RESEARCH ARTICLE

Prognostic role of simple inflammatory biomarkers in patients with severe COVID-19: an observational study

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Abstract

Background/aim: Simple inflammatory biomarkers, such as neutrophil to lymphocyte ratio (NLR), could serve as prognosis indicators in patients with Coronavirus disease 2019 (COVID-19). The utility of on-admission inflammatory biomarkers in predicting outcomes was investigated in patients suffering from severe COVID-19 infection.

Methods: We performed a retrospective study to assess the role of white blood count (WBC), neutrophils (N), lymphocyte (L), platelets (PLTs), C-reactive protein (CRP), reverse transcription polymerase chain reaction (RT-PCR), NLR (N/L), PLR (P/L), dv (derived variation of)-NLR (N/WBC-L), LNR (L/N), dv (derived variation of)-LNR (L/WBC-N), and CLR (CRP/L), in predicting the need for high-flow nasal cannula (HFNC) use, admission to Intensive Care Unit (ICU), and death in adult patients with severe COVID-19 admitted to the Department of Respiratory Medicine from April to September 2021.

Results: One hundred and fifteen patients (60 % males) with a mean age of 57.7 ± 16.3 years were included. Thirty-seven patients (32.2 %) required escalation with HFNC, eight patients (7 %) were admitted to the ICU, and nine patients (7.8%) died. Based on univariate analysis, CRP [odds ratio (OR): 1.25, 95 % confidence interval (CI): 1.1-1.42), LNR (OR: 0.015, 95 % CI: 0.00-0.35), dv-NLR (OR: $5*10^{6}$, 95 % CI: 26.7-$9*10^{9}$), CLR (OR: $7*10^{58}$, 95 % CI: $3*10^{25}$-$2*10^{92}$), length of hospitalization (LOH; OR: 1.44, 95 % CI: 1.22-1.63), dyspnea at presentation (OR: 2.83, 95 % CI: 1.23-6.52), and ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) on admission (OR: 0.967, 95 % CI: 0.952-0.983) were independent predictors for oxygen requirements. However, the multivariate analysis showed that LNR (OR: $1.686e0^{-4}$, 95 % CI: 6.441e00^{-8}-0.441), PaO_2/FiO_2 on admission (OR: 0.965, 95 % CI: 0.941-0.989), and LOH (OR: 1.717, 95 % CI: 1.274-2.314) were the most important predictor for HFNC use. Nasal congestion at presentation (OR: 11.5, 95 % CI: 1.61-82.8) was a unique and independent predictor for ICU admission. As far as death is concerned, the univariate analysis identified elevated CRP (OR: 1.11, 95 % CI: 1.0-1.24), low RT-PCR (OR: 0.829, 95 % CI: 0.688-0.999), high CLR (OR: $3.2*10^{33}$, 95 % CI: 5.8-$1.8*10^{66}$), age (OR: 1.08, 95 % CI: 1.02-1.14), body mass index (BMI) over 30 (OR: 5.25, 95 % CI: 1.26-21.96), the chronic use of angiotensin-converting enzyme inhibitors (OR: 5.72, 95 % CI: 1.35-24.09), nitrates (OR: 14.85, 95 % CI: 1.81-121.8), diuretics (OR: 8.21, 95 % CI: 1.97-34.32), PaO_2/FiO_2 on admission (OR: 0.983, 95 % CI: 0.970-0.998), and nasal congestion at presentation (OR: 9.81, 95 % CI: 1.40-68.68) as independent predictors. However, the multivariate analysis pinpointed that obesity (BMI >30) (OR: 10.498, 95 % CI: 1.107-99.572) remained the most important predictor for death.

Conclusion: LNR and PaO_2/FiO_2 on admission could be used to timely identify patients requiring HFNC during hospitalization, while obesity (BMI >30) could be an independent predictor of death. Nasal congestion emerges as a unique predictor for ICU admission. HIPPOKRATIA 2022, 26 (2):70-77.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by a novel single-chain enveloped ribonucleic acid (RNA) coronavirus, first emerged in China and rapidly led to an unprecedented global healthcare crisis[1,2]. Due to its broad spread and the ensuing increased morbidity and mortality, COVID-19 infection was declared on the 30th of January 2020 a public health emergency of international concern by the World Health Organization (WHO)[3]. Indeed, as of December 2021, the COVID-19 virus has infected more than 271 million people worldwide and has caused more than 5.33 million deaths[4,5].

COVID-19 infection is associated with a spectrum of multisystemic manifestations caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite its multisystemic nature, almost all patients may experience a range of mild to severe symptoms from the respiratory system[1,2,6]. Most (up to 80 %) will exhibit mild symptoms, such as low-grade fever and sore throat. However, few patients will progress into an overwhelming inflammation, known as the "cytokine storm", with life-threatening complications, such as acute respiratory distress syndrome (ARDS), sepsis, and multiple organ dysfunction syndrome (MODS). Patients suffering from severe disease are experiencing high morbidity and mortality. They may require escalation of respiratory support with the use of high flow nasal cannula (HFNC) or intubation, mechanical ventilation, and intensive care unit (ICU) admission[1,2,6,7]. Early diagnosis, disease stratification, and treatment initiation prove to be pivotal in providing optimal therapeutic interventions and reducing the morbidity and mortality of COVID-19 pneumonia[1,7].

Excessive and uncontrolled cytokine production with the resulting hyper-inflammation plays an essential role in COVID-19 pneumonia. In addition, the "cytokine storm" has been recognized as a significant poor prognostic factor in severe COVID-19 disease[1,2,6,7]. When SARS-CoV-2 enters the alveolar cells, it triggers the release of inflammatory products, which in turn activate the macrophages. The activation of macrophages is responsible for the mononuclear cell accumulation in the lung tissue. Excessive lung infiltration with inflammatory cells induces the "cytokine storm", leading to severe pneumonia, acute lung injury, ARDS, and even death. Thus, patients with severe COVID-19 are more likely to display higher levels of inflammation on admission compared to patients with mild disease[1,7]. Therefore, there is an apparent urgency to identify simple biomarkers to early detect high-risk patients with severe COVID-19, to stratify supportive measures accordingly, and to reduce associated mortality and morbidity[1,7].

