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Intubation Biomarkers in COVID Critical Care Patients

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What is known on this subject?

The coronavirus disease-2019 pandemic is an important cause of mortality worldwide and has created a serious burden for intensive care units. Many biomarkers have been studied and found valuable in terms of mortality and are used routinely. Many biomarkers have been researched and proved to be useful in predicting death, and they are now routinely used.

What this study adds?

In this study, in addition to the increase in acute phase reactants compared to the laboratory data of intubated patients admitted to the intensive care unit, we found higher I-granulocyte and neutrophil lymphocyte ratio ratios.

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ABSTRACT

Objective: The coronavirus disease-2019 (COVID-19) pandemic is an important cause of mortality worldwide and has created a serious burden for intensive care units (ICU). Many biomarkers have been studied in terms of mortality and are used routinely. This study aims to look at the laboratory data of patients transferred to the intensive care as well as the laboratory data on the day of intubation to try to figure out which biomarkers can help predict the intubation procedure.

Material and Methods: Patients in the COVID ICU had their records retrospectively reviewed. The study comprised patients who received oxygen therapy at the time of admission and had a positive polymerase chain reaction (PCR) test in the ICU, as well as patients who were endotracheal intubation after 24 h due to respiratory distress and/or other complications. Patients' information was gleaned from the hospital's computer database and patient files. The data of patients hospitalized in the COVID ICU were reviewed retrospectively. Patients who received oxygen therapythe firstirst admission with PCR test positive at ICU and patients who were intubated after 24 h due to respiratory distress and/or other accompanying reasons were included in the study. The data of the patients were obtained from the hospital computer database and patient files.

Results: Lactate dehydrogenase, fibrinogen, ferritin, D-dimer, international normalized ratio (INR), WBC, neutrophil, neutrophil lymphocyte ratio (NLR), I-granulocyte, Sequential Organ Failure Assessment score ($p<0.001$) and pro-C, urea, INR, hemoglobin, lymphocyte scores were compared when the patients were intubated upon admission. There was a statistically significant difference in the values ($p<0.05$).

Conclusion: Acute phase reactants (AFR) increase in COVID-19 pneumonia. In the follow-up of the disease, it can be used in I-granulocytes with NLR as well as the increase in AFR.

Keywords: COVID-19, PLR, I-granulocyte

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Introduction

The coronavirus disease-2019 (COVID-19) pandemic is a leading cause of death worldwide, and it has put a strain on intensive care units (ICU). Many biomarkers have been researched and proven to be useful in predicting death, and they are now frequently employed. This study aims to look at laboratory data from patients who are admitted to the ICU as well as laboratory findings on the day of intubation to determine whether any biomarkers can assist in predicting the intubation phase.

Material and Methods

This retrospective analysis-comprised patients who were followed up in adult ICU in a tertiary hospital center due to COVID-19 between October 1, 2020 and February 1, 2021. After the study was accepted by the hospital's ethical approval, the documents of patients coming to the ICU during the times stated were scanned retrospectively Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (ethical permission number: 2021-58, date: 14.04.2021).

The study's inclusion criteria were 1-) cases in which COVID-19 has been validated through polymerase chain reaction (PCR) testing; 2-) patients who have been diagnosed with acute respiratory distress syndrome (ARDS) according to the Berlin criteria; and 3-) patients aged 18 and over.

Criteria for exclusion: 1-) Patients under the age of 18; 2-) patients without ARDS (n=5); 3-) patients who are pregnant (n=5); 4-) patients with concurrent malignancy (n=5); 5-) patients with a history of organ transplantation and/or immunosuppressive drugs (n=8); 6-) patients with a radiological diagnosis with a negative COVID-19 PCR test (n=7); 9-) ICU patients who were intubated at the time of admission and/or patients who were intubated within the first 24 h of admission to the ICU (n=24). Patients with ARDS with COVID-19 pneumonia (n=154) were involved in the research.

Patients who had a positive PCR test and required high-flow nasal oxygen therapy, non-invasive mechanical ventilation, reservoir mask, nasal cannula mask, or a combination of these at first admission. Patients were also included in the trial if they were intubated after at least 24 h for respiratory distress and/or other reasons. To gather information on the patients, the hospital's computer database and patient files used. The patients' age, gender, concomitant disease status, and laboratory results on the day of admission to the ICU and day of intubation were all studied. The Sequential Organ Failure Assessment score (SOFA) and the Acute Physiology and Chronic Health Evaluation scores were also recorded at the time of admission to the ICU.

Statistical Analysis

The SPSS program used to conduct statistical analysis on the study data. To see if the continuous data fit the normal distribution, one sample Kolmogorov-Smirnov test employed. According to their distribution, quantitative variables were presented as mean and standard deviation or medians in our study (Table 1). Categorical variables were represented using numbers and percentages (Table 1). For continuous data that fit a normal distribution, the Student's t-test used to compare two different groups, whereas the Mann-Whitney U test used for those that did not (Table 2).

