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Research Article

The role of the neutrophil/lymphocyte ratio as a biomarker predicting the severity of COVID-19 infection

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Summary

At the end of 2019, several cases of pneumonia provoked by an unknown causative agent were identified in China. In March 2020, the World Health Organization announced a pandemic of a new strain of Coronavirus - SARS-CoV-2. The neutrophil/lymphocyte ratio (NLR) is a biomarker that has recently become an important diagnostic and prognostic indicator in many diseases. The study's objective was to look for a relationship between NLR and the outcome of Covid-19 infection. Retrospectively, we studied 288 patients (mean age 69.1 ± 12.5) treated in an intensive pulmonology unit over ten months since 01.08.2021. All patients had severe pneumonia caused by SARS-CoV-2 infection, proven by a polymerase chain reaction (PCR) test. Leukocytes, lymphocytes, neutrophils, and NLR were traced. Hundred and seventy-four (60.4%) of the patients died, and the rest were discharged with improvement. Concerning NLR, we found values of 9.52 in the group of the deceased and 7.87 in those discharged, respectively, at the beginning. In the end, this indicator increased in the group of deceased to 15.04, while we found a drop to 7.3 in those discharged. A statistically significant difference was found regarding the outcome of the disease and the change in the NLR values in dynamics (p = 0.005). NLR is a cheap and reliable biomarker that can predict the outcome of Covid-19 infection.

Key words: COVID-19 infection, neutrophil/lymphocyte ratio

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Introduction

At the end of December 2019, four cases of pneumonia of an unknown cause were registered in Wuhan, Hubei Province, China. The disease proceeded with high fever, peculiar X-ray changes, and changes in the blood tests with normal or low values of leukocytes and often a reduced lymphocyte count. The applied antibiotic treatment did not significantly change the disease's course or improve symptoms (Li et al. 2020a).

The ratio of neutrophils to lymphocytes (NLR) is a biomarker that has acquired an increasingly important role as a diagnostic and prognostic indicator in many diseases: inflammatory, infectious, neoplasms, atherosclerosis, and others. It is calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes from a peripheral blood sample.

Our study aimed to determine the relationship between NLR values and the severity of the disease course and its outcome in patients with COVID-19 pneumonia.

Materials and methods

Our study is retrospective in patients with severe COVID-19 pneumonia, treated in the intensive care unit of the pneumology and phthisiology clinic of Dr. Georgi Stranski University Hospital, Pleven, Bulgaria, from 01/08/2021 to 31/05/2022.

A total of 288 patients were followed, with a mean age of 69.1 (± 12.5) years, of whom 129 (44.7%) were women and 159 (55.3%) were men. All patients had proven SARS-CoV-2 infection, confirmed by PCR (+) positive test and severe pneumonic process, established radiologically or via CT, manifested acute respiratory with laboratory evidence.

Patients underwent O2-therapy; most were treated with O2 on a high-flow (HF) cannula.

Depending on the outcome of the disease, the patients were divided into two groups: died and discharged with improvement. There were 174 (60.4%) who died, and 114 (39.6%) who were discharged.

Laboratory indicators were monitored: leukocytes, lymphocytes, neutrophils, and NLR during the hospital stay and in dynamics.

Results are presented as mean ± SEM. The data were tested by one-way ANOVA. A level of $P < 0.05$ was considered significant. All analyses were performed using Excel and SPSS Version 11.0 statistic software package.

Results

Higher values of neutrophils were found in both groups of patients on admission to the clinic; in the deceased, they were 7.23. G/L × 10^9, and those of the discharged - 7.05 G/L × 109. During the disease, neutrophil values increased in patients with a fatal outcome to 7.6 G/L × 109, in contrast to those discharged, in which a decrease of 6.97 G/L × 109 was established.

We found a statistically significant difference between the level of neutrophils and the disease outcome ($p < 0.0001$).

