Research, Society and Development, v. 10, n. 9, e51810918377, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i9.18377

Red Blood Cell Distribution Width (RDW) as a prognostic marker for COVID-19: A literature review

Índice de Anisocitose Eritrocitária (RDW) como um marcador prognóstico para COVID-19: Uma revisão da literatura

Índice de Anisocitosis Eritrocitaria (RDW) como marcador pronóstico para COVID-19: Una revisión de la literatura

Received: 07/18/2021 | Reviewed: 07/23/2021 | Accept: 07/24/2021 | Published: 08/01/2021

Andrezza Cristina Cancian Hortolani Cunha
ORCID: https://orcid.org/0000-0001-8800-4783
Federal University of Triângulo Mineiro, Brazil
E-mail: andrezzacancian@hotmail.com
Anna Cecília Dias Maciel Carneiro
ORCID: https://orcid.org/0000-0003-4865-1286
Federal University of Triângulo Mineiro, Brazil
E-mail: annaceciliamaciel@gmail.com
Sarah Cristina Sato Vaz Tanaka
ORCID: https://orcid.org/0000-0003-4466-6093
Federal University of Triângulo Mineiro, Brazil
E-mail: sarahtanaka20@hotmail.com
Loren Queli Pereira
ORCID: https://orcid.org/0000-0003-2891-443X
Federal University of Triângulo Mineiro, Brazil
E-mail: lorenbiomedica@gmail.com
Fernanda Bernadelli De Vito
ORCID: https://orcid.org/0000-0002-7407-4972
Federal University of Triângulo Mineiro, Brazil
E-mail: fernanda.vito@uftm.edu.br
Helio Moraes de Souza
ORCID: https://orcid.org/0000-0001-8049-348X
Federal University of Triângulo Mineiro, Brazil
E-mail: helio.moraes@uftm.edu.br

Abstract
The Red Cell Distribution Width (RDW) is a component of blood count which gives the variation of erythrocytes, used in laboratory hematology. The analysis of this parameter is in evidence, as the increased levels of RDW seem to be a mortality predictor. The infections of the respiratory tract are in these conditions and the increase of RDW has already been related to severe acute respiratory syndrome (SARS). In December of 2019, the first cases of severe acute pneumonia caused by the SARS-CoV-2 virus emerged in China. The Corona Virus Disease-19 (COVID-19) has as most common clinical manifestations changes in the respiratory tract that range from mild to severe symptoms, requiring respiratory support in severe cases. Current evidence point to the increase of RDW value which is related to severity of the disease and mortality rates due to COVID-19. The large number of severe cases of COVID-19 shows the urgent of the identification of cheap diagnostic parameters and easy detection, which could be used for determining the prognosis of these patients. The RDW has been shown to be a potential biomarker due to the easy obtaining, low cost, and therefore, it can be an important guide to early and effective interventions.
Keywords: Biomarker; COVID-19; Red cell distribution width; SARS-CoV-2.

Resumo
O Índice de Anisocitose Eritrocitária (RDW) é um componente do hemograma que dá a variação dos eritrócitos, utilizado em hematologia laboratorial. A análise desse parâmetro fica em evidência, pois os níveis aumentados de RDW parecem ser um preditor de mortalidade. As infecções do trato respiratório estão nessas condições e o aumento do RDW já foi relacionado à síndrome respiratória aguda grave (SARS). Em dezembro de 2019, surgiram na China os primeiros casos de pneumonia aguda grave causada pelo vírus SARS-CoV-2. O Corona Virus Disease-19 (COVID-19) tem como manifestações clínicas mais comuns alterações no trato respiratório que variam de sintomas leves a graves, necessitando de suporte respiratório em casos graves. As evidências atuais apontam para o aumento do valor do RDW que está relacionado à gravidade da doença e às taxas de mortalidade por COVID-19. O grande número de casos graves de COVID-19 mostra a urgência da identificação de parâmetros diagnósticos baratos e de fácil detecção,

que poderiam ser usados para determinar o prognóstico desses pacientes. O RDW tem se mostrado um potencial biomarcador devido à fácil obtenção, baixo custo e, portanto, pode ser um importante guia para intervenções precoces e eficazes.
Palavras-chave: Biomarcador; COVID-19; Índices de eritrócitos; SARS-CoV-2.

