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OCENA ROLI DIAGNOSTYCZNEJ I PROGNOSTYCZNEJ WYBRANYCH BIOMARKERÓW U PACJENTÓW Z COVID-19

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

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EVALUATION OF THE DIAGNOSTIC AND PROGNOSTIC ROLE OF SELECTED BIOMARKERS IN PATIENTS WITH COVID-19

Introduction

COVID-19, caused by the SARS-CoV-2 virus, has become a global challenge, causing not only mass illnesses, but also a significant burden on health systems around the world. The pandemic, which began in late 2019/early 2020, quickly spread to all continents and led to the introduction of unprecedented preventive measures such as lockdowns, travel restrictions, and mass vaccination campaigns. The impact of COVID-19 on society was comprehensive and multifaceted. Human interactions largely shifted to the virtual world, reducing social life to a minimum. Recession has impacted countries' economies, leading to dramatic declines in income in sectors like tourism, food service, and retail. At the political level, the COVID-19 pandemic has also triggered a number of challenges, such as the need to respond quickly to the changing epidemiological situation, manage the crisis, and secure the supply of essential products, including personal protective equipment and vaccinations. In particular, the pandemic has highlighted the need for rapid and accurate diagnostics for early detection of infection, which is key to limiting the spread of the virus. COVID-19 diagnostics include a variety of methods, including genetic, antigenic, and serological tests, which play a key role in managing the pandemic. However, diagnostics alone are not sufficient. Effective prognostic tools that can predict the course of the disease and identify patients at risk of severe COVID-19 have proven equally essential. Understanding and monitoring biomarkers, has become crucial in the fight against the pandemic. These biomarkers, including inflammatory, coagulation, and organ damage-related markers, can provide valuable information about a patient's health status, enabling early detection of infection, assessment of the risk of complications, and monitoring of response to treatment. Thus, biomarkers play a key role in both the diagnosis and prognosis of COVID-19, with direct relevance to optimizing treatment strategies and patient management. They contribute to improving treatment outcomes, reducing mortality, and easing the burden on health systems worldwide, which is critical in the long-term fight against the pandemic and its health and social consequences.

Purpose of the study

The common goal of the series of studies included in thematically consistent publications was to evaluate the diagnostic and prognostic abilities of selected biomarkers for patients with COVID-19.

Material and method

Two of the six studies in the monothematic publication series were retrospective studies, and the other four were systematic reviews with meta-analyses.

Study one was a single-center retrospective study analyzing the medical records of 400 patients admitted for COVID-19 to Ziv Medical Center (Safed, Israel). The hospital admission secured these patients between April 2020 and December 2021, and RT-PCR testing confirmed COVID-19. We performed two laboratory tests of complete blood counts on each patient. We performed the first test upon the patient's admission to the hospital, and the second test either before the patient's discharge or a few days before their death. We designed the study to determine the predictive significance of the neutrophil-to-lymphocyte ratio in determining severity, length of hospital stay, and mortality among adult COVID-19 patients.

The second study, also designed as a retrospective study, was conducted with regard to the medical documentation of patients diagnosed with COVID-19. For this purpose, the medical documentation of patients of the Hospital Emergency Department of "Kartal Dr. Lütfi Kırdar City Hospital" in Istanbul, Turkey, was analyzed. We analyzed patients who presented to the Hospital Emergency Department between January 1 and May 31, 2022. We looked at the data to see if the NLR could predict what would happen. We found a link between the ratio of neutrophils to lymphocytes and differences in the inflammatory response to COVID-19 that were based on gender.

The third paper was designed and conducted as a systematic review with meta-analysis. The aim of the present study was to determine the diagnostic and predictive value of tissue plasminogen activator in patients with COVID-19. We used predefined keywords to search electronic literature databases such as PubMed Central, Scopus, EMBASE, and Cochrane for this purpose. The final search of the above databases took place on May 4, 2023. The search yielded 1548 publications, from which the meta-analysis

included 13 studies with a total of 1221 patients after removing duplicates and, initially, titles and abstracts.