When tracking lymphocytes, a similar dependence was found in both groups, but in the opposite direction. In both groups of patients, a low lymphocyte count was found on admission, and this decrease was more pronounced in the group with an unfavorable disease outcome. In this group, the mean lymphocyte count from 0.807 × 109/L on admission decreased to 0.505 × 109/L before death. In the discharge group, the mean lymphocyte count was 0.951 × 109/L on admission and 0.945 × 109/L before discharge.

Following the NLR, as a biomarker for COVID-19 infection, we found that the patients admitted to the intensive care unit had higher values than the norm for the indicator in both groups of patients: it was 9.52 in the deceased and 7.87 in the patients with improvement. During dynamic follow-up, an increase in NLR values was found in the deceased - 15.04, while a decrease was reported in the group of discharged patients (average 7.3). A statistically significant difference was found in the value of this indicator, correlating with the disease outcome ($p = 0.005$).

Discussion

Pathogens causing epidemics and pandemics are a major public health challenge. Coronaviruses are large enveloped RNA viruses that cause infections in humans, mammals, and birds and can cause various respiratory, intestinal, liver, and neurological diseases. As of the end of 2019, six types of coronaviruses are known, four of which - 229E, OC43, NL63, and HKU1 cause symptoms of the common cold in immunocompetent individuals (Weiss and Leibowitz 2011). The other two strains are severe acute respiratory syndrome (SARS-CoV), which caused an outbreak in Guangdong Province, China, in 2002–2003 (Zhong et al. 2003); the causative agent of the Middle East respiratory syndrome (MERS-CoV), which became the cause of severe respiratory diseases in 2012 in the countries of the Arabian Peninsula. The latter two strains are zooanthroponoses that lead to death in many of those infected (Wormser, Liu et al. 2014).

At the end of December 2019, cases of pneumonia of an unknown cause were reported in the city of Wuhan, Hubei Province, China. Within a few days, the number of cases increased significantly (Zhu et al. 2020). At the end of January 2020, the World Health Organization declared an emergency epidemic due to the large number of people infected in many countries with a new type of coronavirus, SARS-CoV-2. On 11.03.2020, a pandemic of the new type of coronavirus was declared.

In the past three years, passing through several waves, the COVID-19 infection has affected more than 763,000,000 people and claimed the lives of nearly 10% of them (COVID - Coronavirus Statistics).

Realizing the seriousness of the problem, at the very beginning of the COVID-19 pandemic, many researchers and doctors are looking for not only clinical (Chen et al. 2020; Huang et al. 2020) and radiological (Francone et al. 2020) but also laboratory markers that have a predictive role for the course and outcome of the disease, in order to undertake the earliest possible and most effective treatment.

Inflammatory markers play an important role in the course of inflammatory diseases. The severity and course of inflammatory diseases and many other diseases are related to the body's inflammatory status.

During the last years, NLR has been recognised in clinical practice as a reliable, readily accessible, and inexpensive biomarker, providing information on inflammatory status (Lee et al. 2018). It reflects the balance between innate (neutrophils) and acquired (lymphocytes) immunity (Borisov and Todorieva 2021).

Regarding the question of the normal value of NLR, differences in the reference limits for these indicators have been found, which are influenced by gender, age, and also by race. For example, the NLR reported for blacks and Hispanics are 1.76 and 2.08, respectively, and are lower than those in whites of 2.24 (Azab et al. 2014). A study carried out in South Korea reported NLR values of 1.63 for men and 1.66 for women (Lee et al. 2018). China has also reported lower NLR rates than the USA (Wu et al. 2019).

For the population of the Southern Chaoshan region in China, the reported reference values for NLR were 1.59 ± 0.59 (1.00–2.18) for men and 1.62 ± 0.64 (0.98–2.26) for women. Differences in reference values are indicated not only concerning gender and age but also concerning some regional characteristics (Meng et al. 2017).

