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Severe Acute Respiratory Syndrome -Possible Sources of Error in Diagnosis and their Validity in the Coronavirus Disease Series

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Abstract

Viral diseases (recently monkeypox viral disease) are very common in our era and some viruses such as SARS-CoV-2 threaten humanity by causing a severe acute respiratory syndrome. This disease has been linked to haematological dysfunctions. Spike (S) and Nucleoprotein (N) proteins have been putatively associated with these dysfunctions. There is no currently fully effective detection method and treatment. Therefore, this study highlighted coronavirus disease's diagnosis and prevention methods (COVID-19), an infectious disease caused by a severe acute respiratory syndrome virus. Because the coronavirus strain of severe acute respiratory syndrome has been threatening humans since 2003 and reappeared in 2019 at the end of 2019, causing many deaths by 2022 under the name coronavirus disease. Because the coronavirus disease rapidly spread across the world due to its high transmissibility and prolonged incubation. Therefore, it seems that SARS coronaviruses in the form of SARS-CoV-3, SARS-CoV-4, etc., will not disappear from our world in the future. Thus, in this study, possible sources of error in diagnosis and their validity that can be used today and in the future in the SARS coronavirus disease series are presented in the light of current information.

Keywords: Analytical Error; COVID-19 Disease; RT -PCR; SARS Coronavirus Disease

Abbreviations: S: Spike; N: Nucleoprotein; RT-PCR: Real-Time Reverse Transcription-Polymerase Chain Reaction; BAL: Bronchoalveolar Lavage Specimen; FB: Flexible Bronchoscopy.

Introduction

Potential Sources of Error in the Diagnosis of the SARS Coronavirus Disease Series and Validity of the Methods

The SARS coronavirus disease series (including the disease COVID-19) is continuously threatening humanity [1].

In order to get rid of the SARS coronavirus disease series, the correct diagnosis must first be made. However, previous studies have shown that the reliability and validity for such diseases are extremely low, except for real-time reverse transcription-polymerase chain reaction (RT-PCR) [2,3]. In this study, we aim to explore in detail the reasons that affect the validity and reliability of the assays. There are three sources of error in analytical laboratories: preanalytical, analytical, and post-analytical. For a test to be accurate and reliable, all three sources of error must be eliminated. Possible sources of error were given below one by one.

Preanalytical Sources Of Error

In laboratory results, most errors are made at this stage. The most important of these errors are: insufficient knowledge and experience of the personnel, improper preparation of the patient, wrong barcode, missing sample, wrong sample, inappropriate tube, clotted sample, hemolyzed or lipemic sample, contamination, samples are not delivered to the laboratory under appropriate conditions and in the appropriate time frame [4]. In the diagnosis of SARS coronavirus disease series (including COVID-19), the most likely preanalytical errors are errors in collecting nasopharyngeal swabs, throat swabs, and, in later stages of the disease, bronchoalveolar lavage specimens from the field. Because blood specimens are collected and analyzed continuously in all laboratories, no unusual errors are expected in collecting and analyzing these specimens, except for staff inexperience and carelessness [5-9].

However, because errors are more likely to occur in the collection of nasopharyngeal swabs and throat swabs for diagnosis of the SARS coronavirus disease series (including COVID-19), and bronchoalveolar lavage specimens in the later stages of the disease, these biological specimens should be used to collect biological specimens in this part of the study correctly [9-11].

Collection of a Nasopharyngeal Swab

To collect a nasopharyngeal swab, first cover the patient's mouth with a mask, leaving the nose open. The patient should then be asked which nostril they are breathing through. If your patient breathes through both nostrils, you can collect the specimen by choosing one of the two nostrils. The head should be extended when collecting the sample, and the sample stick advanced to the nasopharynx. When the sample stick touches the nasopharynx, the sample should be collected by slowly rotating the sample stick around itself after waiting for a few seconds to sufficiently absorb the secretion. After collecting the specimen, the portion containing the nasopharyngeal swab should be broken and placed in a sterile test tube. Personnel carrying the specimen should be sent to the laboratory immediately, providing information about the nature of the specimen and warning of contamination [12].