The fourth study was also designed and conducted as a systematic review with meta-analysis, with the aim of assessing the predictive and diagnostic value of Galectin-3 in COVID-19 patients. We conducted a search of literature databases such as PubMed/MEDLINE, EMBASE, SCOPUS, and Cochrane for the study, selecting articles that reported Galectin-3 levels in COVID-19 patients. On November 10, 2023, we conducted the last search and found 351 studies, out of which we finally included 18 studies (2530 patients) in the meta-analysis.

The fifth study was also a systematic review with meta-analysis, related to determining the diagnostic and prognostic abilities of the ST-2 protein based on the available literature. We searched four literature databases (PubMed/MEDLINE, EMBASE, SCOPUS, and Cochrane), concluding the search on October 11, 2023. The meta-analysis included nine studies involving 1,732 patients out of the 275 studies identified in the search.

The sixth study conducted a systematic review and meta-analysis to analyze the diagnostic and predictive ability of COVID-19 severity using levels of surfactant protein D. We searched PubMed, Embase, Web of Science, and Scopus for English-language published articles up to January 21, 2024, for this purpose. We used a systematic review and meta-analysis approach, searching multiple databases for studies that measured SP-D levels in COVID-19 patients and healthy controls. We strictly defined inclusion criteria to select studies with high-quality data, and performed statistical analyses to evaluate the diagnostic and prognostic value of SP-D in the context of COVID-19. The database search revealed 716 articles based on predefined keywords. After reviewing the articles, the meta-analysis included 12 studies involving 892 patients.

Results

In a first-in-human study designed to assess the predictive value of neutrophil-to-lymphocyte ratio (NLR) in the context of survival of patients with COVID-19, four hundred patients with COVID-19 were included, of whom males accounted for 51.5%. The mean age was 64.5 ± 17.1 years. There were 102 deaths and 296 survivors in the case group. The mortality rate was 25.5%. The mean NLR among patients who survived hospital discharge

was 8.4±20.4, which was statistically significantly lower than that of patients who died in hospitals (34.0 ±49.9; p<0.001). Statistical analysis showed statistically significant differences between patients who survived and those who died in the levels of: neutrophils (6.5 ± 4.5 vs. 13.6 ± 9.3; p<0.001), lymphocytes (2.6 ± 12.1 vs. 1.0 ± 1.3; p<0.001), white blood cells (9.6 ± 11.6 vs. 15.5 ± 1.0; p<0.001), hemoglobin (12.2 ± 2.0 vs. 10.0 ± 2.5 g/dL; p<0.001), platelets (269 ± 129 vs. 183 ± 103; p<0.001), acidophilic granulocytes (0.57 ± 0.88 vs. 0.30 ± 0.71; p<0.001) and monocytes (5.1 ± 4.4 vs. 4.1 ± 3.0; p=0.001).

The second study included 513 patients to evaluate the effect of gender on neutrophil-to-lymphocyte ratio in COVID-19 patients. The study population consisted of 47% women and 53% men, with a mean age of 72.42 years. On average, women were significantly older than men. On admission, 73% of patients were classified as having a mild course of COVID-19, and 27% as severe. Overall, 63% of patients survived the infection. NLR values were statistically significantly higher in men than in women (11.24 vs. 8.42; p<0.0001). We also observed higher NLR values for patients with severe COVID-19 compared to those with non-severe COVID-19 (14.81 vs. 8.06), and for those who survived to hospital discharge compared to those who died (12.64 vs. 8.21).