In a study conducted in California in healthy patients in 2011–2012, reference limits of NLR were found between 0.78 and 3.53 (Forget et al. 2017).

The role of NLR in clinical practice is increasing as a marker for cellular immune activation, preceding the clinical manifestation of a wide range of disease processes such as infections, carcinomas, various inflammatory diseases, atherosclerosis, and even psychiatric diseases (Zahorec 2021). In recent years, there has been talk of NLR as a diagnostic and prognostic marker in many disease states - cerebrovascular, cardiovascular, kidney, lung diseases, sepsis, and polytraumas (Park et al. 2018; Lattanzi et al. 2019; Lee et al. 2021; Ali et al. 2022; Moore et al. 2022). Some authors have noted the prognostic nature of NLR in oncology regarding the course of the disease and the treatment outcome (Bartlett et al. 2019). In acute respiratory syndrome (ARDS), NLR is an extremely important factor in predicting the course of the disease (Wang et al. 2018).

In some cases, the COVID-19 infection is severe, with pneumonia and respiratory failure, leading to ARDS and fatal outcomes. The role of biomarkers in predicting the course of the disease is important for timely diagnosis and the correct therapeutic approach to reduce the number of severe cases and those with fatal outcomes.

More and more data are accumulating in the literature about the significance of the NLR ratio in COVID-19 infection. Many authors have indicated that in patients with Covid 19, NLR is reliable as a diagnostic and prognostic marker for the course of the infection.

For example, a study conducted in Rome, Italy (2020) found elevated levels of NLR in patients positive for COVID-19 infection – 7.83 compared to those who tested negative – 2.58. Although high NLR values were found in all cases of this infection, the values were significantly higher in severe cases than in mild disease (10.06 vs 6.02). Mortality in the first group of patients was 71.9%, and in the second – 28.1% (La Torre et al. 2022).

A study in Indonesia conducted in 2020 also reported high NLR rates in moderate and severe COVID-19 cases of pneumonia – 6.54, compared to 2.27, in PCR (+) positive patients without pneumonia. The NLR values in deceased and recovered patients differed significantly (10.88 vs 6.15) (Fuad et al. 2021).

Values of NLR >5.86 were indicated as alarming for severe COVID-19 infection, and NLR >9.47 was associated with a high risk of fatal outcomes in a report from Ethiopia (Tadesse et al. 2022).

NLR levels above 9.1 and 9.0, respectively, were associated with a high risk of fatal outcomes in patients with COVID-19 pneumonia in reports from Romania (Citu et al. 2022) and Iran (Pirsalehi et al. 2020).

Similar results were reported in a study from Islamabad, Pakistan. NLR >4.79 and NLR >9.9 were reported as risky for moderately severe and severe course of the COVID-19 infection (Toori et al. 2021).

Variable levels of NLR have been reported from different regions in China. In a study conducted in Wuhan, China, as early as January 2020, too large a difference in the NLR values of deceased and discharged patients was indicated. Values for NLR >11.75 proved a factor predicting a fatal disease outcome (Yan et al. 2020). These values are very close to those reported in many other reports but different from those reported in other regions of China (Liu et al. 2020).

In a Sri Lankan study, lower levels of NLR >3.6 were also reported as a risk factor for severe disease in patients with COVID-19 infection (Perera et al. 2022).

An increase in NLR during the hospital stay is an indicator predicting a severe course of the disease or a probable fatal outcome. The decrease in NLR values during treatment in patients with moderate-severe and severe forms is a good prognostic sign. The chances of a favorable outcome of the disease in hospitalized patients with moderately severe and severe forms and rising NLR values are small. Those who died with severe COVID-19 pneumonia had an NLR >10 (Fuad et al. 2021).

In a report from Catania, Italy, a study of 411 patients with COVID-19 infection from two independent clinics found high levels of NLR in hospitalized patients. When following them in dynamics, it is noticeable an increase in the value of NLR for all hospitalized patients by about 3 points. In patients with a severe form requiring treatment in an intensive care unit and those who died, this increase was respectively 7.7 and 8.8, i.e., significantly higher than the general population of hospitalized patients (Regolo et al. 2022).