Collection of a Throat Swab

To collect a throat swab, the patient's mouth must first be covered with a mask to keep it open. The head is then stuck out, and after the head is stuck out, gentle pressure is applied to the tongue with a tongue depressor under an adequate light source. A sterile swab is then taken by moving the swab back and forth between the two tonsils behind the uvula without touching the lips, buccal mucosa, uvula, and tongue by moving the swab back and forth in the posterior pharynx and tonsil area for 5 seconds and should be sent to the laboratory [13-16].

Collection of Bronchoalveolar Lavage Specimen (BAL)

This biological sample should be collected by an experienced physician using a bronchoscope. The patient whose collected bronchoalveolar lavage sample should not eat for at least 6 hours. Before taking the sample, a local anesthetic (prilocaine hydrochloride 2%; 5-10 mL) should be applied with the help of a nebulizer, and then a local anesthetic (lidocaine 2% spray) should be administered in the form of an oropharyngeal and oropharyngeal spray (to avoid the side effects of local anesthetics), the dose should not exceed 4 mg/kg. In some cases, mild sedation with benzodiazepines or with the aid of a morphine analog may be required. This is at the discretion of the physician. However, many clinicians recommend sedation before the procedure as it improves airway assessment and returns to BAL. Flexible bronchoscopy (FB) is initially inserted transnasally or transorally for this procedure. If there is involvement, BAL should be applied to the right middle lobe segment, partial segments, or the left upper lobe lingual segments. To the involved segment, FB mouthpiece (wedge position), 100-300 ml of 0.85% NaCl (saline) should be injected bronchoscopically into the canal in 50-ml portions and taken by hand via the injector. Care should be taken to ensure that the physiologic serum used for lavage is at body or room temperature. In addition, at least 70% of the administered fluid should be returned. To increase the return flow, too high pressure should not be applied. This is because high pressure leads to deterioration of the contents of the bronchoalveolar lavage material. The sample collected in this way reflects approximately one million alveoli. Because the agent of the SARS coronavirus disease series (including COVID-19) is sought in this biological material, it should not be filtered (in other cases where cellular contents are to be examined, it should be filtered through several layers of gauze to clear it of mucus and transferred to containers of

ice to preserve cell viability). Samples from different alveoli and distal bronchioles can be collected in the same container. Samples should be collected at the time when the virus can be detected. Nasopharyngeal and pharyngeal swabs, saliva, and blood should be the first choice biological specimens for screening for this virus. BAL is a semi-invasive diagnostic method used to diagnose infectious and non-infectious diseases. The most important thing is to completely disinfect the bronchoscope and perform all procedures under proper safety standards when collecting BAL. 2-3 ml of the tracheal aspirate, bronchoscopic specimens thus obtained should be immediately stored in a sterile tube with a screw cap or an injector sealed with a Luer cap in the refrigerator (between 2-8 0 C) and sent to the laboratory as soon as possible, and should be searched for the cause of the SARS coronavirus disease series (including COVID-19). If desired, specimens may be stored at -20^{0}C or -70^{0}C if feasible. Samples stored at -20^{0}C can remain intact with cell contents for two months. At -70^{0}C, on the other hand, samples can be stored longer.

In addition to the biological samples mentioned above, the blood sample is an important fluid in diagnosing the SARS coronavirus disease series (including COVID-19). However, because this biological fluid is used worldwide, the margin of error is low. Therefore, no information has been provided on how to collect blood samples. If you have any doubts, also ask the laboratory personnel. When collecting these biological fluids that we use for diagnosis, there are always analytical errors in laboratories [10,17].

Possible Analytical Errors

The main possible causes of analytical errors are

- Uncalibrated equipment
- Bubbles or particles in the samples that are out of range
- Rrroneous deviations
- The presence of undefined molecules interferes with the method used or insufficient sensitivity of the kits used to measure specificity and sensitivity.

Elimination of these analytical errors will allow accurate results.

Potential Post-Analytical Errors

Reporting delays include forwarding results to another site or reporting results incorrectly.
Methods Currently Used for Diagnosis

Biochemical Parameters

Currently, no biochemical parameters can be measured with fully sensitive auto analyzers. However, serum, urea, keratin, cystatin C, cholinesterase, direct bilirubin, lactate dehydrogenase, interleukin-6, serum ferritin, D-dimer, and coagulation cascade parameters appear to be among the biochemical parameters of the SARS coronavirus disease series (including COVID-19) [18-24].