Resumen
El índice de anisocitosis eritrocitaria (RDW) es un componente del recuento sanguíneo que da la variación de eritrocitos, que se utiliza en hematología de laboratorio. El análisis de este parámetro es evidente, ya que el aumento de los niveles de ADE parece ser un predictor de mortalidad. Las infecciones del tracto respiratorio se encuentran en estas condiciones y el aumento de RDW se ha relacionado con el síndrome respiratorio agudo severo (SARS). En diciembre de 2019, surgieron en China los primeros casos de neumonía aguda grave causada por el virus SARS-CoV-2. Las manifestaciones clínicas más comunes de la Enfermedad por Virus Corona-19 (COVID-19) son cambios en el tracto respiratorio que varían de síntomas leves a severos, requiriendo asistencia respiratoria en casos severos. La evidencia actual apunta a un aumento en el valor del RDW, que está relacionado con la gravedad de la enfermedad y las tasas de mortalidad por COVID-19. El gran número de casos graves de COVID-19 muestra la urgencia de identificar parámetros diagnósticos económicos y fácilmente detectables que puedan utilizarse para determinar el pronóstico de estos pacientes. El RDW ha demostrado ser un biomarcador potencial debido a su fácil disponibilidad, bajo costo y, por lo tanto, puede ser una guía importante para intervenciones tempranas y efectivas.
Palabras clave: Biomarcador; COVID-19; Índices de eritrocitos; SARS-CoV-2.

1. Introduction

Red blood cells (RBC) are the most common type of blood cell and have the function of delivering oxygen to the body tissues. The diameter of these cells range from 6 to 8 μm and the physiological volume is between 80 and 100 fL (Franco, 2009). The red blood cell distribution width (RDW) is a simple and inexpensive standard parameter component of a complete routine blood count test and quantifies the variation in erythrocytes size, widely used in hematology laboratory for differential diagnosis of anemia (Malka et al., 2014; Salvagno et al., 2015); mainly in differential diagnostic between iron deficiency anemia and thalassemia (Salvagno et al., 2015).

The RDW increased value suggests the presence of anisocytosis, indicating deregulation of erythrocyte homeostasis (Felker et al., 2007; Said et al., 2017). The increase of this parameter is present in many human diseases and therefore, could be a marker for predicting a variety of abnormalities (Salvagno et al., 2015). Current evidence point to the increase of RDW value which is related to severity of the disease and mortality rates due to COVID-19 (Wang, Zhang, et al., 2020). The objective of the current narrative review was to assess evidence demonstrating that RDW is related to the severity and mortality rates of COVID-19.

2. Methodology

This literature review was realized by selecting papers published between 2004 to 2021, in English. These data were collected by search in the databases Elsevier ScienceDirect Complete and PubMed Central in February 2021. The analyses looked for evidence of how RDW has been related to respiratory tract infections in general and the COVID-19 infection, severity and mortality rates. Different combinations of terms and keywords were used to ensure a wide search for the related papers to the theme, like “RDW”, “RDW and Respiratory Infections”, “COVID-19”, “Pathophysiology of COVID-19”, “COVID-19 and hematological parameters”, “RDW and COVID-19”. The studies were selected when the titles and abstracts showed the information which was in the strategy of paper selection, and after that, they were read in full and independently by the authors.

3. Results and Discussion

RDW and Respiratory Tract Infections

Currently, RDW is gaining prominence due to its ability to predict increased risk of death in various conditions such as cardiovascular diseases, sepsis, pneumonia, and other infections related to the respiratory tract (Lee et al., 2013).

Acute and severe pneumonias resulting from virus as avian influenza A (H5N1), influenza A (H1N1), and recently by SARS-CoV-2 returned attention to the susceptibility of the respiratory system to viral infections, reinforcing the necessity of evaluation of multiple laboratorial parameters in this kind of infection (Ruuskanen et al., 2011). The delay in diagnostic and treatment of Influenza A is closely related to the death of patients, because the later it is, mainly in severe cases, the higher are the chances of death by respiratory and renal failure (Rello et al., 2009). Although molecular assays in respiratory tract samples for the diagnostic of Influenza infection are the most recommended nowadays (Álvarez-Lerma et al., 2016), the analysis of multiple diagnostic parameters can assist in analysis of death risk of these patients, and one of this indexes is the RDW (Topaz et al., 2017).

