test profile changes among COVID-19 RT-PCR laboratory tests positive individuals", which, before such tests are carried out, might suggest the occurrence of COVID-19 infection.

Material and methods: The systematic review was done to assess general epidemiology, routine clinical chemistry and hematology/ immunohematology tests done in association with COVID-19 diagnosed cases. Online published articles were searched using PubMed, Hinari, AGORA and Google Scholar search engines, based on the following inclusion criteria: articles on COVID-19 that focus on human coronavirus diseases, their epidemiology, laboratory diagnosis of such diseases, the RT-PCR test, and additional routine laboratory tests. Exclusion criteria included articles that discuss the RT-PCR method only, imaging diagnostic methods, and those that focus on specific groups (such as COVID-19 among diabetes patients, cancer patients and so on). Accordingly, a total of 75 research articles were identified. Of these, 29 papers were selected for systematic review.

Results: From the collected 29 articles on routine clinical chemistry tests, it was concluded that in confirmed COVID-19 cases, aminotransferase enzymes – alanine transaminase (ALT) and aspartate transaminase (AST) – bilirubin, creatine kinase (CK), troponin, lactate dehydrogenase (LDH), creatine and ferritin values were relatively high, whereas the albumin value was reduced. In the hematology/immunohematology tests, total white blood cell (WBC) counts, neutrophil counts, erythrocyte sedimentation rates (ESR), C-reactive protein (CRP) and prothrombin time (PT) increased, whereas lymphocyte counts, platelet counts, and cluster of differentiation 4 (CD4) and cluster of differentiation 8 (CD8) counts decreased. In addition, neutrophil-lymphocyte (N-L) ratios increased, whereas lymphocyte-C-reactive protein (L-C) ratios decreased.

Conclusions: For those individuals with signs and symptoms of COVID-19, leukocytosis with neutrophilia and lymphopenia, high N-L and low L-C ratios, mild increases in aminotransferase and creatinine values with increased CK, troponin and ferritin levels, might be considered as "routine laboratory test results that are supportive of occurrence COVID-19 disease". Further large-scale studies are required to strengthen the present findings. [*Ethiop. J. Health Dev.* 2020; 34(3):226-231]

Key words: COVID-19, clinical chemistry, hematology, immunohematology tests

Introduction

Coronaviruses are known viral infections that cause different degrees of respiratory tract infection in humans. The different human coronavirus (HCoV) strains include HCoV-229E, HCoV-NL63, HCoV-HKU1, HCoV-OC43, Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV). COVID-19 emerged and was first reported in Wuhan, Hubei province, China, in December 2019 (1). The disease spread so swiftly across the world, and it was formally pronounced as a 'pandemic' by March 2020. Although COVID-19 has a relatively low mortality ratio compared to SARS, due to its very fast transmission, it has caused a significant total death toll worldwide (2).

Studies show that common signs and symptoms of COVID-19 patients include fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), headache (13.6%), and gastrointestinal symptoms with diarrhea (3.8%) and vomiting (5.0%) (3,4). Morbidity and mortalities associated with COVID-19 are more often associated with elderly patients, and those with underlying chronic disease conditions such as hypertension, diabetics, asthma and cardiovascular diseases (5).

Globally, as of 9:20 am CEST on July 15, 2020, there were 13,119,239 confirmed cases of COVID-19, including 573,752 deaths, reported to the World Health Organization (WHO). So far, the United States of America leads the world with 3,344,783 confirmed cases and 135,053 deaths (6). In Ethiopia, the first COVID-19 case was reported on 13 March 2020 (7). As at July 14, 2020, there were 8,181 confirmed cases and 146 deaths in the country (8).

To diagnose COVID-19, the laboratory test recommended by WHO, Centers for Disease Control and Prevention (CDC) and other national and international health organizations, and used by many reference laboratories worldwide, is the RT-PCR

Department of Medical Laboratory Sciences, College of Health Sciences, Addis Ababa University, Ethiopia. Email: mistire08@gmail.com

method. This method involves collecting samples mainly from nasopharyngeal and oropharyngeal swabs of suspected individuals (9). In terms of serological tests to detect either SARS-CoV-2 virus antigens or antibodies, to the best of the author's knowledge, there is no highly sensitive and specific test kit approved for the diagnosis of the disease by any international organization, such as WHO or CDC that can be used worldwide, including in Ethiopia. On the other hand, RT-PCR-based diagnosis is expensive for most developing countries and others where technology and/or expertise is not available.