Chest CT Scan and Radiography

Since SARS-CoV-2 causes fibrosis in the lungs of the SARS coronavirus disease series (including COVID-19), lung radiographs provide information about the status of the disease. It has been reported that these lung films, in conjunction with artificial intelligence programs, help diagnose COVID-19 with 60-70% accuracy [25,26].

Diagnosis by Antibody Measurement

Many different companies have produced very different kits for antibody measurement. However, no kit has been produced to date that definitively supports the diagnosis. The sensitivity of some kits is so low as to be almost negligible. This is probably due to the constant mutation of the SARS coronavirus series (including COVID-19), which leads to measurement uncertainties [27]. Currently, three different SARS-CoV-2, A, B, and C forms cause infections in different countries. Therefore, it seems almost impossible to measure a constantly mutating virus using the antigen-antibody principle-based method, and it can only partially inform physicians [28]. The principles of this method and how it works are explained in a previous study [4].

Diagnosis by Measurement Using RT -PCR

The causative agent of the SARS coronavirus series (including COVID-19) is currently definitively identified by viral RNA detection using RT-PCR. However, it is important to remember that false-negative results are possible when biological samples are collected before the disease's incubation period. This method is sensitive enough to detect viral RNA in asymptomatic cases. Until viral PCR testing is confirmed, laboratories need to provide detection by pan-coronavirus testing followed by sequence analysis. It is important to exclude other coronaviruses that may prove positive upon confirmation, especially pan-coronavirus tests (HCoV-229E, HCoV-NL63). This is because beta-coronaviruses, SARS, and MERS-CoV viruses cause zoonotic infections in humans [29,30]. The above methods are currently being used to diagnose COVID-19 disease. However, let us take a look at the scientific knowledge of our world so far. Other biochemical parameters may play a role in the possible diagnosis of the disease in the SARS coronavirus disease series (including COVID-19). Therefore, in this part of the study, we will look at the method and some biochemical parameters that can give us an idea of the SARS coronavirus disease series (including COVID-19) and could be applied in laboratories' future.

Other Possible Methods and Parameters that Could Aid in Diagnosis Include the Following

Hemagglutination Inhibition Test: Members of the Corona family of viruses can agglutinate erythrocytes. In a 1979 study of cattle, the presence of coronavirus was determined by the hemagglutination inhibition test. This test is very simple [31]. An alternative test is available in countries that cannot perform the aforementioned advanced tests. This test should be compared to existing sensitive tests for its sensitivity and adapted to human plasma and serum. All detailed information about the test can be found in the Wang, et al. study [32]. In brief, erythrocyte agglutination has been detected in patients who died because of COVID-19. Therefore, checking whether red cells are agglutinated may also help diagnose COVID-19 disease. To prevent erythrocyte agglutination, the administration of anti-erythrocyte agglutinators to these patients is also expected to reduce clot-related deaths by eliminating agglutination. In addition, it is predicted that the administration of low-weight heparin to these patients will also be beneficial [32].

Hemoglobin Electrophoresis Test: Because SARS-CoV-2, one of the SARS coronaviruses, now targets the beta chain of hemoglobin, hemoglobin electrophoresis may also aid in diagnosis [33]. Theoretically, a break in the beta chain shows a different band in hemoglobin electrophoresis [34-36]. However, evaluating hemoglobin electrophoresis and a complete blood count gives a better indication. Since the beta attack of SARS-CoV-2 hemoglobin is valuable information [37], we think it is useful to provide brief information on this topic. SARS-CoV-2 attacks the beta chain of hemoglobin, which is responsible for oxygen transport to tissues and cells by disrupting the structure of porphyrin and inhibiting heme synthesis. It has been reported that patients with deceased COVID-19 have more than twice as much serum ferritin in their circulation [38]. Iron deficiency and excess are pathological conditions. Therefore, iron metabolism must be strictly controlled. In mammals, iron balance is controlled at the level of intestinal absorption. Hepcidin, a peptide hormone, is the major regulator of systemic iron balance. Hepcidin maintains iron balance by coordinating the use and storage of iron and preventing its leakage into plasma. Hepcidin reduces iron absorption from the small intestine. Hepatic hepcidin synthesis decreases with increased erythropoietic activity, hypoxia, and decreased iron storage in the organism. On the other hand, hepcidin synthesis increases in the presence of iron overload or inflammation [39,40].