Patients with Influenza with high levels of RDW presented an increase of creatinine rate and a reduction of hemoglobin, long periods of hospitalization with more complications, in addition to higher mortality rates (Topaz et al., 2017). Furthermore, it was found that in acute infections, in different moments since the hospitalization, the high levels of RDW were associated with high chances of mortality of these patients (Lee et al., 2013), mainly in adults from 45 years old (Patel et al., 2009).

The SARS in adults was described by Ashbaugh and collaborators in the 1960s, when assessing hypoxemia, tachypnea and, opacities on chest radiographs of patients who had trauma or lung infections. In general, the SARS is identified about seven days after the clinical diagnosis of pneumonia or sepsis (Thompson et al., 2017). This is a relatively common syndrome in patients admitted in intensive care units (ICUs), mainly those requiring mechanical ventilation, which about 40% of these patients die (Bellani et al., 2016)]. It is, therefore, a lethal syndrome and for those who survive it is disabling, as they usually present high risk of muscle weakness, post-traumatic stress disorder, cognitive decline and depression (Herridge et al., 2016).

In a study with 529 patients with SARS, hospitalized in ICUs, it was demonstrated that in those who present higher levels of RDW, the mortality index was increased. Thus, it was found that RDW values could be considered as good predictors for the mortality prognostic in patients diagnostic with SARS, mainly for the ease of obtaining and the very low cost of this test (Yu et al., 2020).

Pathophysiology of COVID-19 and hematological changes

In December of 2019, in China, was related the first cases of patients with pneumonia of unknown etiology. The etiologic agent was quickly identified as a virus belonging to the coronavirus family (CoV), like the already known SARS-CoV and MERS-CoV. The new virus was then called SARS-CoV-2 because of the similarity to the SARS genome and symptoms caused by SARS-CoV-2. The World Health Organization (WHO) defined in February of 2020 that the disease caused by SARS-CoV-2 would be called Corona Virus Disease 19 (COVID-19) (Zhu et al., 2020).

The most common clinical manifestations of COVID-19 are respiratory and may present as mild or even asymptomatic disease and could progress to SARS (Tsatsakis et al., 2020). About 40% of patients who developed SARS in COVID-19 die (Machhi et al., 2020).

The pathophysiology of the infection by SARS-CoV-2 resembles that caused by SARS-CoV, resulting in aggressive inflammatory responses intensely involved in the damage to the respiratory airways (Wong et al., 2004). The infection starts at superior respiratory tract and move forward to lower regions of the lungs in severe cases which the SARS-CoV-2 infects

epithelial and endothelial cells, neurons, microglia and pulmonary macrophages with the aid of the angiotensin-converting enzyme 2 (ACE-2) (Machhi et al., 2020).

In the beginning of the COVID-19 pandemic, the disease seemed to cause only respiratory involvement. However, it was observed that it can also trigger other manifestations that range from cardiac to gastrointestinal, renal, hepatic and/or neurological lesions (Tsatsakis et al., 2020). The viral replication and the release of pathogen-associated molecular pattern (PAMPs) cause a dysfunctional innate immune response. Consequently, it promotes events like vasodilation, increase of capillary permeability and hypoxemia, aggravating an already installed SARS and can often lead to multiple organ failure (Machhi et al., 2020; Zhang et al., 2020).

It is known that in infections by SARS-CoV-2, like in other infectious diseases caused by virus, hematological changes can occur, which could help monitoring the infectious process or indicate its severity, once the hematopoietic system and the homeostasis suffers significant impacts during the COVID-19 evolution (Kosmeri et al., 2020). It was described that hematological markers like hemoglobin, iron, ferritin and RDW levels vary according with the severity of COVID-19 (Taneri et al., 2020), and the RDW has been considered as an important prognostic predictor in severe cases (Wang, Zhang, et al., 2020).

RDW and COVID-19

Since the beginning of the SARS-CoV-2 pandemic, some hematological parameters have been evaluated as possible prognostic indicators of COVID-19, mainly in severe cases. Clinical signals and laboratory data from a study conducted in China with 98 patients with different severity stages of COVID-19 infection and it was observed that the RDW index was higher in the group of severe patients compared to those considered moderate, while the lymphocytes levels, hemoglobin and hematocrit were significantly lower in severe patients group (Wang, Zhang, et al., 2020).

