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COVID-19. Perspective from the clinical laboratory

COVID-19. Perspectiva desde el laboratorio clínico

Asociación Española de Biopatología Médica – Medicina de Laboratorio (AEBM-ML)

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AEBM-ML Information Guide
Asociación Española de Biopatología Médica – Medicina de Laboratorio
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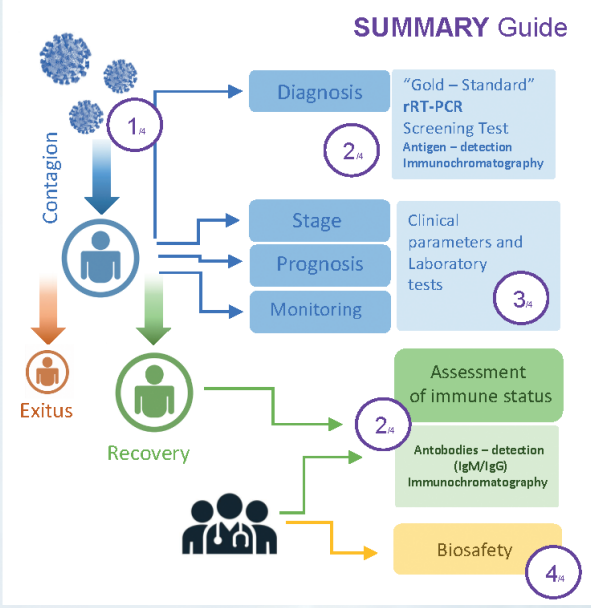
INTRODUCTION

The new coronavirus SARS-CoV-2 (2019-NcoV) belongs to a family of virus that cause infections in human and animals, including mammals and birds. It is believed to have zoonotic origins, suggesting it emerged from a bat-borne virus. Coronavirus virions are spheres approximately 100–160 nanometres in diameter, with viral envelope. They are positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment of approximately 26 – 32 kilobases in length. The infectious disease caused by this virus is called COVID-19 and its common symptoms include fever, cough, and shortness of breath that may progress to viral pneumonia. The time from exposure to onset of symptoms is typically around 5 or 6 days but may range from 1 to 14 days. The time from onset of symptoms to full recovery is around 2 weeks in the case of mild infections and may reach 4-6 weeks in more severe cases. It is primarily spread during close contact with infected patients and their secretions, by contaminated surfaces and by small droplets (with a diameter greater than 5 µm) produced when people cough, sneeze or talk. There is no evidence about vertical transmission, although current data suggest virus absence in amniotic fluid, umbilical cord and breast milk. This document provides a summary of the key aspects to be considered by the clinical laboratory such as diagnosis, main alterations in laboratory tests, most representative mortality predictors, transportation of biological samples and safety procedures recommended in the laboratory.

SUMMARY Guide



INFECTION SUSPECTED

Clinical picture compatible with **Acute Respiratory Failure**

Clinical picture of Acute Respiratory Failure in an inpatient or a patient with hospital admission criteria

A

B

Clinical picture of Acute Respiratory Failure of any degree of severity that belongs to one of the following groups:

- Health or social – health staff
- Other essential services

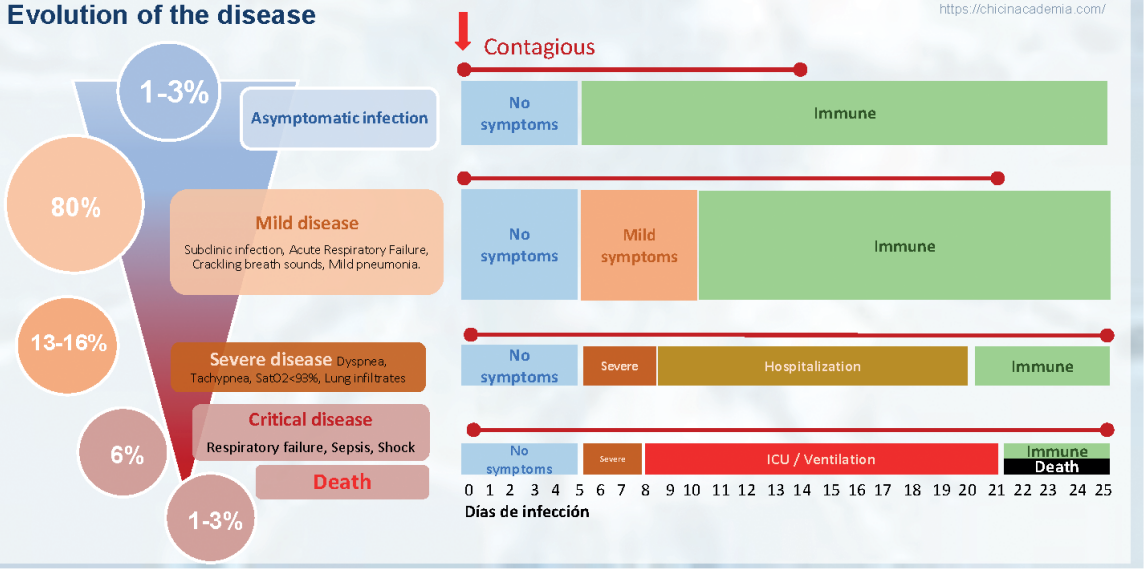
Ministerio de Sanidad, Consumo y Bienestar Social. Documentos técnicos para profesionales. Coronavirus / Zhou et al. Lancet 2020 Mar 11 28;395(10229):1054-1062/ Huang et al. Lancet. 2020 Feb 15;395(10223):497–506 / Guan et al. N Engl J Med. 2020 Feb 28

Related symptoms

Fever: 77-98%
Dry cough: 46-82%
Dyspnea: 3-31%
Fatigue: 11-52%
Expectoration: 27-34%
Myalgia: 11-44%
Headache: 7-14%
Diarrhea: 2 -10%
Anosmia / dysgeusia: described

Evolution of the disease

References: WHO. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) 2020 https://chicinacademia.com/



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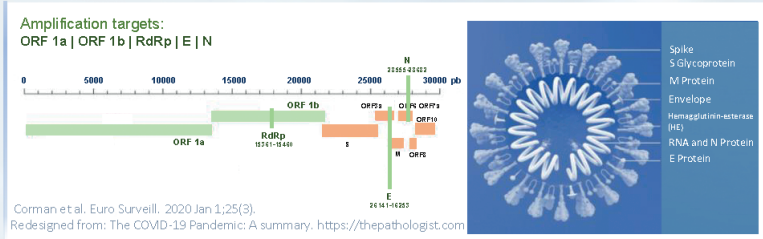
DIAGNOSIS

rRT-PCR

The standard method of testing COVID-19 is based on detection of unique RNA viral sequences through amplification of genetic material by rRT-PCR (real time reverse-transcription polymerase chain reaction). In order to achieve a complete diagnosis, two PCR reactions must be performed (screening and confirmation in an alternative gene).



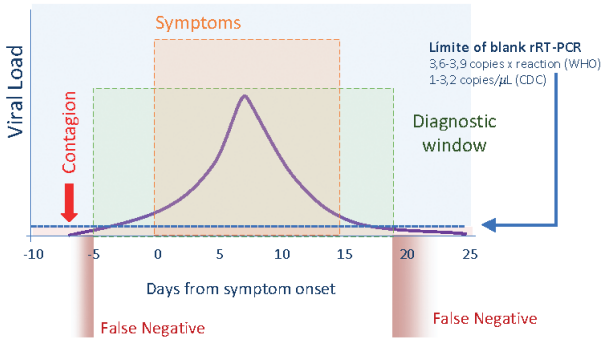
Corman et al. Euro Surveill. 2020 Jan 1;25(3).
Redesigned from: The COVID-19 Pandemic: A summary. https://thepathologist.com

Ministerio de Sanidad, Consumo y Bienestar Social. Documentos técnicos para profesionales. Coronavirus

Diagnostic Performance

Bronchoalveolar lavage fluid **93%**
Sputum **72%**
Nasal swabs **63%**
Fibrobronchoscope brush biopsy **46%**
Pharyngeal swabs **32%**
Feces: **29%**
Blood: **1%**
Urine: **0%**

Wang et al. JAMA. 2020 Mar 11



Reference: Lippi et al. Clin Chem Lab Med. 2020 Mar 15;0(0)

Reference specimens

1. **Upper tract**
Nasopharyngeal and oropharyngeal swabs in ambulatory patients.