Several inflammatory biomarkers, such as the C-reactive protein (CRP), the ratios of neutrophils to lymphocytes (NLR), lymphocytes to neutrophils (LNR), platelet to lymphocyte (PLR), dv (derived variation of)-NLR (N/WBC-L), and CRP to lymphocytes (CLR) have been recognized as useful indicators for ongoing inflammation and prognosis of various diseases. They are all simple to be calculated, fast to be obtained, inexpensive, and widely available, as they are based on routinely performed parameters in everyday clinical practice[1,2,6,7]. So, obtaining the levels of the biomarkers mentioned above upon admission could allow early disease stratification in specifying high-risk COVID-19 patients with severe disease.

We aimed to investigate the clinical utility of on-admission inflammatory biomarkers/hematological ratios in predicting: i) the need for escalation of respiratory support with HFNC use, ii) ICU admission, and iii) death.

Methods

Study design

The prospectively collected electronic and clinical administrative data of our hospital from April 2021 to September 2021, during the Delta surge of the COVID-19 pandemic, were retrospectively reviewed. The Scientific Board of the University General Hospital of Larissa, Greece, approved the study protocol (decision No 42937, date: 29/11/2021), which was subsequently registered on ClinicalTrials.gov (Registration number: NCT05145751). We handled all participants' data according to the Declaration of Helsinki[8] and the Health Insurance Portability and Accountability Act (HIPAA)[9]. Our study involved the collection of existing data and diagnostic tests. Hence, it included anonymized patient data and did not require informed consent from the participants. Finally, we reported our results according to the STROBE statement[10].

Eligibility criteria

We evaluated for eligibility all consecutive adult patients (18 years or older) admitted to the Department of Respiratory Medicine with a verified severe SARS-CoV-2 infection. We defined severe COVID-19 infection as any of the following conditions: respiratory distress patients with respiratory rate ≥30 breaths/minute, SpO_2 (oxygen saturation) ≤93 % on room air, and a ratio of arterial oxygen partial pressure to fractional inspired oxygen PaO_2/FiO_2 ≤300 mmHg[11]. According to the WHO recommendations[5], the diagnosis of COVID-19 infection was set using real-time polymerase chain reaction (PCR) performed on a nasopharyngeal sample. Patients were treated according to the COVID-19 treatment guidelines of the National Institute of Health (NIH)[12]. We excluded patients with autoimmune disorders and patients with malignancy and recent chemotherapy.

Data extraction/Outcome definition

Patients' demographics, medical history, vaccination status, pharmacotherapy, on-admission symptoms, and the on-admission values of white blood count (WBC), neutrophils (N), lymphocyte (L), platelets (PLTs), CRP, and nasopharyngeal reverse transcription PCR (RT-PCR) were recorded. Additionally, the following ratios based on-admission values: NLR (N/L), PLR (P/L), dv (derived variation of)-NLR (N/WBC-L), LNR (L/N), dv (derived variation of)-LNR (L/WBC-N), and CLR (CRP/L) were calculated. Furthermore, our patients' on-admission hemodynamic and respiratory status was documented in

terms of systolic arterial blood pressure, heart rate, and PaO_2/FiO_2 ratio. The length of hospital stay (LOH), need for escalation of respiratory support using HFNC, ICU admission, and death were also recorded. The follow-up period was determined until death, admission to ICU, use of HFNC, or whatever outcome came first.

Statistical analysis

We use means (or median values) and standard deviations [or interquartile ranges (IQR)] to summarize continuous data according to the Shapiro-Wilk test for normal distribution. We also summarize nominal and ordinal variables in counts and percentages. We controlled the role of individual potential outcome predictors through a univariate analysis for each study endpoint. We report our results in odds ratio (OR) and their 95 % confidence interval (95 % CIs). Logistic and linear regressions served for dichotomous and continuous data. In every case, we estimated the corresponding diagnostic accuracy using sensitivity, specificity, and the area under the curve (AUC) of the receiver-operating characteristic (ROC) curves. Ultimately, we estimated the optimal cut-off value for continuous data's highest sensitivity and specificity. We set the level of statistical significance at $p < 0.05$. A trained author carried out all statistical analyses using the statistical environment R[13].

Results

Study sample

One hundred and fifteen consecutive patients (69 males, 60 %) with a mean age of 57.7 ± 16.3 years were included. The mean length of hospital stay was eight days. Most were non-smokers (88 patients, 76.5 %) and occasionally consumed alcohol (106 patients, 92.2 %). Arterial hypertension (47 patients, 40.9 %) and hyperlipidemia (36 patients, 31.1 %) constituted the most common registered comorbidities. The mean systolic arterial pressure and heart rate on admission were 124.8 (IQR: 12.8) mmHg and 79 (IQR: 13) beats/min, respectively. Almost half patients (n =58) presented with severe illness based on PaO_2/FiO_2 values (<300, IQR: 50.4), while the rest of them were categorized under critical illness (PaO_2/FiO_2 >300, IQR: 49.6). Moreover, fever was recognized as the more common symptom (n =109), followed by weakness and cough. (Table 1). The on-admission laboratory values are depicted in Table 2. Of note, none of our patients was vaccinated against COVID-19. Ultimately, 37 (32.2 %) patients required escalation of respiratory support with HFNC, eight patients (7 %) were admitted to the ICU, and nine patients (7.8 %) died (Table 2).

Predictors for escalation of respiratory support with HFNC

The univariate analysis identified that CRP (OR: 1.25, 95 % CI: 1.1-1.42), LNR (OR: 0.015, 95 % CI: 0.00-0.35), dv-NLR (OR: 5 $*10^6$, 95 % CI: 26.7-9 $*10^9$), and CLR (OR: 7 $*10^{58}$, 95 % CI: 3 $*10^{25}$-2 $*10^{92}$), LOH (OR: 1.44, 95 % CI: 1.22-1.63), dyspnea at presentation (OR: 2.83, 95 % CI: 1.23-6.52), and PaO_2/FiO_2 on admission (OR: 0.967, 95 % CI: 0.952-0.983) were independent predictors for oxygen requirements. Table 3 shows the diagnostic accuracy parameters of our univariate analysis, including the optimal cut-off points, sensitivity, specificity, and AUC values. However, the multivariate analysis showed that LNR (OR: 1.686 $e0^{-4}$, 95 % CI: 6.441 $e00^{-8}$-0.441), PaO_2/FiO_2 on admission (OR: 0.965, 95 % CI: 0.941-0.989), and LOH (OR: 1.717, 95 % CI: 1.274-2.314) were independent and the most important predictors for oxygenation requirement (Table 4, Figure 1).