Another study, also conducted in China, with 45 patients diagnosed with COVID-19 in moderate and severe conditions, in a period of 20 days, observed that, as the disease progressed to severe stage, the count of the leukocyte count, neutrophils, the neutrophil to lymphocyte ratio, the platelet to lymphocyte ratio, the red cell distribution width variation coefficient (RDW-CV) and the parameters of the standard deviation of the volume distribution width red blood cells (RDW-SD) were gradually increasing. Thus, both RDW-CV and RDW-SD were considered predictive biomarkers of severe disease, showing between 65% and 76% of diagnostic accuracy (Wang, Deng, et al., 2020).

The Cincinnati COVID-19 Emergency Department showed in a prospective and observational study that the increase of RDW increase is associated with the severity of the disease. The evaluation was carried out with 49 patients with COVID-19, 16 with severe forms which 12 had severe acute kidney injury (AKI) and eight of these required renal replacement therapies. They also observed that the RDW increased according to the worsening of medical condition by around 17,7% in severe cases, with the increase in RDW associated with a risk of 9.2 to 16 times greater in chances of patients with COVID-19 become severe and have acute renal failure. The cases of this study were considered mild when the RDW values were in the normal range (11.6 - 14.6%) and the moderates slightly above normal medical (14,8%) (Henry et al., 2020).

In a cohort study carried out in Massachusetts, Boston, in April 2020, showed that high values of RDW have relation with high levels of COVID-19 mortality. It was analyzed 1641 patients, and those which showed RDW values higher than 14,5% at the hospitalization moment by COVID-19 were associated with high risk of mortality (from 11% to 31%). This risk remained statistically significant even when associated with other parameters like D-dimer and absolute lymphocyte count. These patients also showed from six to 12 times more chances to die in 48 hours after the hospitalization (Foy et al., 2020). A number of studies have reinforced this evidence, like showed in a meta-analysis carried out in Australia. The RDW values were significantly higher in patients with COVID-19 considered severe (severe clinical manifestations and/or intensive care

support or even death), when compared with the patients that showed mild symptoms (Zinellu & Mangoni, 2021).

Although the evidences of this laboratory parameter can provide, like a risk stratification between patients diagnosed with COVID-19, the exact physiopathology behind this association had not completed elucidated yet, but it can be explained by some potential mechanisms (Foy et al., 2020).

At first, the COVID-19 is associated with the increase in production and release of leukocytes and platelets by bone marrow. The stimulation of marrow can modify the kinetics of the erythrocytes, resulting in a higher range of these cells size and, in consequence, higher levels of RDW (Foy et al., 2020). Secondly, patients with COVID-19 have a hyperinflammatory state; therefore, the overproduction of inflammatory cytokines could be responsible for an insufficient erythropoiesis and, as a consequence, cause erythrocytes structural and functional changes like, for example, a decrease of deformability causing a faster elimination of them (Gong et al., 2020). Thirdly, both bone marrow suppression and destruction, have also been linked with the immunological deregulation after COVID-19 infection, because the patients had a decrease in red blood cells production and developed an answer to offset this, which consists of the release of immature erythroid progenitor cells in peripheral blood, larger than the mature ones, which contributes to the increase in RDW levels (Wang, Zhang, et al., 2020). And, finally, it has been suggested which arterial hypoxemia leads to an increase in erythropoietin secretion, thus causing, an increase of RDW levels through mechanisms that involve the regulation of erythrocyte maturation and survival (Karampitsakos et al., 2020).

4. Conclusion

The severe form of COVID-19 is characterized by the necessity of mechanical ventilation, intensive care therapy and high rates of mortality. Thus, it is necessary to identify these patients through accurate and suitable prognostic information to facilitate early intervention while seeking to avoid the aggravation of patient and improve the management of medical resources. Therefore, identifying potential routine biomarkers which are available in non-invasive laboratory tests and with quickly response, could be a valuable tool to the stratification of high-risk patients to this disease and, the studies presented here show that the RDW could be considered an important prognostic predictor in severe cases of patients with COVID-19, opening perspectives to preliminary and effective interventions. New studies are needed to establish the analysis of RDW as a predictor of mortality and severity for COVID-19 and, after that, use this parameter in the clinic. Nowadays, our research group is developing researches in this area.

Acknowledgments

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001 and Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG).

