

GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2 Cross Ref DOI: 10.30574/gscarr Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

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Neutrophil-to-lymphocyte ratio in combination with d-dimer, an indicator for the severity of COVID-19 with comorbidity: A literature review

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GSC Advanced Research and Reviews, 2022, 12(03), 013-017

Publication history: Received on 25 July 2022; revised on 27 August 2022; accepted on 29 August 2022

Article DOI: https://doi.org/10.30574/gscarr.2022.12.3.0226

Abstract

Introduction: A new coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially detected in Wuhan, China.

Material and Methods: Literature search of the latest articles published in PubMed, Google Scholar, and Cochrane Library databases from 2019 to 2021 was carried out. All articles were searched independently by two reviewers (W and X.X., with 10 and 5 years of experience in Radiology, respectively).

Results: Thirty seven articles were identified and screened for eligibility. Of these, 25 articles were included in this review. Cardiovascular disease, CHD, DM, hypertension and COPD are comorbidities hypertension and COPD are comorbidities increasing the risk of severity in COVID-19 subjects.

Conclusion: Neutrophil-to-lymphocyte Radio in combination with D-Dimer index is a competent marker for predicting COVID-19 severity. The primary preferred technique for diagnosing COVID-19 is RT-PCR of SARS-CoV-2 RNA. Chest-CT scan is a common easy practice producing rapid COVID-19 diagnosis.

Keywords: Comorbidities; COVID-19; Diagnostic value; Indicator; Severity

1. Introduction

A new coronavirus, named as severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) was initially recognized in Wuhan. China in the end of 2019. As this virus is so infectious that asymptomatic individuals may also be source of infection [1,2]. On 11th February 2020 World Health Organization (WHO) pronounced this illness as corona virus disease 2019 (COVID-19) [4]. The main feature of the disease is pneumonia [5]. Patients diagnosed with COVID-19 will experience a set of clinical symptoms like pain in the pharynx, febrile cough, sore throat, myalgia, gastrointestinal penetrations, rhinorrhea, lethargy, anorexia, headache, diarrheal, nausea or vomiting, breathing shortness and acute respiratory distress syndrome (ARDS) [4]. Many patients require intensive care unit (ICU) admittance because of the severity of the clinical state. The presence of certain comorbidity may also put COVID-19 patients in greater risk for the fatality.

World Health Organization has reported that individuals with particular medical conditions and old age population are more prone to develop more severe disease [3]. Therefore, the clinical symptoms of subjects who have no pre-existing illness are more indicative of the actual circumstances of SARS-CoV-2 infected patients. However, predispose factors

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and disease severity indicators in this particular subjects have not been largely studied. Hence, these subjects should receive more attention in order to detect risk factors for poor outcomes earlier.

In addition, the high-risk subjects should also receive closed observation as well as therapy so that the emergence of critical illness and death can be lowered [4]. It is believed that having one or more comorbidities and immunocompromised condition are related to the majority of deaths among COVID-19 patients. Many lives could be saved by identifying the main risk factors and applying proper clinical intervention. Various studies reported that kidney disease, COPD, CHD, liver disease, cardiovascular disease, DM, and high blood pressure are among serious risk factors for COVID-19. This study described the correlation between diagnostic value and severity of COVID-19 subjects with comorbidity.

2. Material and methods

We used PubMed, Google Scholar, and Cochrane Library databases to search for the latest articles published from 2019 to 2021 (3-year span), using Boolean search strategies with the keywords: "comorbidities", "coronavirus", "COVID-19", "SARS-CoV-2", "diagnostic value", or "severity". We also performed a manual screening of the included study reference lists and relevant review articles to retrieve additional journals. The initial search of the manuscript was conducted on January 1st, 2021, and was performed again on January 3, 2020 and January 6, 2020.

Two reviewers (W and X.X., with 10 and 5 years of experience in Radiology, respectively) searched all the articles independently. They carried out an abstract screening and examined the full paper for eligibility for the study. Any disagreements will be resolved by consensus.

3. Results and discussion

3.1. Correlation between diagnostic value and severity of covid-19 patient with comorbidities

Intensive Care Unit (ICU) admittance, breathing failure necessitating mechanical ventilator, vasopressor therapy, continuous renal replacement therapy (CCRT), and ECMO are all considered as signs of severe COVID-19. It is regarded having comorbidity if at least one of these conditions present, they are hypertension, DM, CHD, stroke, CKD, high lipid level, bronchiectasis, asthma, lung problem, liver illness, malignant illness, autoimmune disease, and HIV or other viral infection [4,7,8].

The Severity and comorbidities of the patients were determined using a variety of factors. Febrile was determined as body temperature of >= 37.3°C. Sepsis as well as septic shock was determined based on Third International Consensus Definition of Sepsis as well as Septic Shock 2016. Acute liver injury was described as the peak value of serum alanine aminotransferase (ALT) over 3 folds of the upper limit of normal (ULN). The diagnosis of AKI was based on KDIGO clinical practice guideline. The diagnosis of ARDS was based on Berlin Definition. Acute cardiac injury was established if cardiac biomarker serum level was above the normal range or if current abnormalities were demonstrated on electrocardiography as well as echocardiography.