Predictors for ICU admission

The univariate analysis identified that nasal congestion (OR: 11.5, 95 % CI: 1.61-82.8) at presentation was an independent predictor for ICU admission. Moreover, none of the admission values of studied laboratory parameters was predictive for the ICU admission in our study sample (Table 3). Since nasal congestion was our unique predictor, we did not proceed with multivariate analysis.

Predictors for death

The univariate analysis identified elevated CRP values (OR: 1.11, 95 % CI: 1.0-1.24), low RT-PCR (OR: 0.829, 95 % CI: 0.688-0.999), and high CLR (OR: 3.2 $*10^{33}$, 95 % CI: 5.8-1.8 $*10^{66}$) as independent predictors of death. Similarly, age (OR: 1.08, 95 % CI: 1.02-1.14), body mass index (BMI) over 30 (OR: 5.25, 95 % CI: 1.26-21.96), the chronic use of angiotensin-converting enzyme inhibitors (OR: 5.72, 95 % CI: 1.35-24.09), nitrates (OR: 14.85, 95 % CI: 1.81-121. 8), diuretics (OR: 8.21, 95 % CI: 1.97-34.32), PaO_2/FiO_2 on admission (OR: 0.983, 95 % CI: 0.970-0.998), and nasal congestion at presentation (OR: 9.81, 95 % CI: 1.40-68.68) were risk factors for death (Table 3). However, the multivariate analysis pinpointed that obesity (BMI >30) (OR: 10.498, 95 % CI: 1.107-99.572) remained the most important predictor for death (Table 5, Figure 2).

Discussion

Based on the results of our study, LNR and PaO_2/FiO_2 on admission, along with LOH, are the most important predictors of the need for escalation of respiratory support with HFNC in hospitalized patients with severe COVID-19 disease. Likewise, obesity (BMI >30) is an independent predictor of death, while nasal congestion is a unique predictor for ICU admission, respectively. Of note, elevated CRP, high CLR, and PaO_2/FiO_2 on admission were also found to be independent predictors for death, based on univariate analysis; however, the multivariate analysis highlighted that obesity is the most important predictor.

A large body of evidence indicates that hemogram-derived ratios play an important role in COVID development and prognosis[14-16]. Our results agree with the current literature, suggesting an association between several biomarkers and COVID-19 disease[17-19]. Accumulating evidence depicts that CRP, a non-specific marker of inflammation, is associated with the severity and prognosis of COVID-19 pneumonia[17-19]. However, Karimi et al[19] suggested that fur-

Table 1: Baseline characteristics of the 115 adult patients with severe COVID-19 admitted to the Department of Respiratory Medicine that comprised our study's sample.

	No	%
Gender		
Male	69	60
Females	46	40
Smoking		
Yes	27	23.5
No	88	76.5
Pack-years (smoking)		
10-25	7	6.1
26-50	12	10.4
51-75	6	5.2
76-100	2	1.7
Alcohol consumption		
Yes	106	92.2
No	9	7.8
Alcohol (units)		
1	97	84.5
2	2	1.7
3	5	4.3
4	2	1.7
Comorbidities		
Arterial Hypertension	47	40.9
Hyperlipidaemia	36	31.3
Diabetes Mellitus	15	13
Coronary Artery Disease	16	13.9
COPD	3	2.6
Bronchial asthma	9	7.8
Heart failure	3	2.6
Atrial fibrillation	9	7.8
Chronic kidney disease	4	3.5
Active malignancy	0	(-)
Obesity	18	15.7
Immunosuppression	0	(-)
Pharmacotherapy		
ACE inhibitors	17	14.8
ATII antagonists	26	22.6
Ca^{2+} antagonists	10	8.7
B-blockers	30	26.1
Nitro lingual	4	3.5
Diuretics	19	16.5
Bronchodilators	14	12.2
Anticoagulants	10	8.7
Antiplatelets	17	14.8
Hypo-lipidemic	35	30.4
Insulin	1	0.9
Antibiabetics	15	13

n: number, COPD: chronic obstructive pulmonary disease, ACE: angiotensin-converting enzyme, ATII: angiotensin II receptor.

ther research is needed to identify the best-fitted predictive biomarker for COVID-19 patients. Additionally, Lua et al[17] reported that the heterogeneity of patients suffering from COVID-19 indicates that multiple biomarkers should be used to evaluate their dynamic clinical course. Hence, we examined the on-admission values of several simple inflammatory biomarkers[20-23]. Moreover, Cillóniz et al[22] found that on-admission CLR values are helpful in predicting ICU admission, and Capone et al[23] found that dv-NLR is a predictive tool for the treatment response in patients with several types of malignancies.

Our study showed that elevated CRP with a cut-off value of 3.2 mg/L and AUC 0.740 could predict the need to escalate respiratory support with HFNC. Similarly, elevated CRP with a cut-off value of 4.83 and AUC 0.673 (sensitivity 0.67, specificity 0.75) is an independent predictor for death.

Table 2: Presentation, on-admission laboratory values, and outcome of the study's sample admitted to the Department of Respiratory Medicine with severe COVID-19 disease.