Studies indicate that the SARS-CoV-2 virus attaches to angiotensin-converting enzyme 2 (ACE2) receptors that are found on the surface of different organs and system-forming cells of the body, including alveolar epithelial cells, intestinal epithelial cells, liver cells, and heart, and renal tubules (10). Thus, it is reasonable to consider any abnormal findings of metabolic and/or organ function tests to be indicative of COVID-19 disease. Accordingly, the presence of ACE2 receptors in specific body parts either creates the opportunity of virus attack, or, in association with the respiratory system attack of COVID-19 infection or other organs/system, results in abnormal biochemical profiles of COVID-19 patients.

Moreover, studies show that after individuals have acquired SARS-CoV-2, the viral infection leads to signs and symptoms of diseases, usually those associated with a suppressed immune system, and/or the virus creates opportunities for other infectious diseases, such as bacterial, attacks, and also disturbs the normal hematology and immune-hematology profiles of COVID-19-infected individuals (11).

Therefore, the objective of this study was to assess routine hematology, immunology, and clinical chemistry test profile changes among individuals who had tested positive following COVID-19 RT-PCR laboratory tests. The suggested routine laboratory tests are relatively available in most clinical laboratories, results are issued within short periods, and they may assist in the management of COVID-19 disease. By conducting these auxiliary tests, those patients who show results indicating COVID-19 infection can then be tested using the RT-PCR test. Restricting the extent of RT-PCR testing in this way will save money, as well as quickly identify cases in the community.

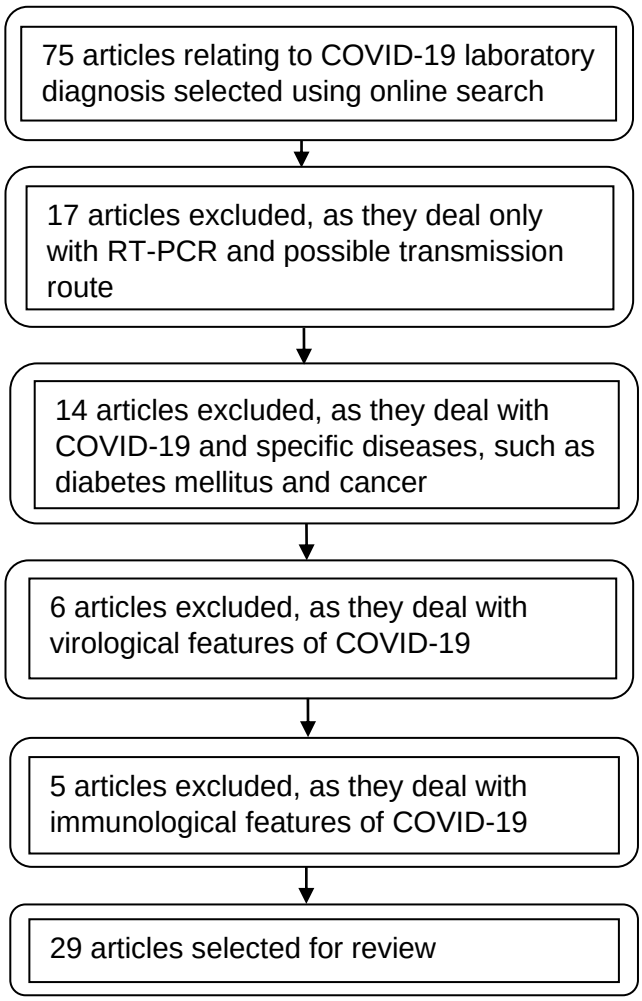
Material and methods

Search approach: Different online databases, including PubMed, Hinari, AGORA, Google Scholar, and as well reported news articles related to COVID-19 diseases, were examined. Online materials published from January 1, 2020 to June 1, 2020 were included in the study. The search terms used, separately and in combination, included 'COVID-19 laboratory tests', 'COVID-19 nucleic acid tests', 'COVID-19 epidemiology', 'COVID-19 and liver function tests', 'COVID-19 and renal function tests', 'COVID-19 and cardiac markers', 'COVID-19 and hematology tests' and 'COVID-19 and immunological tests'.