References

Álvarez-Lerma, F., Marín-Corral, J., Vila, C., Masclans, J. R., González de Molina, F. J., Martín Loeches, I., Group, H. N. G. S. S. (2016). Delay in diagnosis of influenza A (H1N1)pdm09 virus infection in critically ill patients and impact on clinical outcome. *Crit Care*, *20*(1), 337. https://doi.org/10.1186/s13054-016-1512-1

Bellani, G., Laffey, J. G., Pham, T., Fan, E., Brochard, L., Esteban, A., Group, E. T. (2016). Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA*, *315*(8), 788-800. https://doi.org/10.1001/jama.2016.0291

Felker, G. M., Allen, L. A., Pocock, S. J., Shaw, L. K., McMurray, J. J., Pfeffer, M. A., Investigators, C. (2007). Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. *J Am Coll Cardiol*, *50*(1), 40-47. https://doi.org/10.1016/j.jacc.2007.02.067

Foy, B. H., Carlson, J. C. T., Reinertsen, E., Padros I Valls, R., Pallares Lopez, R., Palanques-Tost, E., Higgins, J. M. (2020). Association of Red Blood Cell Distribution Width With Mortality Risk in Hospitalized Adults With SARS-CoV-2 Infection. *JAMA Netw Open*, *3*(9), e2022058. https://doi.org/10.1001/jamanetworkopen.2020.22058

Franco, R. S. (2009). The measurement and importance of red cell survival. *Am J Hematol*, *84*(2), 109-114. https://doi.org/10.1002/ajh.21298

Gong, J., Ou, J., Qiu, X., Jie, Y., Chen, Y., Yuan, L., Hu, B. (2020). A Tool for Early Prediction of Severe Coronavirus Disease 2019 (COVID-19): A Multicenter Study Using the Risk Nomogram in Wuhan and Guangdong, China. *Clin Infect Dis*, *71*(15), 833-840. https://doi.org/10.1093/cid/ciaa443

Henry, B. M., Benoit, J. L., Benoit, S., Pulvino, C., Berger, B. A., Olivera, M. H. S., Lippi, G. (2020). Red Blood Cell Distribution Width (RDW) Predicts COVID-19 Severity: A Prospective, Observational Study from the Cincinnati SARS-CoV-2 Emergency Department Cohort. *Diagnostics (Basel)*, *10*(9). https://doi.org/10.3390/diagnostics10090618

Herridge, M. S., Moss, M., Hough, C. L., Hopkins, R. O., Rice, T. W., Bienvenu, O. J., & Azoulay, E. (2016). Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. *Intensive Care Med*, *42*(5), 725-738. https://doi.org/10.1007/s00134-016-4321-8

Karampitsakos, T., Dimakou, K., Papaioannou, O., Chrysikos, S., Kaponi, M., Bouros, D., Hillas, G. (2020). The role of increased red cell distribution width as a negative prognostic marker in patients with COPD. *Pulm Pharmacol Ther*, *60*, 101877. https://doi.org/10.1016/j.pupt.2019.101877

Kosmeri, C., Koumpis, E., Tsabouri, S., Siomou, E., & Makis, A. (2020). Hematological manifestations of SARS-CoV-2 in children. *Pediatr Blood Cancer*, *67*(12), e28745. https://doi.org/10.1002/pbc.28745

Lee, J. H., Chung, H. J., Kim, K., Jo, Y. H., Rhee, J. E., Kim, Y. J., & Kang, K. W. (2013). Red cell distribution width as a prognostic marker in patients with community-acquired pneumonia. *Am J Emerg Med*, *31*(1), 72-79. https://doi.org/10.1016/j.ajem.2012.06.004

Machhi, J., Herskovitz, J., Senan, A. M., Dutta, D., Nath, B., Oleynikov, M. D., Kevadiya, B. D. (2020). The Natural History, Pathobiology, and Clinical Manifestations of SARS-CoV-2 Infections. *J Neuroimmune Pharmacol*, *15*(3), 359-386. https://doi.org/10.1007/s11481-020-09944-5

Malka, R., Delgado, F. F., Manalis, S. R., & Higgins, J. M. (2014). In vivo volume and hemoglobin dynamics of human red blood cells. *PLoS Comput Biol*, *10*(10), e1003839. https://doi.org/10.1371/journal.pcbi.1003839

Patel, K. V., Ferrucci, L., Ershler, W. B., Longo, D. L., & Guralnik, J. M. (2009). Red blood cell distribution width and the risk of death in middle-aged and older adults. *Arch Intern Med*, *169*(5), 515-523. https://doi.org/10.1001/archinternmed.2009.11