	Mean (Median)	Standard deviation (IQR)
Presentation		
Systolic arterial pressure (mmHg)	124.8	12.8
Heart rate (bpm)	79	13
P/F ratio	298	44.7
Fever	109	94.8
Dyspnoea	35	30.4
Cough	55	47.8
Pharyngeal pain	6	5.2
Nasal congestion	5	4.3
Weakness	65	56.5
Headache	18	15.7
Confusion	3	2.6
Muscle/Joint pain	27	23.5
Chest pain	7	6.1
Abdominal pain	2	1.7
Nausea/Vomiting	10	8.7
Diarrhoea	21	18.3
Labs on admission		
WBC	5,100*	3,300*
Neutrophils	3,590*	2,910*
Lymphocyte	920*	490*
Platelets	182,000*	71,500*
CRP	2.47*	3.99*
RT-PCR	20.4*	7.1*
NLR	4.32*	3.39*
LNR	0.232*	0.186*
PLR	198*	141*
dv-NLR (N/WBC-L)	0.901*	0.058*
dv-LNR (L/WBC-N)	0.677*	0.162*
CLR (CRP/L)	0.00288*	0.00482*
PaO2/FiO2 ratio on admission		
Severe illness P/F <300	58	50.4
Critical illness P/F >300	57	49.6
Outcome		
HFNC		
No	78	67.8
Yes	37	32.2
ICU		
No	107	93
Yes	8	7
Death		
No	106	92.2
Yes	9	7.8

In the second column, mean or median values are presented and in the third column corresponding standard deviations or interquartile ranges (IQR) to summarize continuous data according to the Shapiro-Wilk test for normal distribution; IQR: interquartile ranges, WBC: white blood count, CRP: C-reactive protein, RT-PCR: reverse transcription polymerase chain reaction, N: neutrophils, L: lymphocyte, P: platelets, NLR: neutrophils/lymphocytes, PLR: platelets/ lymphocytes, dv-NLR: (derived variation of)-NLR, LNR: lymphocytes/ neutrophils, dv-LNR: (derived variation of)- LNR, CLR: CRP/ lymphocytes P/F ratio: PaO2 (arterial blood oxygen partial pressure)/FiO2 (fraction of inspired oxygen) ratio, HFNC: high flow nasal cannula, ICU: intensive care unit.

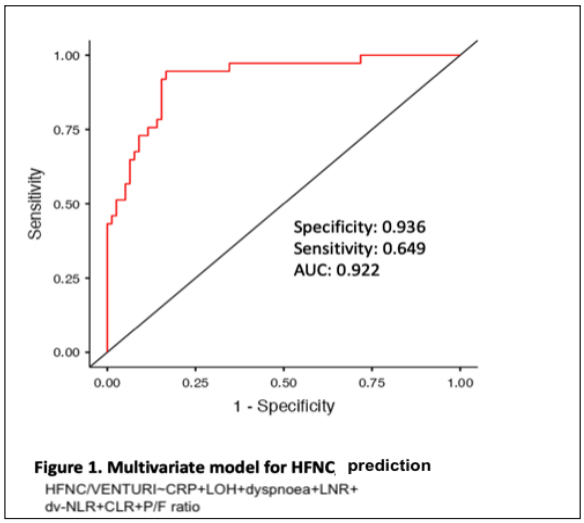

Figure 1: Graph presenting the multivariate model for the high-flow nasal cannula use prediction.

AUC: area under the curve, HFNC: high-flow nasal cannula,CRP: C-reactive protein, LOH: length of hospitalization, LNR: lymphocytes/neutrophils, CRP: C-reactive protein, LNR: lymphocytes/ neutrophils, dv-NLR: (derived variation of)-NLR(neutrophils/ lymphocytes), CLR: CRP/ lymphocytes, P/F ratio: PaO2 (arterial blood oxygen partial pressure)/FiO2 (fraction of inspired oxygen) ratio

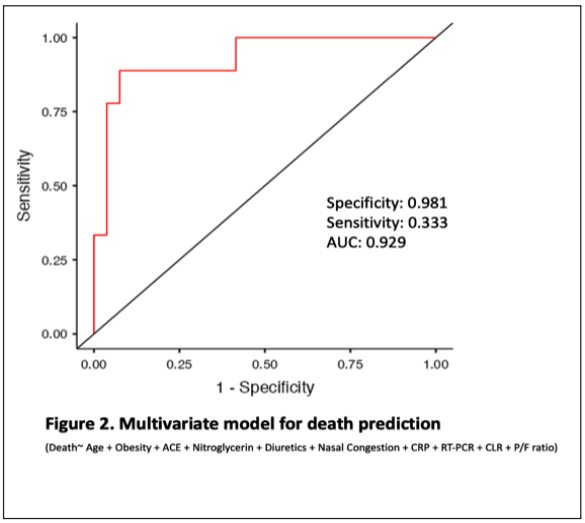

Figure 2. Graph presenting the multivariate model for death prediction.

AUC: area under the curve, ACE: angiotensin-converting enzyme, CRP: C-reactive protein, RT-PCR: reverse transcription polymerase chain reaction, CLR: CRP/ lymphocytes, P/F ratio: PaO_2 (arterial blood oxygen partial pressure)/FiO_2 (fraction of inspired oxygen) ratio

Likewise, LNR with a cut-off value of 0.231 served as an independent predictor for the need for escalation of respiratory support with HFNC use, dv-NLR could predict the need for escalation of respiratory support, while CLR with a value of 4.7 $*10^{-3}$ could serve as a predictor for death.

However, it should be highlighted that despite the verified accuracy of NLR in predicting the overall patient outcome, our study failed to identify any correlation between NLR and the need for escalation of respiratory support with HFNC, ICU admission, or death[19,24]. A possible explanation could be that the optimal NLR predictive value is reached at peak values compared to on-admission values. Although on-admission values of NLR may predict COVID-19 outcome, its predictive accuracy increases for a few days after admission when NLR reaches its peak[19,24]. Ullah et al[20] found that NLR values acquired during the seventh day after admission could accurately predict mortality and ICU admission.

Nevertheless, multivariate analysis showed that only LNR and PaO_2/FiO_2 on admission and LOH could be independent predictors for HFNC and only obesity for death. Regarding PaO_2/FiO_2 on admission, it seems that it serves as a reliable prognostic marker for patients suffering from COVID-19. With a cut-off value <274 mmHg, the performance of this biomarker proves to be more than satisfactory (71.79 % sensitivity and 85.25 % specificity)[25]. Our study used a cut-off value of <300 mmHg -based on existing guidelines- and PaO_2/FiO_2 was found to be an independent predictor for escalation of respiratory support with an AUC of 0.757. In addition, Sinatti et all[25] found that PaO_2/FiO_2 was more reliable and useful in identifying patients who required closed respiratory monitoring or more aggressive treatment when compared with CRP, NLR, PLR, and LDH. Based on our results, a future analysis of PaO_2/FiO_2 with LNR seems reasonable.