Table 1. Sociodemographic and clinical the research population's features n=154

	Mean ± SD/n	%/min-max
Age	63.07±14.57	18-85
BMI (kg/m²)	28.06±4.98	18-42
Gender		
- Male	86	55.8%
- Female	68	44.2%
Comorbidities		
- Diabetes mellitus	58	37.66%
- Hypertension	55	35.7%
- COPD	18	11.68%
- Coronary artery disease	23	14.9%
- Chronic renal failure	9	5.84%
- Neurodegenerative disease	15	9.74%
- Liver failure	3	1.9%
- Heart failure	4	2.59%
PaO_2/FiO_2 admission		
- Moderate ARDS	81	52.59%
- Severe ARDS	73	47.41%
APACHE score	18.50±8.79	7-29
SOFA score at admission	6.32±2.95	4-20
LOS	18.38±12.65	2-55
Lenght of stay in hospital	18.40±12.62	2-73
Mechanic ventilation days	14.47±10.65	1-54
Intubation days	3.03±1.41	2-6

COPD: Chronic obstructive pulmonary disease, ARDS: Acute respiratory distress syndrome, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment score, LOS: lenght of stay in ICU, ICU: Intensive care unit, BMI: Body mass index, SD: Standard deviation, min: Minimum, max: Maximum

To examine categorical data between two groups, the chi-square test was used (Tables 2, 3).

Results

The sociodemographic and clinical characteristics of the study population has been described in Table 1. Eighty six (55.8%) of the patients were of male gender. Fifty five (35.7%) of the patients had hypertension, 58 (37.66%) had diabetes mellitus, 18 (11.68%) had chronic obstructive pulmonary disease, 23 (14.9%) had coronary artery disease, 15 (9.74%) had neurodegenerative disease, and 9 (5.84%) had chronic renal failure. The patients' average number of mechanical ventilator days was 14.47±10.65, their intensive care days were 18.38±12.65, and their hospital days were 18.50±8.79. The patients' average intubation day was 3.03±1.41. Additionally, laboratory data on the day the patients were admitted to the ICU and day they were intubated were compared and statistically significant results were obtained (lactate dehydrogenase, fibrinogen, ferritin, D-dimer, international normalized ratio (INR), white blood cell, neutrophil, neutrophil lymphocyte ratio (NLR), I-granulocyte, SOFA score ($p<0.001$), procalcitonin, blood urea nitrogen, INR, hemoglobin, lymphocyte ($p<0.05$) (Table 2). Comparison of laboratory data on the day of admission to the ICU and day of intubation.

Table 2. Laboratory results from the day of admission to the intensive care unit and the day of intubation n=154

	Admission to intensive care	Intubated	p value
Glucose (mg/dL)	192.12±108.51	199.25±11.65	0.450
BUN (mg/dL)	74.99±65.57	96.27±107.02	0.03
Creatinine (mg/dL)	1.6±1.43	1.57±1.40	0.29
AST (U/L)	83.46±296.94	154.96±560.14	0.94
ALT (U/L)	71.80±88.77	135.16±551.92	0.37
Fibrinogen (mg/dL)	641.45±699.43	500.08±215.96	0.000
INR	1.21±0.56	1.27±0.57	0.02
D-dimer (mg FEU/mL)	3.36±4.89	5.69±5.41	0.000
LDH (U/L)	509.43±398.23	731.42±816.84	0.000
Ferritin (ng/mL)	1427.56±1868.67	1749.2±1994.81	0.03
WBC (10^9/L)	11.38±8.52	15.13±8.99	0.000
HB (g/dL)	11.88±2.44	11.08±2.59	0.007
Platelet	243.39±122.56	231.76±125.69	0.36
Lymphocyte (10^9/L)	0.98±1.21	0.84±1.41	0.007
Neutrophil (10^9/L)	10.05±8.57	14.55±11.79	0.000
CRP (mg/L)	137.24±91.42	145.54±275.24	0.18
PCT (ng/mL)	4.89±31.71	3.56±9.31	0.008
NLR	20.34±30.17	32.72±40.27	0.000
PLR	442.08±406.24	495.11±400.94	0.169
I-granulocyte (10^9/L)	0.45±0.620	1.10±8.97	0.000
Mortality	140 (80.92%)	34(24.28%)	0.000
SOFA	6.52±2.83	10.11±3.4	0.000

BUN: Blood urea nitrogen, LDH: Lactate dehydrogenase, AST: Aspartate transaminase, ALT: Alanine aminotransferase, WBC: White blood cell, HB: Hemoglobin, PCT: Procalcitonin, CRP: C-reactive protein, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, I-granulocyte: Immature granulocyte, SOFA: Sequential Organ Failure Assessment score

The treatments and complications that occurred throughout the intensive care follow-up are summarized in Table 3. Tocilizumab was used in 13 (8.4%) of the patients, anakinra in 22 (14.3%), dexamethasone in 40 (26%) of the patients, plasmapheresis in 22 (14.3%) of the patients, stem cell therapy in 2 (1%) of the patients, pulse methylprednisolone in 66 (42.9%) of the patients, and intravenous immunoglobulin therapy in 17 (9.7%). In 73 (47.4%) of the patients, secondary bacterial infection developed. Positivity in culture in 46 (29.9%) patients. A total of 132 patients (85.8%) died. Septic shock was observed in 103 (66.9%), diabetic ketoacidosis 21 (13.6%), acute renal failure 52 (33.1%), elevated liver enzymes 11 (7.1%), and pulmonary thromboembolism 3 (1.9%) of the patients.