Other Possible Biochemical Parameters that May Play a Role in the Diagnosis

Hepcidin: Since SARS-CoV-2, one of the SARS coronavirus disease series, increases iron by binding to the beta portion of hemoglobin, the amount of hepcidin will inevitably increase due to free iron [41,42]. When we combine this information, the measurement of hepcidin accumulation represents a new biomarker candidate indicating the presence of COVID-19. In addition, we are not in favor of suppressing the increased iron due to COVID-19, which we mentioned here. This is because the Fenton reaction forms free radicals in large quantities [43]. Although free radicals are harmful to the organism, they also have a benefit due to their bacteriostatic effect [43,44]. The increased iron in COVID-19 associated with the disease may play an important role in killing bacteria via the enzyme myeloperoxidase [45], so we believe suppressing the increased iron in the circulation by COVID-19 is not the right option.

Maresin-1: Maresin 1, this molecule, which is a lipid regulator, also has anti-inflammatory properties. In studies of the SARS coronavirus disease series, inflammation levels have been elevated, especially at COVID-19. Therefore, it is thought that Maresin 1 may be a useful biomarker for diagnosing this disease [46,47].

Relaxin: Since relaxin is a molecule that decreases inflammation [48,49], we think it is useful to measure this molecule in COVID-19 when inflammation is elevated.

Measurement of Surfactants: Patients with COVID-19 experience respiratory failure syndrome. This could be due to a decrease in surfactants in the lungs' alveoli [50]. Therefore, it is predicted that the measurement of surfactants in COVID-19 may aid in diagnosis. In addition, it is predicted that the replacement of surfactant will help keep the alveoli open by decreasing surface tension and may also eliminate respiratory failure syndrome. If the SARS coronavirus disease series occur in the future, measurement of surfactants in these series may also be beneficial.

Conclusion

If the SARS coronavirus disease series continues in the future, in that case, control of the disease will play an important role in the rapid and accurate diagnosis and treatment of this disease, as well as following the recommendations applied by countries and recommended to their citizens. However, as mentioned above, the most important role in controlling the disease depends on the correct diagnosis of the laboratories and the treatment protocols followed by physicians depending on this diagnosis. It is believed that eliminating the potential sources of error identified in this study will help ensure that the diagnosis is made quickly and accurately. This will be a means of quickly bringing the epidemic under control.

References

1. Goldsmith CS, Tatti KM, Ksiazek TG, Rollin PE, Comer JA, et al. (2004) Ultrastructural characterization of SARS

coronavirus. Emerg Infect Dis 10(2): 320-326.

2. Udugama B, Kadhiresan P, Kozlowski HN, Malekjahani A, Osborne M, et al. (2020) Diagnosing COVID-19: The Disease and Tools for Detection. ACS Nano 14(4): 3822-3835.

3. Silva SJRD, Silva CTAD, Guarines KM, Mendes RPG, Pardee K, et al. (2020) Clinical and Laboratory Diagnosis of SARS-CoV-2, the Virus Causing COVID-19. ACS Infect Dis 6(9): 2319-2336.

4. Aydin S (2015) A short history, principles, and types of ELISA, and our laboratory experience with peptide/protein analyses using ELISA. Peptides 72: 4-15.

5. Wikramaratna PS, Paton RS, Ghafari M, Lourenco J (2020) Estimating the false-negative test probability of SARS-CoV-2 by RT-PCR. Euro Surveill 25(50): 2000568.

6. Woloshin S, Patel N, Kesselheim AS (2020) False Negative Tests for SARS-CoV-2 Infection - Challenges and Implications. N Engl J Med 383(6): e38.

7. Maki DG (2021) In suspected COVID-19, RT-PCR with nasal plus throat swabs has 97% sensitivity vs. nasopharyngeal swabs. Ann Intern Med 174(9): JC107.

8. Lai TW, Xiang FF, Zeng JF, Huang YZ, Jia, LP, et al. (2020) Reliability of induced sputum test is greater than that of throat swab test for detecting SARS-CoV-2 in patients with COVID-19: A multi-center cross-sectional study. Virulence 11(1): 1394-1401.