Inclusion and exclusion criteria: During online searches of the data, inclusion criteria included papers on COVID-19 that focus on human coronavirus diseases, epidemiology, laboratory diagnosis, RT-PCR test, and additional routine laboratory tests. Articles dealing with COVID-19 in relation to animal-to-human transmission, disease virology and detailed immunological features, the imaging diagnostic method, RT-PCR methods only, and papers that focus on specific groups (such as diabetes patients, hypertension and cardiac patients, and cancer patients) were excluded from the analysis.

Data extraction: Data extraction used in the present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (12). The eligibility of each selected paper for the study was assessed based on its publication title, publication period, abstract, background, objective and methodology, and results. During each analysis, basic inclusion and exclusion criteria were used to assess whether the article was appropriate to include in the present study. Finally, from a total of 75 research articles examined, 29 were selected for the study.

Figure 1: **Flow diagram of literature selection**



Results

Clinical chemistry tests: In most COVID-19 infection, RT-PCR test confirmed cases, routine clinical chemistry tests were performed to assess liver, renal, and cardiac functions. Among these organ function tests, aspartate transaminase (AST), alanine transaminase (ALT), total and direct bilirubin, and albumin were included under liver function tests; whereas troponin, creatine kinase muscle-brain isoenzymes (CK-MB), lactate dehydrogenase (LDH) and ALT were included under cardiac function tests. In addition, urea and creatinine were mentioned as markers for renal function tests, and laboratory tests such as ferritin and others indicators were sometimes included, depending on the specific disease condition of COVID-19 cases.

Among the liver function tests, except albumin, all other panel test values increased in most COVID-19 cases. On the other hand, patients with COVID-19 indicated high values of creatinine in renal function tests, as well as high values of CK-MB, troponin and LDH in cardiac function tests. The picture of routine clinical chemistry tests is summarized in Table 1.

Table 1: **List of routine clinical chemistry tests with abnormal findings during COVID-19 infection**

Clinical chemistry test	**Normal reference range**	**Findings compared with the normal reference range**	**Reference(s)**
Albumin	3.4-5.4 g/dL	Decreased	13,14
Lactate dehydrogenase (LDH)	140-280 IU/L	Increased	13,14,15
Alanine aminotransferase (ALT)	Below 40 IU/L	Increased	13,14,15.16
Aspartate aminotransferase (AST)	Below 40 IU/L	Increased	13,14,15,16
Total bilirubin	Below 2 mg/dl	Increased	13,14,15
Creatinine	Below 1.5 mg/dl	Increased	13,14,15
Cardiac troponin (Troponin T)	0-14 ng/ml	Increased	13,14,15
Ferritin	30-400 ng/ml	Increased	13,14
CK-MB	0-25 IU/L	Increased	16

Hematology/immunohematology tests: The hematology/ immunohematology routine test profile of COVID-19 cases were also summarized. Most papers indicated that COVID-19 positive cases had leukocytosis with an increased number of neutrophils and decreased lymphocyte count. In addition, prothrombin time (PT) values were increased with decreased platelet count results. Besides, inflammatory markers, including CRP and ESR values were increased in most observations. Among the routine immunohematology tests, both CD4 and CD8 T-cell counts were decreased. A summary of hematology/immunohematology profiles is shown in Table 2.

Table 2: **List of routine hematology/ immunohematology tests with abnormal findings during COVID-19 infection**

Hematology and immuno-hematology test	Normal reference range	Findings compared with the normal reference range	Reference(s)
Total WBC count	4,000-10,000/mm^3	Increased	13,14
		Decreased	16
Lymphocyte count	20-35%	Decreased	13,14,16,17
Neutrophil count	40-75%	Increased	13,14
Platelet count	150,000-400,000/mm^3	Decreased	13,14,16
Prothrombin time (PT)	10-12 seconds	Increased	13,14
High sensitive C-reactive protein (hsCRP)	Up to 1.5 mg/L	Increased	13,14,16
Erythrocyte sedimentation rate (ESR)	Below 20 mm/hr	Increased	14
CD4	500–1,200 cells/mm3	Decreased	17
CD8	200-800cells/mm^3	Decreased	17

Thus, this disturbance of the hematology and immunohematology profiles in COVID-19 cases may result in hyper-inflammatory condition, as indicated by the neutrophil-to-lymphocyte (10^9/L) ratio (NLR) and lymphocyte (number/μL)/-to-C-reactive protein (mg/dL) ratio (LCR). Accordingly, in COVID-19 disease progression, there will be increased NLR levels and low LCR levels, which indicate an enhanced inflammatory process (18).