Several large cohorts have proved the association of LOH and escalation to HFNC with respiratory failure, acute respiratory distress syndrome, and admission to ICU[26,27]. In our study, the mean LOH was eight days (IQR: 4.5), and it was independently associated with HFNC use (OR: 1.717, 95 % CI: 1.274-2.314). Moreover, obesity was the only and most influential independent predictor for death. From the early stages of the COVID-19 pandemic, obesity has been identified as a critical risk factor for severe COVID-19 manifestations. In a recent study from Hungary, obesity was also specified as the most significant risk factor for death and ICU admission, even in younger patients <65 years old. The authors stated that a possible explanation could be the higher rates of obesity in the 40-64 age subgroup. However, in elderly patients, although the effect of obesity on mortality was lower, its negative effect on ICU admission and the need for respiratory support was the same. The authors concluded that it is mandatory to accurately facilitate BMI calculation along with phenotype obesity screening, "allowing a more accurate and detailed risk assessment regarding the effects of obesity"[28].

Lastly, although none of the investigated biomarkers was proven predictive for ICU admission, nasal congestion was the single and more important predictor. In a recent study from Skourtis et al[29], nasal congestion was recognized as a "non-typical symptom" of COVID-19 along with rhinorrhea, gastrointestinal symptoms, etc. On the other hand, fever, cough, shortness of breath, and

Table 3: Univariate analysis of predictors for high-flow nasal cannula use, admission to intensive care unit, and death.