9. Tsang NNY, So HC, Ng KY, Cowling BJ, Leung GM, et al. (2021) Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis. Lancet Infect Dis 21(9): 1233-1245.

10. Davidson KR, Ha DM, Schwarz MI, Chan ED (2020) Bronchoalveolar lavage as a diagnostic procedure: a review of known cellular and molecular findings in various lung diseases. J Thorac Dis 12(9): 4991-5019.

11. Centers for Disease Control and Prevention (CDC) (2021) Interim guidelines for collecting and handling clinical specimens for COVID-19 testing.

12. Marty FM, Chen K, Verrill KA (2020) How to Obtain a Nasopharyngeal Swab Specimen. The New England Journal of Medicine.

13. Centers for Disease Control and Prevention (CDC). (n.d.). Influenza specimen collection.

14. Gomez S, Prieto C, Folgueira L (2016) A prospective study to assess the diagnostic performance of the Sofia® Immunoassay for Influenza and RSV detection. J Clin Virol 77: 1-4.

15. The Joint Commission (2021) National Patient Safety Goals® for the hospital program.

16. Sokolovs D, Tan KW (2017) Ear, nose and throat emergencies. Anaesth. Intensive Care Med 21(4): 200-204.

17. Collins AM, Rylance J, Wootton DG, Wright AD, Wright AK, et al. (2014) Bronchoalveolar lavage (BAL) for research; obtaining adequate sample yield. J Vis Exp 85: 4345.

18. Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, et al. (2020) Longitudinal Association Between Markers of Liver Injury and Mortality in COVID-19 in China. Hepatology 72(2): 389-398.

19. Shanshool MT, Shanshool ET, Al_Ghuraibawi DFF (2021) The Effects of COVID-19 on Some Liver Enzymes Patients at Al Furat General Hospital in Baghdad. Biochem Physiol 10: 1.

20. Allarakia BMA, Gattan H, Ahmadi BMA, Abdeen RH, Bazaid MB, et al. (2020) Laboratory Biomarkers Associated with Severity and Mortality of COVID-19. Clin Lab 68(2).

21. Gupta A, Tamimi AOA, Halwani R, Alsaidi H, Kannan M, et al. (2022) Lipocalin-2, S100A8/A9, and cystatin C: Potential predictive biomarkers of cardiovascular complications in COVID-19. Exp Biol Med (Maywood).

22. Ye Q, Wang H, Xia X, Zhou C, Liu Z, et al. (2020) Safety and efficacy assessment of allogeneic human dental pulp stem cells to treat patients with severe COVID-19: structured summary of a study protocol for a randomized controlled trial (Phase I / II). Trials 21(1): 520.

23. Ahirwar AK, Takhelmayum R, Sakarde A, Rathod BD, Jha PK, et al. (2022) The study of serum hsCRP, ferritin, IL-6 and plasma D-dimer in COVID-19: a retrospective study. Horm Mol Biol Clin Investig.

24. Landau N, Shoenfeld Y, Negru L, Segal G (2021) Exploring the pathways of inflammation and coagulopathy in COVID-19: A narrative tour into a viral rabbit hole. Int Rev Immunol 41(4): 414-422.

25. Elmokadem AH, Bayoumi D, Hedibah SAA, Morsy AE (2021) Diagnostic performance of chest CT in differentiating COVID-19 from other causes of ground-glass opacities. Egypt J Radiol Nucl Med 52: 12.

26. Zhu Z, Xingming Z, Tao G, Dan T, Li J, et al. (2021) Classification of COVID-19 by Compressed Chest CT Image through Deep Learning on a Large Patients Cohort. Interdiscip Sci 13(1): 73-82.

27. Uysal BB, Yavuzer S, Islamoglu MS, Cengiz M (2022) Measurement of antibody levels in patients with COVID-19 over time by immunofluorescence assay: a longitudinal observational study. J Int Med Res 50(1): 3000605211069279.

28. Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomsonet EC, et al. (2021) SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol 19: 409-424.

29. Iglesia JLDI, Villa TF, Rivero A, Carvajal A, Simon EB, et al. (2020) Predictive factors of COVID-19 in patients with negative RT-qPCR. Semergen 1: 6-11.