Discussion

The present systematic study assesses the profiles of supportive laboratory tests of COVID-19 RT-PCR-confirmed cases using routine clinical chemistry and hematology/immunohematology test parameters. The study findings indicate that for COVID-19-positive cases, from routine clinical chemistry tests, such as liver function tests, aminotransferase and lactate dehydrogenase enzymes increased; while albumin decreased; in renal function tests, creatinine increased; and among cardiac markers, CK-MB, troponin and ferritin markedly increased.

A study conducted by Petrosillo *et al.*, which compares the clinical chemistry aminotransferase enzymes of different coronaviruses, indicates an average increment value up to 31.5% in COVID-19 cases, whereas these enzyme values decreased in cases of SARS and MERS, to 23% and 25.5%, respectively (19). On the other hand, hypoalbuminemia results shown during COVID-19 infections were similar in cases of SARS infection (20). The increment of aminotransferase enzymes may be associated either with cardiac problems associated with COVID-19, where AST together with CK, LDH and troponin could be high; or in the case of SARS-CoV-2, virus migration in the intestines and blood may infect the liver and damage hepatocytes, which could increase ALT, AST and bilirubin values (21). These abnormal liver function test results may be seen in up to half of patients with COVID-19 infection. Studies also indicates that those with pre-existing liver disease, and older patients, are at risk of severe liver injury (22). Similarly, in COVID-19 positive patients, the presence of previous chronic cardiac and renal diseases, as well being the patients aged, will contribute more for abnormal cardiac and renal function tests results.

Thus, the mild to severe increase in aminotransferase values and decreased albumin values (23), as well as increased routine renal and cardiac function test results, might be considered as suggestive of suspected cases of COVID-19 infection.

On the other hand, from hematology and immunohematology tests, the present analysis indicates that the WBC count increased, with decreased lymphocytes and increased neutrophil count. In contrast, in the case of MERS, and H1N1 infections the WBC count decreased up to 14% and 65%, respectively (19, 24). However, similar to COVID-19 cases, very low lymphocyte counts observed in SARS and MERS cases (19). In the case of COVID-19, occurrences of leukocytosis with neutrophilia and lymphopenia may be associated with bacterial infection (11).

The present study also indicates that during COVID-19 infection, platelet count decreased with an increase in PT time. Other similar studies also indicate that

thrombocytopenia is seen up to 12% in COVID-19 cases (18) and is relatively high in MERS patients too (25). On the other hand, other studies report decreased platelet counts in the case of SARS and MERS, up to 44.8% and 36%, respectively (18,19). Low platelet count and high PT time, in the case of COVID-19 infections, may indicate the severity of infection (26,27).

In terms of inflammatory markers, this paper indicates that CRP and ESR values increased, with decreased CD4 and CD8 counts. The presence of high neutrophil count and high CRP values with low lymphocyte numbers in COVID-19 positive individuals will create increased NLR and decrease LCR values (18). In our study, monocyte values did not differ from normal values in the case of COVID-19, whereas marked monocytosis is seen in the case of MERS (28).

On the other hand, the increased number of neutrophils in the case of COVID-19, as seen in this study, might be associated with the formation of the neutrophil extracellular traps (NETs), as is the case in viral influenza virus infection, where the formed NETs lodge in and damage the areas of alveoli in the lungs (29).

Conclusions

In conclusion, individuals with signs and symptoms of COVID-19 mostly show abnormal results in routine hematology and immunohematology tests, such as high WBC count, high NLR and low LCR. In addition, individuals infected with COVID-19 show abnormalities in clinical chemistry tests, summarized as mild increases in aminotransferase and creatinine values, and increased CK, troponin and ferritin levels.

These routine laboratory clinical chemistry and hematology/immunohematology abnormal test results might be considered as "supportive and/or suggestive test for COVID-19 infection", and may assist in the screening of patients to refer for RT-PCR laboratories for confirmation tests and better management of cases.

These "supportive and suggestive routine laboratory tests during COVID-19 infections", in the absence of RT-PCR laboratories, might consider as suggestive of suspected cases of COVID-19 infection. To strengthen this systematic review, additional large-scale studies are needed in line with new episodes of the disease.