In a retrospective study⁹, the prevalence of severe COVID-19 among middle-aged subjects with no comorbidity was less than that of in older ones (15.1% vs 57.1%) and greater than in younger subjects (15.1% vs 2.6%). Moreover the occurrence of complications in these particular subjects was less than that of common individuals aside from ARDS and acute liver injury. The study also obtained that increased NLR as well as D-dimer level at admittance were predisposed aspects in developing serious COVID-19. Various researches have shown that COVID-19 sufferers with comorbidity were prone to have severe organ damage associated with existing illnesses. Despite having mild symptoms in its early course, some COVID-19 individuals experienced instantaneous progression to acute respiratory failure, metabolic acidosis, septic shock, ARDS or death. Recognizing predispose factors in critically ill subjects early can be useful in providing proper caring so that fatality can be reduced.

A study by Aysegul Karahasan Yagci et al reported that there were changes in the levels of neutrophil count, lymphocyte count, and D-dimer of COVID-19 patients. Inflammatory markers, like ESR, IL-6, and CRP also elevated. Nevertheless, The correlation of severity as well as clinical appearance with biochemical markers of COVID-19 subjects has not been widely studied.

Various discrepancies were present in the laboratory results between mild/moderate subjects and severe/critical ones, like leukocytes, neutrophil, and lymphocyte, HDL-C, plasma glucose, serum potassium, total bilirubin (TBIL), albumin,

AST, ALT, LDH, D-dimer, ESR, serum amyloid A, CRP and PCT. Previous studies suggest that procalcitonin in serum is elevated in the occurrence of severe bacterial, fungal and systemic inflammatory response syndromes which commonly stable with virus infections, indicating the likelihood of various infections in critically ill subjects. It has been known that HDL-C plays protective role in various illness states, like viral pneumonia. Serum HDL-C level may decline while serum total cholesterol/HDL-C ratio may rise proportionately in community-acquired pneumonia. This phenomenon demonstrated that SARS-CoV-2 infection can be correlated to myocardial insult, hepatic injury and other organ damage. Age >52 years old (CRP >64.79 mg/L, LDH >245 U/L, D-dimer > 0.96 mcg/mL, serum amyloid A >100.02 mg/L, or albumin <36 g/L, are signs of COVID-19 progressivity to critical stage requiring closed monitoring. Lymphocyte count, serum potassium, HDL-C, and procalcitonin can be prognostic indicators as well [11].

Individuals conditions at admittance, such as old age, comorbidity, lymphocytopenia, hypoalbuminemia, and other abnormal markers can prognosticate the COVID-19 severity. These should also be considered when stratifying risk. It has been reported that COVID-19 progresses quickly in critically all individuals. Thus closed observation and prompt management are highly crucial for them in order to improve their outcomes [12].

Based on the WHO guideline, the principal and favoured procedure to diagnose COVID-19 is upper respiratory sample taken with via nasopharyngeal as well as oropharyngeal swabs, and its virus detection using real time PCR. Thorax CT, a routine diagnostic shows typical imaging features of COVID-19, comprising ground-glass opacity, multifocal patchy consolidation, and/or interstitial alterations with a peripheral distribution [13].

Similar to other molecular examinations, the accuracy of RT-PCR for diagnosing COVID-19 depends highly on the preanalytical stage, namely patient selection, sample collection, and performance of RT-PCR test kit.

Our study assessed thorax CT findings of SARS-CoV-2 RT-PCR positive subjects. Imaging radiography, particularly thoracic x-ray and CT scan has a pivotal role in diagnosing thoracic abnormalities. Total severity score (TSS) was proposed to measure the inflammatory state of the lungs, which then correlated it to clinical features. Thoracic CT Scan features and haematological findings ascertain the clinical severity of confirmed Covid-19 subjects significantly. The most pronounced outcome of our research was the reverse correlation of viral load with thorax CT TSS. Viral load in nasopharyngeal sample was remarkably low in inpatients as well as outpatients with poor lesions on CT. The CT severity was associated with age, as elderly subjects were scored highest severity (p <0.01). Coexisting disease was associated with hospitalization. It could be inferred that despite high viral load in nasopharyngeal swab specimen in the early course of the disease, it does not relate with alterations in thorax CT. In further stage, the viral load in nasopharyngeal swab specimen reduces while in lower respiratory tract sample is greater in amount, making it more reliable than that of from nasopharynx. Thorax CT scoring is deemed a reliable way for diagnosing COVID-19. Repeated CT scoring is necessary for the follow-up [9,14-20].

Currently RT PCR methods can estimate the viral load for diagnosing COVID-19. The cycle threshold (CT) values of the PCR reaction are reversely corelated to viral load; in which below average CT value indicates excessive viral loads and the other way around, high viral loads correlate with disease severity and infectivity [21].

Currently the capability of CT value in detecting real viral load is being debated as its outcome. Experts varies among different kits and techniques. It relies on the sample collection technique as well. It also relies on sample collection timing related to onset of symptoms [21-23].

4. Conclusion

In conclusion, among middle-aged COVID-19 patients who do not have comorbidity, lungs and coagulation system are most seriously affected by SARS-CoV-2. Hence, closed observation and early therapy initiation to overcome the disturbances in respiratory as well as coagulation are necessary for this particular patients. The combination of NLR and D-dimer > 1 mcg/ml index has a potential to be prognostic biomarker as it can reliably predict the disease severity. Its performance is better than that of SOFA score. Comorbidities such as COPD, cardiovascular disease, CHD, diabetes, and high blood pressure are predispose factors for the severity of COVID-19. Upper respiratory sample taken from nasopharyngeal as oropharyngeal swabs, RT-PCR, and chest CT are foremost and favored methods to diagnose COVID-19.

Compliance with ethical standards

Acknowledgments

The authors received no specific grants from any funding agency in the public, commercial, or non-for-profit sectors.

Disclosure of conflict of interest

Widiastuti Soewondo has no known conflict of interest.

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