30. Leung K, Wu JT, Leung GM (2021) Real-time tracking and prediction of COVID-19 infection using digital proxies of population mobility and mixing. Nat Commun 12: 1501.

31. Miller RB, Wilkie BN (1979) The indirect fluorescent antibody technique as a method for detecting antibodies in aborted fetuses. Can J Comp Med 43(3): 255-261.

32. Kruse RL, Huang Y, Smetana H, Gehrie EA, Amukele TK, et al. (2021) A rapid, point-of-care red blood cell agglutination assay detecting antibodies against SARS-CoV-2. Biochem Biophys Res Commun 553: 165-171.

33. W Liu, Li H (2022) COVID-19: Attacks the 1-beta Chain of Hemoglobin to Disrupt Respiratory Function and Escape Immunity. ChemRxiv.

34. Cavezzi A, Troiani E, Corrao S (2020) COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clin Pract 10(2): 1271.

35. Rapozzi V, Juarranz A, Habib A, Ihan A, Strgar R (2021) Is haem the real target of COVID-19? Photodiagnosis Photodyn Ther 35: 102381.

36. Wenzhong L, Li H (2020) COVID-19:Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. ChemRxiv.

37. Torti L, Maffei L, Sorrentino F, Fabritiis PD, Miceli R, et al. (2020) Impact of SARS CoV-2 in Hemoglobinopathies with Immune Disfunction and Epidemiology. A Protective Mechanism from Beta Chain Hemoglobin Defects? Mediterr J Hematol Infect Dis 12(1): e2020052.

38. Prasad S, Patel S, Behera AK, Gitismita N, Shah S, et al. (2022) Early Biochemical Markers in Predicting the Clinical Outcome of COVID-19 Patients Admitted in Tertiary Care Hospital in Chhattisgarh, India. Journal of Laboratory Physicians.

39. Camaschella C, Nai A, Silvestri L (2020) Iron metabolism and iron disorders revisited in the hepcidin era. Haematologica 105(2): 260-272.

40. Means Jr RT (2022) Hepcidin, iron, and COVID-19: is there an erythroid connection? J Investig Med 70(4): 861-862.

41. Lechuga GC, Silva FS, Sacramento CQ, Trugilho MRO, Valente RH, et al. (2021) SARS-CoV-2 Proteins Bind to Hemoglobin and Its Metabolites. Int J Mol Sci 22(16): 9035.

42. D'Angelo G (2013) Role of hepcidin in the pathophysiology and diagnosis of anemia. Blood Res 48(1): 10-15.

43. Zhao Z (2019) Iron and oxidizing species in oxidative stress and Alzheimer's disease. Aging Med (Milton) 22(2): 82-87.

44. Huy LAP, He H, Huy CP (2008) Free radicals, antioxidants in disease and health. Int J Biomed Sci 4(2): 89-96.

45. Klebanoff SJ, Kettle AJ, Rosen H, Winterbourn CC, Nauseef WM (2013) Myeloperoxidase: a front-line defender against phagocytosed microorganisms. J Leukoc Biol 93(2): 185-198.

46. Regidor PA, Rosa XDL, Santos FG, Rizo JM, Gracia Banzo R, et al. (2021) Acute severe SARS COVID-19 patients produce pro-resolving lipids mediators and eicosanoids. Eur Rev Med Pharmacol Sci 25(21): 6782-6796.

47. Ferreira I, Falcato F, Bandarra B, Rauter AP (2022) Resolvins, Protectins, and Maresins: DHA-Derived Specialized Pro-Resolving Mediators, Biosynthetic Pathways, Synthetic Approaches, and Their Role in Inflammation. Molecules 27(5): 1677.

48. Brecht A, Bartsch C, Baumann G, Stangl K, Dschietzig T (2011) Relaxin inhibits early steps in vascular inflammation. Regul Pept 166(1-3): 76-82.

49. Martin B, Weber BAG, Reddy R, Romero G, Chattopadhyay A, et al. (2018) Relaxin reverses inflammatory and immune signals in aged hearts. PLoS One 13: e0190935.

50. Veldhuizen RAW, Zuo YY, Petersen NO, Lewis JF, Possmayer F (2021) The COVID-19 pandemic: a target for surfactant therapy?. Expert Rev Respir Med 15(5): 597-608.