2. **Lower tract**
Lower respiratory specimens (sputum and/or endotracheal aspirate or bronchoalveolar lavage) in patients with severe respiratory disease

A sensitivity and specificity greater than 70% is highly recommended for rapid tests.

Rapid Test: Viral Antigens

Reference specimen
Nasopharyngeal swabs or Deep sputum

Viral protein antigen detection.
Useful for initial screening

Lower diagnostic performance than rRT-PCR

Immunochromatography

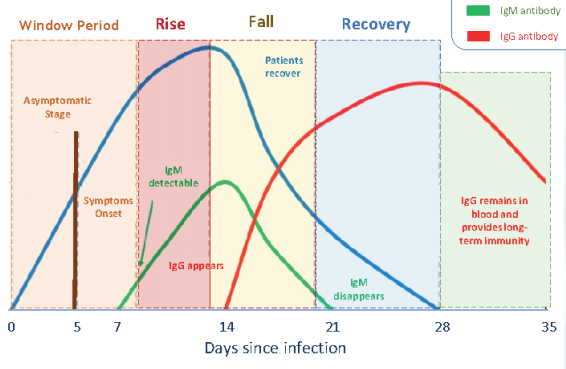
Rapid Test: IgM/IgG Antibodies

Reference specimen: Serum, Plasma or Blood

IgM (5-7 days from symptom onset) and IgG (14 days from symptom onset) detection
Useful for Assessment of immune status

Not recommended for initial screening due to the window period (time from infection to antibodies onset)

Reference: COVID-19 IgM/IgG Rapid diagnostic test. Biopanda Reagent



Test Results			Probable Clinical Significance
PCR	IgM	IgG	
-	-	-	Negative
+	-	-	Window Period
+	+	-	Early stage of infection
+	+	+	Active phase of infection
+	-	+	Late or recurrent stage of infection
-	+	-	Early stage of infection. PCR result may be a false-negative.
-	-	+	Past infection
-	+	+	Recovery stage of infection

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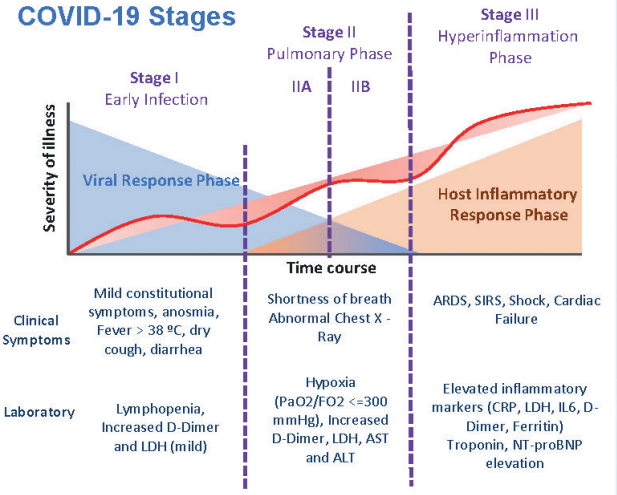
LABORATORY REPORT

Frequent altered tests

Tests	Clinical Significance
Leucocytes	(Additional) bacterial infection
Neutrophiles	
Lymphocytes	Decreased immunological response
Hemoglobin	Anemia
Platelets	Consumption by disseminated coagulation
Prothrombin time	Coagulation activation and/or disseminated coagulopathy
D – Dimer	
Albumin	Liver failure
Aspartate aminotransferase	
Alanine aminotransferase	
Total Bilirubin	
Creatinine	Kidney damage
Lactate dehydrogenase	Lung damage/ multiorganic damage
Erythrocyte sedimentation rate	Inflammation
Troponin	Heart damage
C – Reactive Protein	Viral infection / Viral sepsis
Procalcitonin	(Additional) bacterial infection
Ferritin	Severe inflammation
Cytokines (Interleukin 6)	Cytokine Storm Syndrome (CSS)