Rello, J., Rodríguez, A., Ibañez, P., Socias, L., Cebrian, J., Marques, A., Group, H. N. S. W. (2009). Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care*, *13*(5), R148. https://doi.org/10.1186/cc8044

Ruuskanen, O., Lahti, E., Jennings, L. C., & Murdoch, D. R. (2011). Viral pneumonia. *Lancet*, *377* (9773), 1264-1275. https://doi.org/10.1016/S0140-6736(10)61459-6

Said, A. S., Spinella, P. C., Hartman, M. E., Steffen, K. M., Jackups, R., Holubkov, R., Doctor, A. (2017). RBC Distribution Width: Biomarker for Red Cell Dysfunction and Critical Illness Outcome? *Pediatr Crit Care Med*, *18*(2), 134-142. https://doi.org/10.1097/PCC.0000000000001017

Salvagno, G. L., Sanchis-Gomar, F., Picanza, A., & Lippi, G. (2015). Red blood cell distribution width: A simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci*, *52*(2), 86-105. https://doi.org/10.3109/10408363.2014.992064

Taneri, P. E., Gómez-Ochoa, S. A., Llanaj, E., Raguindin, P. F., Rojas, L. Z., Roa-Díaz, Z. M., Muka, T. (2020). Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. *Eur J Epidemiol*, *35*(8), 763-773. https://doi.org/10.1007/s10654-020-00678-5

Thompson, B. T., Chambers, R. C., & Liu, K. D. (2017). Acute Respiratory Distress Syndrome. *N Engl J Med*, *377*(6), 562-572. https://doi.org/10.1056/NEJMra1608077

Topaz, G., Kitay-Cohen, Y., Peled, L., Gharra, W., Kaminer, K., Eitan, M., Shilo, L. (2017). The association between red cell distribution width and poor outcomes in hospitalized patients with influenza. *J Crit Care*, *41*, 166-169. https://doi.org/10.1016/j.jcrc.2017.05.014

Tsatsakis, A., Calina, D., Falzone, L., Petrakis, D., Mitrut, R., Siokas, V., Docea, A. O. (2020). SARS-CoV-2 pathophysiology and its clinical implications: An integrative overview of the pharmacotherapeutic management of COVID-19. *Food Chem Toxicol*, *146*, 111769. https://doi.org/10.1016/j.fct.2020.111769

Wang, C., Deng, R., Gou, L., Fu, Z., Zhang, X., Shao, F., Li, C. (2020). Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. *Ann Transl Med*, *8*(9), 593. https://doi.org/10.21037/atm-20-3391

Wang, C., Zhang, H., Cao, X., Deng, R., Ye, Y., Fu, Z., Lu, Z. (2020). Red cell distribution width (RDW): a prognostic indicator of severe COVID-19. *Ann Transl Med*, *8*(19), 1230. https://doi.org/10.21037/atm-20-6090

Wong, C. K., Lam, C. W., Wu, A. K., Ip, W. K., Lee, N. L., Chan, I. H., Sung, J. J. (2004). Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol*, *136*(1), 95-103. https://doi.org/10.1111/j.1365-2249.2004.02415.x

Yu, X. S., Chen, Z. Q., Hu, Y. F., Chen, J. X., Xu, W. W., Shu, J., & Pan, J. Y. (2020). Red blood cell distribution width is associated with mortality risk in patients with acute respiratory distress syndrome based on the Berlin definition: A propensity score matched cohort study. *Heart Lung*, *49*(5), 641-645. https://doi.org/10.1016/j.hrtlng.2020.04.008

Zhang, J. J. Y., Lee, K. S., Ang, L. W., Leo, Y. S., & Young, B. E. (2020). Risk Factors for Severe Disease and Efficacy of Treatment in Patients Infected With COVID-19: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis. *Clin Infect Dis*, *71*(16), 2199-2206. https://doi.org/10.1093/cid/ciaa576

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., & Team, C. N. C. I. a. R. (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*, *382*(8), 727-733. https://doi.org/10.1056/NEJMoa2001017

Zinellu, A., & Mangoni, A. A. (2021). Red Blood Cell Distribution Width, Disease Severity, and Mortality in Hospitalized Patients with SARS-CoV-2 Infection: A Systematic Review and Meta-Analysis. *J Clin Med*, *10*(2). https://doi.org/10.3390/jcm10020286