In a report from Doha, Qatar, on 519 patients with COVID-19 infection treated in the intensive care unit, an NLR level >6.55 was found to be a risk factor for severe disease and probable fatal outcomes (Ali et al. 2022).

Despite the variation in NLR values reported in different reports, high NLR values are strongly believed to predict the severity and course of COVID-19 infection (Li et al. 2020b). Values of NLR >5 are alarming for an urgent treatment approach. At NLR >7, a severe course of the disease is expected, and NLR >10 is an indicator of an expected death outcome.

Dynamic monitoring of the indicator is extremely important: many studies have shown that its increase over time is a bad prognostic sign. Our obtained results are close to those reported worldwide.

Our study is a retrospective study of patients with severe COVID-19 pneumonia and respiratory failure treated in an intensive care unit. For this reason, patients had high NLR values on admission, similar to those reported for severe COVID-19 infections.

At follow-up over time, we found an increase in NLR values in patients who died compared to those discharged. Our results agree with results reported by reports in Italy, Indonesia, and Qatar and confirm the correlation of this indicator with the severity and prognosis of the disease.

The Covid-19 infection still exists, albeit in a modified form. The COVID-19 pandemic is far from resolved, as the Lancet stated in January 2023 (The Lancet 2023).

Conclusion

Early diagnosis, timely measures, and successful disease control are extremely important. NLR is an inexpensive, easily accessible, and reliable laboratory indicator that can be used not only as a diagnostic but also as a prognostic criterion for the risk of severe course and fatal outcome of COVID-19 infection.

References

Ali HS, Ananthegowda DC, Ebrahim EMA, Kannappilly N, Al Wraidat M, Mohamed AS, Khatib MY (2022) Neutrophil-to-lymphocyte ratio as a predictor of clinical outcomes in critically ill COVID-19 patients: A retrospective observational study. Health Science Reports 5(5): e844. https://doi.org/10.1002/hsr2.844

Azab B, Camacho-Rivera M, Taioli E (2014) Average values and racial differences of neutrophil lymphocyte ratio among a nationally representative sample of United States subjects. Zhang J (Ed.). PLOS ONE 9: e112361. https://doi.org/10.1371/journal.pone.0112361

Bartlett EK, Flynn JR, Panageas KS, Ferraro RA, Sta.Cruz JM, Postow MA, Coit DG, Ariyan CE (2019) High neutrophil-to-lymphocyte ratio (NLR) is associated with treatment failure and death in patients who have melanoma treated with PD-1 inhibitor monotherapy. Cancer 126: 76–85. https://doi.org/10.1002/cncr.32506

Borisov B, Todorieva D (2021) Changes in innate immunity in patients with chronic kidney disease. Current Trends in Immunology 22: 35–41.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 395: 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

Citu C, Gorun F, Motoc A, Sas I, Gorun OM, Burlea B, Tuta-Sas I, Tomescu L, Neamtu R, Malita D, Citu IM (2022) The Predictive Role of NLR, d-NLR, MLR, and SIRI in COVID-19 Mortality. Diagnostics 12: 122. https://doi.org/10.3390/diagnostics12010122

COVID - Coronavirus Statistics (2024) COVID - Coronavirus Statistics. www.worldometers.info

Forget P, Khalifa C, Defour J-P, Latinne D, Van Pel M-C, De Kock M (2017) What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Research Notes 10: 12. https://doi.org/10.1186/s13104-016-2335-5

Francone M, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, Panebianco V, Andreoli C, Colaiacomo MC, Zingaropoli MA, Ciardi MR, Mastroianni CM, Pugliese F, Alessandri F, Turriziani O, Ricci P, Catalano C (2020) Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. European Radiology 30: 6808–6817. https://doi.org/10.1007/s00330-020-07033-y