			HFNC/VENTURI				ICU				Death			
Parameter	**Reference**	**Comparator**	**Odds ratio (95 % CI)**	**Cut-off Value**	**Sensitivity/ Specificity**	**AUC**	**Odds ratio (95 % CI)**	**Optimal cut-off Value**	**Sensitivity/ Specificity**	**AUC**	**Odds ratio (95% CI)**	**Optimal cut-off value**	**Sensitivity/ Specificity**	**AUC**
Age (years)			1.09 (0.99 - 1.045)		0.56 / 0.54	0.580	1.02 (0.97 - 1.06)	61	0.625 / 0.0560	0.589	1.08 (1.02 - 1.14)	67	0.66 / 0.71	0.777
Length of hospitalization (days)			1.44 (1.22 - 1.63)		0.514 / 0.91	0.806	1.08 (0.98 - 1.19)	10	0.625 / 0.654	0.661	0.96 (0.86 - 1.13)	9	0.44 / 0.56	0.499
Gender	Male	Females	0.74 (0.33 - 1.66)	(-)	0.577 / 0.351	0.536	0.83 (0.20 - 3.93)	(-)	0.375 / 0.60	0.487	1.22 (0.31 - 4.80)	(-)	0.57 / 0.40	0.524
Smoking	No	Yes	0.52 (0.19 - 1.44)	(-)	0.269 / 83.8	0.554	0.44 (0.05 - 3.78)	(-)	0.76 / 0.125	0.559	0.39 (0.046 - 3.22)	(-)	0.11 / 0.75	0.567
Alcohol	No	Yes	1.77 (0.45 - 7.017)	(-)	0.06 / 0.89	0.522	0.00 (0.00 - Inf)	(-)	0.92 / 0.00	0.542	0.0 (0.0 - Inf)	(-)	0.00 / 0.91	0.542
Comorbidities														
Arterial Hypertension	No	Yes	1.15 (0.52 - 2.55)	(-)	0.397 / 0.568	0.517	0.45 (0.08 - 2.38)	(-)	0.58 / 0.25	0.585	1.09 (0.48 -7.50)	(-)	0.55 / 0.60	0.580
Dyslipidaemia	No	Yes	1.55 (0.68 - 3.54)	(-)	0.282 / 0.622	0.548	0.71 (0.13 - 3.73)	(-)	0.68 / 0.25	0.534	1.85 (0.46 - 7.34)	(-)	0.44 / 0.70	0.571
Diabetes Mellitus	No	Yes	0.74 (0.218 - 2.49)	(-)	0.141 / 0.892	0.516	0.00 (0.00 - Inf)	(-)	0.86 / 0.00	0.570	0.82 (0.09 -7.07)	(-)	0.11 / 0.87	0.510
Coronary Artery Disease	No	Yes	0.952 (0.30 - 2.97)	(-)	0.141 / 0.865	0.503	0.00 (0.00 - Inf)	(-)	0.85 / 0.00	0.575	1.87 (0.35 - 9.96)	(-)	0.22 / 0.87	0545
COPD	No	Yes	1.067 (0.09 - 12.28)	(-)	0.02 /0.973	0.497	0.00 (0.00 - Inf)	(-)	0.97/ 0.00	0.514	0.0 (0.0 - Inf)	(-)	0.00 / 0.97	0.514
Bronchial asthma	No	Yes	0.95 (0.30 - 2.97)	(-)	0.077 / 0.914	0.499	4.76 (0.80 - 28.08)	(-)	0.93/ 0.25	0.592	4.04 (0.70 - 23.21)	(-)	0.22 / 0.93	0.578
Heart failure	No	Yes	1.056 (0.09 - 12.06)	(-)	0.026 / 0.973	0.515	0.00 (0.00 - Inf)	(-)	0.97/ 0.00	0.514	6.5 (0.53 - 79.65)	(-)	0.11 / 0.98	0.546
Atrial fibrillation	No	Yes	1.059 (0.25 - 4.49)	(-)	0.077 / 0.919	0.502	0.00 (0.00 - Inf)	(-)	0.92/ 0.00	0.542	1.53 (0.16 - 13.82)	(-)	0.11 / 0.95	0.518
Chronic kidney disease	No	Yes	0.00 (0.00 - Inf)	(-)	0.051 / 1.00	0.526	0.00 (0.00 - Inf)	(-)	0.96/ 0.00	0.519	0.0 (0.0 - Inf)	(-)	0.00 / 0.96	0.529
Active malignancy	No	Yes	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	
Obesity	No	Yes	2.464 (0.88 - 6.864)	(-)	0.115 / 0.757	0.564	3.68 (0.79 - 17.03)	(-)	0.86 / 0.37	0.617	5.25 (1.26 - 21.96)	(-)	0.44 / 0.87	0.656
Immunosuppression	No	Yes	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	
Pharmacotherapy														
ACE inhibitors	No	Yes	2.812 (0.986 - 8.024)	(-)	0.103 / 0.757	0.570	2.04 (0.37 - 11.09)	(-)	0.86 / 0.25	0.555	5.72 (1.35 -24.09)	(-)	0.44 / 0.88	0.661
ATII antagonists	No	Yes	0.725 (0.274 - 1.915)	(-)	0.244 / 0.811	0.527	0.00 (0.00 - Inf)	(-)	0.76 / 0.25	0.621	0.97 (0.19 - 5.01)	(-)	0.22 / 0.77	0.502
Ca2+ antagonists	No	Yes	0.5 (0.1 - 2.481)	(-)	0.103 / 0.946	0.524	0.00 (0.00 - Inf)	(-)	0.91 / 0.00	0.547	3.5 (0.62 - 19.7)	(-)	0.44 / 0.75	0.573
B-blockers	No	Yes	0.872 (0.354 - 2.151)	(-)	0.269 / 0.757	0.513	1.78 (0.398 - 7.94)	(-)	0.75 / 0.375	0.561	2.46 (0.61 - 9.85)	(-)	0.22 / 0.98	0.600
Nitrates	No	Yes	6.79 (0.682 - 67.689)	(-)	0.013 / 0.919	0.534	0.00 (0.00 - Inf)	(-)	0.96 / 0.00	0.519	14. 85 (1.81 - 121. 8)	(-)	0.222 / 0.981	0.602
Diuretics	No	Yes	1.68 (0.612 - 4.611)	(-)	0.14 / 0.784	0.538	1.76 (0.32 - 9.49)	(-)	0.84 /0.25	0.546	8.21 (1.97 - 34.32)	(-)	0.57 / 0.88	0.712
Bronchodilators	No	Yes	0.537 (0.14 - 2.056)	(-)	0.14 / 0.919	0.530	1.03 (0.11 - 9.09)	(-)	0.88 / 0.125	0.502	0.89 (0.10 - 7.74)	(-)	0.11 / 0.88	0.506
Anticoagulants	No	Yes	0.895 (0.218 - 3.676)	(-)	0.09 / 0.919	0.504	0.00 (0.00 - Inf)	(-)	0.91 / 0.00	0.547	1.34 (0.15 - 12.02)	(-)	0.11 / 0.91	0.513
Antiplatelets	No	Yes	0.859 (0.279 - 2.648)	(-)	0.154 / 0.865	0.509	0.81 (0.09 - 7.05)	(-)	0.85 /0.25	0.512	1.73 (0.32 - 9.15)	(-)	0.22 / 0.86	0.540
Lipid lowering drugs	No	Yes	1.652 (0.719 - 3.795)	(-)	0.269 / 0.622	0.555	0.74 (0.14 - 3.90)	(-)	0.69 /0.25	0.529	1.93 (0.48 - 7.62)	(-)	0.44 / 0.71	0.576
Insulin	No	Yes	0.00 (0.00 - Inf)	(-)	0.013 / 1.00	0.506	0.00 (0.00 - Inf)	(-)	0.99 / 0.00	0.505	0.0 (0.0 - Inf)	(-)	0.00 / 0.99	0.505