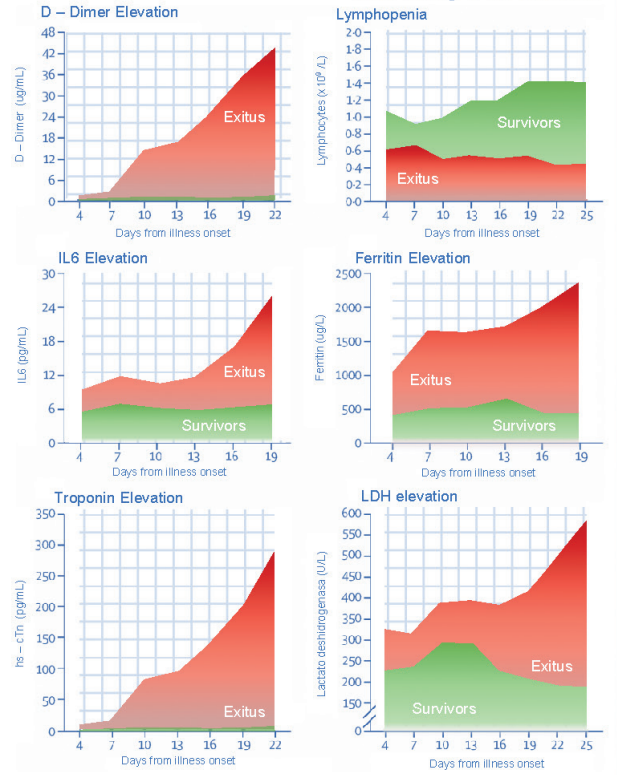
It is recommended starting treatment with Tocilizumab if IL-6 values are higher than 40 pg/mL

COVID-19 Stages



Reference: Siddiqi et al Jhealun 2020 Mar 12

Mortality Predictors



Reference: Zhou et al. Lancet 2020; 395: 1054–62

ARDS Evaluation

(acute respiratory distress syndrome)

PaO_2 / FiO_2 <= 300

$SatO_2 / FiO_2$ <= 315

Pneumonia Evaluation

Mild: $SatO_2$ > 90%

Severe: $SatO_2$ < 90%

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BIOSAFETY

Ministerio de Sanidad, Consumo y Bienestar Social. Documentos técnicos para profesionales. Coronavirus / Manual de bioseguridad en el laboratorio. OMS

Clinical Laboratory: Routine Samples

Biochemistry, Hematology, Immunology, Microbiology and Anatomical Pathology

Personnel handling routine clinical samples (biochemistry, hematology, urine, serology) of diagnosed patients or under suspicion of SARS-CoV-2 infection, must follow biosafety standard guidelines and general recommendations established for Biosafety Level 2 (BSL-2) laboratories. All the details concerning these guidelines can be consulted online in World Health Organization (WHO) Laboratory Biosafety Manual.
https://www.who.int/csr/resources/publications/biosafety/Biosafety7.pdf

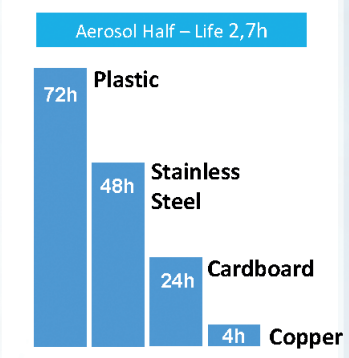
Following sample processing, all work surfaces and equipment will be decontaminated using the usual disinfectants

Standard Individual Protection Equipment (IPE)

- Disposable gloves
- Protection gown
- Safety splash googles (if there is a risk of splashing)
- Mask (if there is a risk of aerosols or direct contact with patients/people)