Fuad M, Oehadian A, Prihatni D, Marthoenis M (2021) Neutrophil-to-lymphocyte ratio and Covid-19 symptom-based severity at admission. Althea Medical Journal 8(1). https://doi.org/10.15850/amj.v8n1.2255

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 395: 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

La Torre G, Marte M, Massetti AP, Carli SM, Romano F, Mastroianni CM, Minorenti M, Alessandri F, Ajassa C, Fusconi M, De Vincentiis M, de Meo D, Villani C, Cardi M, Pugliese F, COVID-Collaborative group (2022) The neutrophil/lymphocyte ratio as a prognostic factor in COVID-19 patients: a case-control study. European Review for Medical and Pharmacological Sciences 26(3): 1056–1064. https://doi.org/10.26355/eurrev_202202_28017

Lattanzi S, Brigo F, Trinka E, Cagnetti C, Di Napoli M, Silvestrini M (2019) Neutrophil-to-Lymphocyte Ratio in Acute Cerebral Hemorrhage: a System Review. Translational Stroke Research 10(2): 137–145. https://doi.org/10.1007/s12975-018-0649-4

Lee H, Kim I, Kang BH, Um S-J (2021) Prognostic value of serial neutrophil-to-lymphocyte ratio measurements in hospitalized community-acquired pneumonia. Zivkovic AR (Ed.). PLOS ONE 16: e0250067. https://doi.org/10.1371/journal.pone.0250067

Lee JS, Kim NY, Na SH, Youn YH, Shin CS (2018) Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean

platelet volume in healthy adults in South Korea. Medicine 97: e11138. https://doi.org/10.1097/MD.0000000000011138

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z (2020a) Early transmission dynamics in Wuhan, China, of novel coronavirus–Infected pneumonia. New England Journal of Medicine 382: 1199–1207. https://doi.org/10.1056/NEJMoa2001316

Li X, Liu C, Mao Z, Xiao M, Wang L, Qi S, Zhou F (2020b) Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. Critical Care 24: 647. https://doi.org/10.1186/s13054-020-03374-8

Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, Zhang M, Tan J, Xu Y, Song R, Song M, Wang L, Zhang W, Han B, Yang L, Wang X, Zhou G, Zhang T, Li B, Wang Y, Chen Z, Wang X (2020) Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. Journal of Translational Medicine 18: 206. https://doi.org/10.1186/s12967-020-02374-0

Liu L (2014) Fields Virology, 6th Edn. Clinical Infectious Diseases 59: 613–613. https://doi.org/10.1093/cid/ciu346

Meng X, Chang Q, Liu Y, Chen L, Wei G, Yang J, Zheng P, He F, Wang W, Ming L (2018) Determinant roles of gender and age on SII, PLR, NLR, LMR and MLR and their reference intervals defining in Henan, China: A posteriori and big-data-based. Journal of Clinical Laboratory Analysis 32(2): e22228. https://doi.org/10.1002/jcla.22228

Moore JS, Robertson LJ, Price R, Curry G, Farnan J, Black A, Nesbit MA, McLaughlin JA, Moore T (2022) Evaluation of the performance of a lateral flow device for quantitative detection of anti-SARS-CoV-2 IgG. Clinical Immunology Communications 2: 130–135. https://doi.org/10.1016/j.clicom.2022.09.001

Park J-S, Seo K-W, Choi B-J, Choi S-Y, Yoon M-H, Hwang G-S, Tahk S-J, Shin J-H (2018) Importance of prognostic value of neutrophil to lymphocyte ratio in patients with ST-elevation myocardial infarction. Medicine 97: e13471. https://doi.org/10.1097/MD.0000000000013471