Oral antibiabetics	No	Yes	0.738 (0.218 - 2.496)	(-)	0.141 / 0.892	0.516	0.00 (0.00 - Inf)	(-)	0.86 / 0.00	0.570	0.82 (0.09 - 7.07)	(-)	0.011 / 0.87	0.510
Presentation														
Systolic arterial pressure (mmHg)			0.987 (0.957 - 1.017)	(-)	1.0/0.0	0.556	1.017 (0.962 -1.077)	(-)	1.0/0.0	0.555	1.001 (0.949 - 1.055)	(-)	1.0/0.0	0.553
Heart rate (bpm)			1.007 (0.977 - 1.038)	(-)	1.0/0.0	0.525	1.002 (0.947 -1.059)	(-)	1.0/0.0	0.484	1.013 (0.962 - 1.066)	(-)	1.0/0.0	(-)
PaO2/FiO2 ratio			0.967 (0.952 - 0.983)	(-)	0.949/0.405	0.757	0.993 (0.977 -1.008)	(-)	1.0/0.0	0.654	0.983 (0.970 - 0.998)	(-)	1.0/0.0	0.7.35
Fever	No	Yes	0.453 (0.08 - 2.36)	(-)	0.962 / 0.081	0.521	Inf (0.0 - Inf)	(-)	0.06 / 100	0.528	0.39 (0.04 - 3.81)	(-)	0.89 / 0.05	0.532
Dyspnoea	No	Yes	2.83 (1.23 - 6.52)	(-)	0.23 / 0.54	0.614	0.30 (0.03 - 2.59)	(-)	0.68 / 0.125	0.596	0.63 (0.12 - 3.21)	(-)	0.22 / 0.89	0.545
Cough	No	Yes	1.69 (0.771 - 3.74)	(-)	0.436 / 0.432	0.566	3.55 (0.68 -18.39)	(-)	0.54 / 0.75	0.646	2.32 (0.55 - 9.79)	(-)	0.67 / 0.54	0.602
Pharyngeal pain	No	Yes	0.406 (0.05 -3.601)	(-)	0.064 / 0.97	0.519	0.00 (0.00 - Inf)	(-)	0.94 / 0.0	0.528	2.52 (0.26 - 24.30)	(-)	0.11 / 0.93	0.532
Nasal congestion	No	Yes	3.353 (0.536 - 20.99)	(-)	0.026 / 0.919	0.528	11.5 (1.61 - 82.8)	(-)	0.97 / 0.25	0.611	9.81 (1.40 - 68.68)	(-)	0.22 / 0.97	0.597
Weakness	No	Yes	0.625 (0.284 - 1.37)	(-)	0.603 / 0.514	0.558	0.75 (0.18 - 2.17)	(-)	0.43 / 0.50	0.535	0.590 (0.15 - 2.32)	(-)	0.44 / 0.45	0.566
Headache	No	Yes	0.781 (0.256 – 2.383)	(-)	0.167 / 0.865	0.516	0.756 (0.09 – 6.55)	(-)	0.84 / 0.125	0.517	0.0 (0.0 - Inf)	(-)	0.00 / 0.83	0.585
Confusion	No	Yes	4.4 (0.386 – 50.15)	(-)	0.013 / 0.946	0.521	0.00 (0.00 – Inf)	(-)	0.97 / 0.0	0.514	0.0 (0.0 - Inf)	(-)	0.00 / 0.97	0.514
Muscle/Joint pain	No	Yes	0.677 (0.257 – 1.78)	(-)	0.256 / 0.811	0.534	0.451 (0.05 – 3.78)	(-)	0.75 / 0.125	0.559	0.0 (0.0 - Inf)	(-)	0.00 / 0.74	0.627
Chest pain	No	Yes	0.834 (0.154 – 4.515)	(-)	0.064 / 0.946	0.505	0.00 (0.00 – Inf)	(-)	0.935 / 0.00	0.553	0.0 (0.0 - Inf)	(-)	0.00 / 0.93	0.533
Abdominal pain	No	Yes	0.00 (0.00 – Inf)	(-)	0.026 / 1.0	0.513	0.00 (0.00 – Inf)	(-)	0.98 / 0.00	0.509	0.0 (0.0 - Inf)	(-)	0.00 / 0.98	0.509
Nausea/Vomiting	No	Yes	0.895 (0.218 – 3.676)	(-)	0.09 / 0.919	0.504	1.55 (0.17 -14.09)	(-)	0.92 / 0.125	0.520	0.0 (0.0 - Inf)	(-)	0.00 / 0.96	0.547
Diarrhoea	No	Yes	1.379 (0.516 – 3.688)	(-)	0.167 / 0.784	0.525	1.54 (0.281 – 8.245)	(-)	0.82 / 0.25	0.536	0.53 (0.063 - 4. 54)	(-)	0.11 / 0.81	0.539
Labs on admission														
WBC			1.00 (0.99 – 1.00)	$5.1*10^3$	0.459 / 0.448	0.506	1.00 (0.99 – 1.00)	$4.8*10^3$	0.50 / 0.41	0.378	1.0 (0.99 - 1.0)	$5*10^3$	0..44 / 0.45	0.453
Neutrophiles			1.00 (0.99 – 1.00)	$3.7*10^3$	0.513 / 0.538	0.558	1.00 (0.99 – 1.00)	$3.5*10^3$	0.50 / 0.49	0.418	1.0 (0.99 - 1.0)	$3.6*10^3$	0.55 / 0.50	0.484
Lymphocyte			1.00 (0.99 – 1.00)	880	0.43 / 0.42	0.372	0.99 (0.99 – 1.00)	850	0.375 / 0.47	0.357	1.0 (0.99 - 1.0)	890	0.44 / 0.47	0.376
Platelets			1.00 (0.99 – 1.00)	$1.8*10^5$	0.513 / 0.487	0.471	1.0 (0.99 – 1.00)	150.000	0.50 / 0.49	0.341	1.0 (0.99 - 1.0)	$185*10^3$	0.56 / 0.54	0.450
CRP			1.25 (1.11 – 1.42)	3.2	0.702 / 0.705	0.740	1.05 90.94 – 1.176)	3.45	0.62 / 0.62	0.630	1.11 (1.0 - 1.24)	4.83	0.67 / 0.75	0.673
RT-PCR			0.988 (0.910 – 1.07)	20.27	0.48 / 0.46	0.468	0.90 (0.75 – 1.07)	20.1	0.50 / 0.44	0.369	0.829 (0.688 - 0.999)	20.15	0.44/0.44	0.701
NLR			1.035 90.964 – 1.12)	4.431	0.54 / 0.56	0.633	0.94 (0.76 – 1.16)	4.31	0.50 / 0.49	0.509	1.02 (0.92 - 1.14)	4.32	0.55 / 0.50	0.594
LNR			0.015 (0.00 – 0.35)	0.231	0.46 / 0. 46	0.367	0.196 (0.002 – 20.6)	0.231	0.62 / 0.50	0.491	0.0 (0.0 - Inf)	0.232	0.55 / 0.50	0.406
PLR			1.00 (0.99 – 1.00)	203	0.54 / 0.55	0.578	0.99 (0.99 – 1.00)	198.3	0.50 / 0.50	0.487	1.00 (0.99 - 1.00)	220	0.66 / 059	0.570
dv-NLR (N/WBC-L)			$5*10^8$ (26.7 – $9*10^9$)	0.90	0.594 / 0.60	0.678	22.1 (0.00 – Inf)	0.91	0.75 / 0.71	0.644	0.0 (0.0 - Inf)	0.91	0.67 / 0.67	0.611
dv-LNR (L/WBC-N)			0.99 (0.05 -21.38)	0.69	0.567 / 0.576	0.517	3.84 (0.01 – 1392)	0.71	0.62 / 0.62	0.571	0.09 (0.00 - 14.1)	0.697	0.56 / 0.56	0.481
CLR (CRP/L)			$7*10^{58}$ ($3*10^{25}$ – $2*10^{92}$)	0.004	0.65 / 0.731	0.742	Inf (0.00 – Inf)	0.004	0.75 / 0.63	0.66	$3.2*10^{33}$ (5.8 - $1.8*10^{66}$)	$4.7*10^{-2}$	0.66 / 0.77	0.720