Biological Safety Cabinet (BSC) Class II

- Any sample likely to produce aerosols containing small droplets (vortex, sample sonication in a open tube). Appropriate sealable centrifuge rotors and sealable buckets must be employed. Rotors will be loaded and unloaded inside the biological safety cabinet.
- Samples dilution and aliquoting
- Inactivation of samples
- Inoculation of bacterian or mycological culture media
- Preparation and chemical or thermal fixation of smear tests



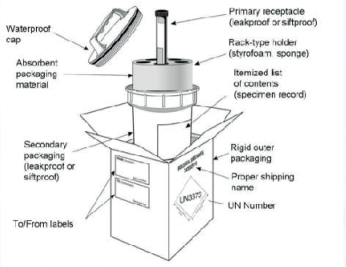
Viability and infectivity on various surfaces (hours)

Doralemen et al. N Engl J Med. 2020 Mar 17

TRANSPORTATION OF BIOLOGICAL SPECIMENS

Categorization

Biological specimens from infected patients or under suspicion of infection by SARS-CoV-2 will be classified as **infectious substances category B**



Specimen Packing

Infectious substances subclassified as Category B (UN 3373) and packaged in accordance with **Packing Instruction P650** may be considered safe and compliant for all modes of transportation:
Robust and leak proof **Basic triple packaging.** The primary receptacle capacity won´t be more than 1 liter. Total packaging won´t exceed 4 liters or kilos. Dry ice won´t be considered in the total weight.

The triple packaging system must comprise three layers:

1. **Impermeable primary receptacle**
2. **Impermeable second layer**
3. **Rigid third layer**

Dry ice or ice must be contained only on the primary receptacle.

All the simple related information must be placed between the second and the third layer.

Specimens	Virus Transport Medium	Transport conditions: Biological specimen Category B
Respiratory specimens		
Nasopharyngeal and oropharyngeal swabs	Yes	Refrigerated (4 ºC) in 24 – 48 hours
Nasopharyngeal lavage/aspirate	No	Refrigerated (4 ºC) in 24 hours
Bronchoalveolar lavage	No	Refrigerated (4º C) in 24 hours
Endotracheal aspirate	No	Refrigerated (4 ºC) in 24 hours
Sputum	No	Refrigerated (4 ºC) in 24 hours
Other samples		
Serum (2 samples in acute phase and convalescence, 14-30 days respectively)	No	Refrigerated (4 ºC)
Lung biopsy/necropsy	No	Refrigerated (4 ºC) in 24 hours
Total blood	No	Refrigerated (4 ºC)
Urine	No	Refrigerated (4 ºC)
Feces	No	Refrigerated (4 ºC)

Reference: Ministerio de Sanidad, Consumo y Bienestar Social. Documentos técnicos para profesionales. Coronavirus