Perera N, de Silva A, Kumbukage M, Rambukwella R, Indrakumar J (2022) Neutrophil lymphocyte ratio as a marker of in-hospital deterioration in COVID-19: Observations from a resource constraint setting. Clinical Pathology 15: 2632010X2210908. https://doi.org/10.1177/2632010X221090898

Pirsalehi A, Salari S, Baghestani A, Vahidi M, Jalilian Khave L, Esmaeil Akbari M, Bashash D (2020) Neutrophil-to-lymphocyte ratio (NLR) greater than 6.5 may reflect the progression of COVID-19 towards an unfavorable clinical outcome. Iranian Journal of Microbiology. https://doi.org/10.18502/ijm.v12i5.4609

Regolo M, Vaccaro M, Sorce A, Stancanelli B, Colaci M, Natoli G, Russo M, Alessandria I, Motta M, Santangelo N, Fiorito L, Giarrusso O, Giangreco F, Arena A, Noto P, Ciampi C, Carpinteri G, Malatino L (2022) Neutrophil-to-lymphocyte ratio (NLR) is a promising predictor of mortality and admission to intensive care unit of COVID-19 patients. Journal of Clinical Medicine 11: 2235. https://doi.org/10.3390/jcm11082235

Tadesse Z, Bekele Bayissa A, Diriba T, Chernet N, Tsegaye S, Tsega M (2022) Neutrophil-to-lymphocyte ratio and cut-off values as predictor of severity and mortality in COVID-19 patients in Millennium COVID-19 Care Center, Addis Ababa, Ethiopia. International Journal of General Medicine 15: 6739–6755. https://doi.org/10.2147/IJGM.S375565

The Lancet (2023) The COVID-19 pandemic in 2023: far from over. Lancet (London, England) 401(10371): 79. https://doi.org/10.1016/S0140-6736(23)00050-8

Toori KU, Qureshi MA, Chaudhry A, Safdar MF (2021) Neutrophil to lymphocyte ratio (NLR) in COVID-19: A cheap prognostic marker in a resource constraint setting. Pakistan Journal of Medical Sciences 37(5): 1435–1439. https://doi.org/10.12669/pjms.37.5.4194

Wang Y, Ju M, Chen C, Yang D, Hou D, Tang X, Zhu X, Zhang D, Wang L, Ji S, Jiang J, Song Y (2018) Neutrophil-to-lymphocyte ratio as a prognostic marker in acute respiratory distress syndrome patients: a retrospective study. Journal of Thoracic Disease 10: 273–282. https://doi.org/10.21037/jtd.2017.12.131

Weiss SR, Leibowitz JL (2011) Coronavirus Pathogenesis. In: Advances in Virus Research. Elsevier, 85–164. https://doi.org/10.1016/B978-0-12-385885-6.00009-2

Wu L, Zou S, Wang C, Tan X, Yu M (2019) Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in Chinese Han population from Chaoshan region in South China. BMC Cardiovascular Disorders 19: 125. https://doi.org/10.1186/s12872-019-1110-7

Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, Deng Y, Wang H, Chen R, Yu Z, Li Y, Shang J, Zeng L, Zhao J, Guan C, Liu Q, Chen H, Gong W, Huang X, Zhang Y, Liu J, Dong X, Zheng W, Nie S, Li D (2020) Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross-sectional study. Journal of Medical Virology 92: 2573–2581. https://doi.org/10.1002/jmv.26061

Zahorec R (2021) Neutrophil-to-lymphocyte ratio, past, present and future perspectives. Bratislava Medical Journal 122: 474–488. https://doi.org/10.4149/BLL_2021_078

Zhong N, Zheng B, Li Y, Poon L, Xie Z, Chan K, Li P, Tan S, Chang Q, Xie J, Liu X, Xu J, Li D, Yuen K, Peiris J, Guan Y (2003) Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. The Lancet 362: 1353–1358. https://doi.org/10.1016/S0140-6736(03)14630-2

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W (2020) A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine 382: 727–733. https://doi.org/10.1056/NEJMoa2001017