HFNC: high-flow nasal cannula, ICU: intensive care unit, COPD: chronic obstructive pulmonary disease, ACE: angiotensin-converting enzyme, ATII: angiotensin II receptor, WBC: white blood count, CRP: C-reactive protein, RT-PCR: reverse transcription polymerase chain reaction, N: neutrophils, L: lymphocyte, P: platelets, NLR: neutrophils/lymphocytes, PLR: platelets/ lymphocytes, dv-NLR: (derived variation of)-NLR, LNR: lymphocytes/ neutrophils, dv-LNR: (derived variation of)- LNR, CLR: CRP/ lymphocytes P/F ratio: PaO_2 (arterial blood oxygen partial pressure)/FiO_2 (fraction of inspired oxygen) ratio.

Table 4: The multivariate analysis showing that the length of hospitalization, neutrophils to lymphocyte ratio, and the PaO_2 (arterial blood oxygen partial pressure)/FiO_2 (fraction of inspired oxygen) ratio at admission constituted valuable predictors of high-flow nasal cannula use.

Model Coefficients - HFNC							
						95 % Confidence Interval	
Predictor	**Estimate**	**SE**	**Z**	**p**	**Odds ratio**	**Lower**	**Upper**
Intercept	2.893	3.651	0.792	0.428	18.040	0.014	23108.668
CRP	0.211	0.143	1.483	0.138	1.235	0.934	1.634
Length of Hospitalization	0.540	0.152	3.548	< .001	1.717	1.274	2.314
Dyspnoea 1 – 0	-0.493	0.724	-0.682	0.495	0.611	0.148	2.522
LNR	-8.688	4.015	-2.164	0.030	1.686e0-4	6.441e00-8	0.441
dv-NLR	5.416	3.229	1.677	0.094	224.900	0.401	126137.448
CLR	-53.480	103.102	-0.519	0.604	5.944e-24	1.032e-111	3.425e+64
PaO_2/FiO_2 on admission	-0.036	0.013	-2.864	0.004	0.965	0.941	0.989

Estimates represent the log odds of "HFNC = 1" vs. "HFNC = 0"; HFNC: high-flow nasal cannula, CRP: C-reactive protein, LNR: lymphocytes/ neutrophils, dv-NLR: (derived variation of)-NLR (neutrophils/ lymphocytes), CLR: CRP/ lymphocytes, P/F ratio: PaO_2 (arterial blood oxygen partial pressure)/FiO_2 (fraction of inspired oxygen) ratio.

Table 5: The multivariate analysis showing that obesity constituted a viable predictor of death.

Model Coefficients - DEATH							
						95 % Confidence Interval	
Predictor	**Estimate**	**SE**	**Z**	**p**	**Odds ratio**	**Lower**	**Upper**
Intercept	-4.055	5.939	-0.683	0.495	0.017	1.527e0-7	1970.064
Age	0.053	0.046	1.161	0.246	1.054	0.964	1.153
Obesity (BMI >30): 1 - 0	2.351	1.148	2.048	0.041	10.498	1.107	99.572
ACE: 1 - 0	1.137	1.162	0.978	0.328	3.116	0.320	30.369
Nitroids: 1 - 0	1.529	1.556	0.983	0.326	4.614	0.219	97.389
Diouretics: 1 - 0	0.655	1.020	0.642	0.521	1.924	0.261	14.200
Nasal Congestion: 1 - 0	2.046	1.572	1.302	0.193	7.739	0.355	168.470
CRP	0.088	0.113	0.778	0.436	1.092	0.875	1.363
RT-PCR	-0.197	0.145	-1.356	0.175	0.822	0.618	1.091
CLR	10.293	100.191	0.103	0.918	29522.422	1.541e-81	5.656e+89
PaO_2/FiO_2 on admission	-1.603e−4	0.012	-0.013	0.989	1.000	0.977	1.024

Estimates represent the log odds of "DEATH = 1" vs. "DEATH = 0"; BMI: body mass index, ACE: angiotensin-converting enzyme, CRP: C-reactive protein, RT-PCR: reverse transcription polymerase chain reaction, CLR: CRP/ lymphocytes, P/F ratio: PaO_2 (arterial blood oxygen partial pressure)/FiO_2 (fraction of inspired oxygen) ratio.

fatigue-weakness were classified as "typical symptoms". In a cohort of 570 patients, a higher proportion of patients with "non-typical symptoms", such as nasal congestion, were linked to a milder disease with fewer hospital and ICU admission rates. However, it should be noted that the rate of nasal congestion in this single-center study was only 6.7 % compared to 76.3 % for fever and 29.1 % for cough and that the authors stated that "non-typical symptoms" are asked less frequently during medical history when compared to "typical symptoms" because they are considered to be of less clinical importance[29].

To the best of our knowledge, this is the first study to examine the association of CRP, NLR, LNR, PLR, dv-NLR, and CLR with the need to escalate respiratory support with HFNC use, ICU admission and death in hospitalized patients with severe COVID-19 disease in Greek population. However, our study has several significant limitations. Firstly, it is a retrospective study with a relatively small sample size from a single center that could justify why none of the investigated biomarkers was prognostic for ICU admission or why after multivariate analysis, CRP and CLR were outnumbered by obesity. Nevertheless, all the included data were prospectively collected. Secondly, we did not carry out specific measures of inflammatory mediators such as interleukins because such an investigation was out of the scope and the basic idea of this study which was to investigate widely available biomarkers based on routinely performed parameters in everyday clinical practice, simple to be calculated, fast to be obtained and inexpensive. In addition, our study was solely based on data available in the patients' Hospital files. No additional lab tests, such as Interleukin levels, were included since they are not routinely measured at our hospital. Thirdly, although all blood samples were obtained upon admission, not all patients were on the same day from the symptom onset. Nonetheless, all data were acquired prospectively. Equally important, our study could have omitted several other clinical parameters, but we limited our recordings to the purpose of our study aim.

Future multicenter, large-scale prospective experimental studies would be worthy, as the above-investigated biomarkers are simple, fast, inexpensive, and widely available. Their use could help simplify the risk stratification of severe COVID-19 infection on admission and point out the subgroup of patients requiring closer surveillance. Moreover, further

experimental studies, including several laboratory values, such as interleukin, would be useful, along with composite studies in the form of meta-analyses or systematic reviews. Finally, based on the suggestion by Lua et al[14] identifying several simple to obtain, inexpensive, and widely available biomarkers, as those utilized in this study, along with clinical predictors such as obesity, might be the first step to develop a severity of disease classification/scoring system. This instrument could serve as a morbidity and/or mortality estimation tool that could be of utmost importance to guarantee prompt and timely treatment.

Conclusion

LNR and PaO_2/FiO_2 on admission could be used to timely identify patients requiring HFNC during hospitalization, while obesity could serve as an independent predictor of death. LOH is also a significant predictor for HFNC use. Nasal congestion seems to be a unique predictor for ICU admission. A large-scale multicenter cohort study might help to extract more significant conclusions regarding the utility of simple, easy-to-calculate, and inexpensive biomarkers in patients suffering from severe COVID-19.

Conflicts of interest

The authors declare that there is no conflict of interest.

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