A third study to evaluate the role of tissue plasminogen activator (t-PA) as a diagnostic and predictive marker for COVID-19 patients showed that t-PA levels among COVID-19-positive and COVID-19-negative patients differed and were 26.67 ± 40.65 vs. 4.68 ± 3.83, respectively (SMD = 2.49; 95% CI: 1.85 to 3.14; p < 0.001). The mean t-PA level among patients requiring ICU admission was 24.06 ± 12.44 vs. 16.55 ± 10.01 in patients not treated in the ICU (SMD = 0.69; 95% CI: -0.68 to 2.05; p = 0.32). Moreover, t-PA levels among patients with severe COVID-19 compared to patients without severe COVID-19 were 11.89 ± 9.05 and 16.87 ± 20.39, respectively (SMD = 2.74; 95% CI: -0.71 to 6.19; p = 0.12). The t-PA values were, respectively: 15.33 ± 8.01 for patients who survived hospital discharge and 19.04 ± 11.88 for patients who died in the hospital due to COVID-19 (SMD = -0.50; 95% CI: -2.45 to 1.44; p = 0.61).

The fourth study, which examined the diagnostic and predictive abilities of Galectin-3, revealed a difference in the levels of this marker between patients with and without COVID-19. 15.73±13.03 vs. 8.72±5.82 pg/ml, respectively (SMD = 2.59; 95%CI: 1.52 to 3.67; p<0.001). Galectin-3 levels were also statistically different between patients

with COVID-19 who had a severe course and those who did not (18.83±15.5 pg/mL vs. 12.43±10.29 pg/mL; SMD = 2.64; 95%CI: 1. 45 to 3.83; p<0.001), and between COVID-19 patients who survived and those who died (6.24±6.74 pg/mL vs. 13.72±15.92 pg/mL; SMD = -1.79; 95%CI: -2.78 to -0.80; p<0.001).

In the fifth study relating to the evaluation of the diagnostic and prognostic value of ST2 protein, pooled analysis of all studies showed that sST2 levels were significantly elevated in patients with COVID-19 compared to those without COVID-19 (39.3±44.23 vs. 6.74±6.25; SMD= 3.52; 95%CI: 1.72 to 5.32), significantly higher in severe than non-severe cases (94.07±74. 71 vs. 25.53±7.36; SMD=3.87; 95%CI: 2.69 to 5.05) and different between survivors and non-survivors (43.18±21.54 vs. 119.11±113.98; SMD= -2.84; 95%CI: -4.49 to - 1.19), with significant differences in means and confidence intervals reported in these groups (p<0.001).

Analysis of data in the sixth study, which evaluated the diagnostic and prognostic potential of surfactant protein D (SP-D), showed that SP-D levels in these patient groups differed and were 44.38±74.71 and 21.29±31.8, respectively (SMD = 1.39; 95%CI: 0.35 to 2.43; p=0.009). Pooled analysis of SP-D values among patients with severe and non-severe COVID-19 were 58.28±101.8 and 94.69±114.22, respectively (SMD = 0.44; 95%CI: -0.78 to 1.66; p=0.48). SP-D levels also detected no statistically significant differences in COVID-19 patients who survived and died in the hospital (27.18±16.4 vs. 29.12±14.14; SMD = 0.07; 95%CI: -0.28 to 0.42; p=0.70).

Conclusions

The conducted studies support the following conclusions:

- Biomarkers such as the neutrophil-to-lymphocyte ratio (NLR) are simple and readily available indicators that can be calculated from a baseline blood smear, making them extremely useful in clinical practice. Its prognostic value in assessing disease severity, length of hospitalization, and mortality in patients with COVID-19 has been widely confirmed;
- The study's findings also indicate the growing potential of modern biomarkers such as Galactin-3 (Gal-3), tissue plasminogen activator (tPA), or ST2 protein in COVID-19 diagnosis and risk stratification;

- Further research is required in light of the evolving SARS-CoV-2 mutations to select and validate the most recent and effective biomarkers for diagnosis and risk stratification in the context of the new viral variants, which, given their widespread infectivity and mutagenicity, may still pose a global threat.