Table 3. Medical treatments and complications

	Total (n=154)
Dexamethasone	40 (26%)
Tocilizumab	13 (8.4%)
Anakinra	22 (14.3%)
Stem cell therapy	2 (1.3%)
Methylprednisolone pulse therapy	66 (42.9%)
IVIG	17 (9.7%)
Secondary bacterial infection	73 (47.4%)
Positivity in culture	46 (29.9%)
Septic shock	103 (47.4%)
Mortality	132 (66.9%)
Acute renal failure	51 (33.1%)
Diabetic ketoacidosis	21 (13.6%)
Elevated liver enzymes	11 (7.1%)
Deep vein thrombosis	2 (0.06%)
Pulmonary embolism	3 (1.9%)
Plasmapheresis	22 (14.3%)

IVIG: Intravenous immunoglobulin

Discussion

COVID-19 has various clinical manifestations, including asymptomatic pneumonia, ARDS, and even mortality. As a result, determining the seriousness of COVID-19 and implementing effective early therapies are critical steps in lowering mortality. Lymphocytosis is a common complication of viral infections. By collecting and neutralizing viruses, lymphocytes safeguard the body. A drop of lymphocyte count was seen in COVID-19 patients in our study. Because the angiotensin-converting enzyme 2 receptor is expressed in lymphocytes, one possible explanation for this observation is direct infection and death of lymphocytes by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). The importance of NLR in the diagnosis and prognosis of viral infection has been highlighted in numerous research. NLR, for example, has abetter sensitivity than neutrophil and lymphocyte counts alone, according to Han et al. (2), and can be employed as a preferred diagnostic technique to screen patients infected with influenza virus. Furthermore, NLR has been linked to chronic hepatitis B virus infection and can be used to predict recurrence (3,4) Lymphocytes play a major role in the immunological response triggered by a viral infection (5).

Systemic inflammation inhibits cellular immunity, decreasing CD4+ T lymphocytes and an increase in CD8+ suppressor T-cells (6). Thus, virus-induced inflammation increases NLR. High NLR may indicate COVID-19 progression. In this context, in our study, we found the NLR on the day of intubation to be higher and statistically significant than the NLR on the day of admission to the ICU ($p<0.001$). Neutrophils, along with mononuclear cells, are the first cells infected with SARS-CoV-2 and attracted to the alveoli, recruited by interferons, interleukin-6 (IL), IL-1, and other cytokines with a C-C motif chemokine ligand-2 motif. Cytokines cause immature granulocytes (I-granulocytes) to be produced and released by the bone marrow, which subsequently returns to the endothelium of the lungs, producing further inflammation and ARDS. In COVID-19-related hyperinflammation, neutrophils are thought to transform into immature forms, leading to degranulation, cytokine production, and increased interferon response (7,8,9). The NLR was linked with disease severity and organ dysfunction in a study of 42 critically ill persons with COVID-19 (10). Septic patients have higher I-granulocyte levels than patients with severe SARS-CoV-2 infection, according to previous research. Found that patients with ventilator-associated pneumonia had a significant peak in both absolute I-granulocyte counts and I-granulocyte percentages compared to those who did not (11).

COVID-19 patients with severe disease exhibited greater immature granulocyte levels but lower lymphocyte and platelet counts than COVID-19 patients without severe disease, according to a morphological analysis of 27 COVID-19 positive and 18 COVID-19-negative patients (12). In our investigation, the difference in I-granulocyte levels between intubated and non-intubated groups was statistically significant ($p=0.001$). As a result, I-granulocyte and NLR may be indicators of illness progression and the process leading to intubation.

The retrospective aspect of this study is one of its many flaws. Because the physician decided to intubate, the time it took to intubate varies. Furthermore, the causes of death have not been thoroughly investigated. More research is needed to determine if the onset of symptoms, the length of hospitalization, and the pharmacotherapies used affect the patient's clinical outcome.

Conclusion

In COVID-19 pneumonia, acute phase reactants (AFRs) known to rise. It can be employed in I-granulocytes with NLR as well as the increase in AFR in illness follow-up. The information obtained from a complete blood count is useful in clinical practice since it is affordable and quick to obtain. The use of these indicators in normal blood testing can aid clinicians in monitoring and predicting COVID-19 severity and prognosis.

Ethics

Ethics Committee Approval: Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (ethical permission number: 2021-58, date: 14.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.T., G.H.A., G.T., Concept: D.T., G.H.A., G.T., Design: D.T., G.H.A., G.T., Data Collection or Processing: D.T., G.H.A., G.T., Analysis or Interpretation: D.T., G.H.A., G.T., Literature Search: D.T., G.H.A., G.T., Writing D.T., G.H.A., G.T.

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