RECOMMENDED REFERENCES

1. Ministerio de Sanidad, Consumo y Bienestar Social - Profesionales - Documentos técnicos para profesionales - Coronavirus [Internet]. [cited 2020 Mar 20]. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos.htm
2. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 2020. DOI: 10.1515/cclm-2020-0198. [Epub ahead of print]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32119647
3. 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. DOI: 10.1515/cclm-2020-0240. [Epub ahead of print]. Available from: https://doi.org/10.1515/cclm-2020-0240
4. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020;25(3).
5. The COVID-19 Pandemic: A Summary. (n.d.). Retrieved March 30, 2020. Available from: https://thepathologist.com/subspecialties/the-covid-19-pandemic-a-summary
6. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020. DOI: 10.1056/NEJMoa2002032. [Epub ahead of print]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32109013
7. 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.
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England) [Internet] 2020;6736(20):1-9.
9. Van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med 2020. DOI: 10.1056/NEJMc2004973. [Epub ahead of print]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32182409
10. Lippi G, Simundic A-M, Plebani M. Potential preanalytical and analytical vulnerabilities in the laboratory diagnosis of coronavirus disease 2019 (COVID-19). Clin Chem Lab Med 2020. DOI: 10.1515/cclm-2020-0285. [Epub ahead of print]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Potential+preanalytical+and+analytical+vulnerabilities+in+the+laboratory+diagnosis+of+coronavirus+disease+2019+(COVID-19).
11. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis 2020. DOI: 10.1093/cid/ciaa344. [Epub ahead of print]. Available from: https://doi.org/10.1101/2020.03.02.20030189
12. Coronavirus - semFYC. (n.d.). Retrieved March 30, 2020. Available from: https://www.semfyc.es/coronavirus/
13. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA 2020. DOI: 10.1001/jama.2020.3786 [Epub ahead of print]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32159775
14. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020. DOI: 10.1001/jamainternmed.2020.0994. [Epub ahead of print]. Available from: https://doi.org/10.1001/jamainternmed.2020.0994
15. Siddiqi HK, Mehra MR. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal - The Journal of Heart and Lung Transplantation. J Heart Lung Transplant 2020. DOI: 10.1016/j.healun.2020.03.012. [Epub ahead of print]. Available from: https://www.jhltonline.org/article/S1053-2498(20)31473-X/abstract
16. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al. Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. J Med Virol 2020. DOI: 10.1002/jmv.25727. [Epub ahead of print]. Available from: https://doi.org/10.1002/jmv.25727
17. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020. DOI: 10.1016/j.tmaid.2020.101623. [Epub ahead of print]. Available from: https://doi.org/10.1016/j.tmaid.2020.101623
18. Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic Utility of Clinical Laboratory Data Determinations for Patients with the Severe COVID-19. J Med Virol 2020. DOI: 10.1002/jmv.25770. [Epub ahead of print]. Available from: https://doi.org/10.1002/jmv.25770
19. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta 2020;505:190-1. DOI: 10.1016/j.cca.2020.03.004. Available from: https://doi.org/10.1016/j.cca.2020.03.004
20. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol 2020. DOI: 10.1002/ajh.25774. [Epub ahead of print]. Available from: https://doi.org/10.1002/ajh.25774
21. Meyer B, Drosten C, Müller MA. Serological assays for emerging coronaviruses: challenges and pitfalls. Virus Research 2014;194:175-83. Available from: https://doi.org/10.1016/j.virusres.2014.03.018
22. Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. Clin Chem Lab Med 2020. DOI: 10.1515/cclm-2020-0272. [Epub ahead of print]. Available from: https://doi.org/10.1515/cclm-2020-0272
23. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England) 2020;395(10229):1033-4. DOI: 10.1016/S0140-6736(20)30628-0. Available from: https://doi.org/10.1016/S0140-6736(20)30628-0
24. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. Prog Cardiovasc Dis 2020. DOI: 10.1016/j.pcad.2020.03.001. [Epub ahead of print]. Available from: https://doi.org/10.1016/j.pcad.2020.03.001
25. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020. DOI: 10.1007/s00134-020-06028-z. [Epub ahead of print]. Available from: https://doi.org/10.1007/s00134-020-05991-x
26. 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. DOI: 10.1016/j.cca.2020.03.022. Available from: https://doi.org/10.1016/j.cca.2020.03.022
27. IFCC Information Guide on COVID-19 - IFCC. (n.d.). Retrieved April 3, 2020. Available from: https://www.ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19/
28. Pineda D, Prieto S. Interpretación de la Gasometría en el laboratorio clínico. 2ª ed. AEBM-ML. Disponible en: https://www.aebm.org/images/activos/publicaciones/Manual-Gasometria-AEBM-ML-2ed-2017.compressed.pdf
29. Organización Mundial de la Salud. Manual de Bioseguridad en el Laboratorio. 3ª ed. Disponible en: https://www.who.int/topics/medical_waste/manual_bioseguridad_laboratorio.pdf
30. Recomendaciones de la SANAC para los laboratorios de análisis clínicos/bioquímica clínica relativas al manejo de muestras de pacientes con sospecha de infección por coronavirus 2019-ncov. Disponible en: https://sanac.org/images/site/RECOMENDACIONES_SANAC_MANEJO_MUESTRAS_COVID-19.pdf