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List of abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CDC	Centers for Disease Control and Prevention
CK	Creatine kinase
CK-MB	Creatine kinase muscle brain isoenzymes
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
HCoV	Human coronavirus
LCR ratio	Lymphocyte-to-C-reactive protein
LDH	Lactate dehydrogenase
NET	Neutrophil extracellular trap
NLR	Neutrophil-to-lymphocyte ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PT	Prothrombin time
RT-PCR	Real-time polymerase chain reaction
SARS-CoV	Severe acute respiratory syndrome coronavirus
WBC	White blood cell
WHO	World Health Organization

References

1. World Health Organization. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases. Interim guidance. 2 March 2020. https://apps.who.int/iris/bitstream/handle/10665/331329/WHO-COVID-19-laboratory-2020.4-eng.pdf?sequence=1&isAllowed=y
2. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: Are they closely related? Clinical Microbiology and Infection. 2020;26(6):729-34.
3. 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(18):1708-20.
4. Guo YR, Cao QD, Hong ZH, Tan YY, Chen SD, Jin HJ, *et al.* The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Mil Med Res. 2020;7(1):11.
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
6. World Health Organization. Coronavirus Disease (COVID-19) Dashboard. Data last updated: 2020/6/1, 1:55pm CEST. Accessed July 15, 2020. https://covid19.who.int/?gclid=EAIaIQobChMIrLTZi6zP6gIVD-vtCh2xdQVWEAAYASAAEgImWvD_BwE
7. World Health Organization. First case of COVID-19 confirmed in Ethiopia. WHO Regional Office for Africa. www.afro.who.int/news/first-case-covid-19-confirmed-ethiopia. Accessed May 26, 2020.
8. Ethiopia COVID-19 Monitoring platform. https://www.covid19.et/covid-19/ Accessed July 15, 2020.
9. Lippi G, Plebani M. The novel coronavirus (2019-nCoV) outbreak: Think the unthinkable

and be prepared to face the challenge. Diagnosis (Berl). 2020;7(2):79-81.
10. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Frontiers of Medicine. 2020;14:185-92.
11. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med. 2020;58(7):1063-9.
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Loannidis JPA, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. BMJ. 2009; 339.
13. International Federation of Clinical Chemistry and Laboratory Medicine. IFCC information guide on COVID-19. March 26, 2020. https://www.ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19/
14. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020;58(7):1131-4.
15. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, *et al.* Covid-19 in critically ill patients in the Seattle region — Case series. N Engl J Med. 2020;382(21):2012-22.
16. Su L, Ma X, Yu H, Zhang Z, Bian P, Ha Y, *et al.* The different clinical characteristics of coronavirus disease cases between children and their families in China – the character of children with COVID-19. Emerg Microbes Infect. 2020;9(1):707-13.
17. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol. 2020. https://doi.org/10.1002/jmv.25819
18. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, *et al.* Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. Journal of Infectious Diseases. 2020; 221(11).
19. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: Are they closely related? Clinical Microbiology and Infection. 2020. https://doi.org/10.1016/j.cmi.2020.03.026
20. Su YJ, Lai YC. Comparison of clinical characteristics of coronavirus disease (COVID-19) and severe acute respiratory syndrome (SARS) as experienced in Taiwan. Travel Medicine and Infectious Diseases. 2020. https://doi.org/10.1016/j.tmaid.2020.101625
21. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: Little cause for concern. Gastroenterology and Hepatology. 2020;5(6):529-30.
22. Alqahtani SA, Schattenberg JM. Liver injury in COVID-19: The current evidence. Review article. United European Gastroenterology Journal (URG). 2020;8(5):509-19.
23. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: Management and challenges. Gastroenterology and Hepatology. 2020;5(5):428-30.
24. Tang X, Du R, Wang R, Cao T, Guan L, Yang C, *et al.* Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1. CHEST. 2020;158(1):195-205.
25. 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(9):752-61.
26. Perlman S. Another decade, another coronavirus. N Engl J Med. 2019;382(8):760-2.
27. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta. 2020;506:145-8.
28. Park GE, Kang CI, Ko JH, Cho SY, Ha YE, Kim YJ, *et al.* Differential cell count and CRP level in blood as predictors for Middle East respiratory syndrome coronavirus infection in acute febrile patients during nosocomial outbreak. J Korean Med Sci. 2017;32(1):151-4.
29. Narasaraju T, Yang E, Samy RP, Ng HH, Poh WP, Liew AA, *et al.* Excessive neutrophils and neutrophil extracellular traps contribute to acute lung injury of influenza pneumonitis. Am J Pathol. 2011:17(1):199-21.