Dynamic NLR and PLR in predicting Covid-19 severity: a retrospective cohort study

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Article

Keywords: Covid19, NLR, PLR, trend, cutoff, prognosis, mortality, invasive ventilation, CPAP, ICU

Posted Date: April 19th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1323528/v2>

Abstract

Background: the hyperinflammation phase of severe SARS-CoV-2 is characterized by complete blood count alterations. In this context, the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) can be used as prognostic factors. We study NLR and PLR trends at different timepoints and compute optimal cutoffs to predict four outcomes: use of Continuous Positive Airways Pressure (CPAP), ICU admission, invasive ventilation and death.

Methods: we retrospectively included all adult patients with SARS-CoV-2 pneumonia admitted from 23rd January 2020 to 18th May 2021. Data were extracted using ICD9 codes and our Covid-19 registry. Analyses included descriptive statistics and non parametric tests to study the ability of NLR and PLR to distinguish the patients' outcomes at each timepoint. ROC curves were built for NLR and PLR at each timepoint (minus discharge) in order to identify cutoffs to distinguish severe and non severe disease and their statistical significance was assessed with the Chi-square test. NLR and PLR were compared with DeLong's test.

Results: we included 2169 patients. NLR and PLR were higher in severe Covid-19 at all the timepoints, with a difference that gets bigger and a trend that is steeper in more severe disease. Both ratios were able to distinguish the outcomes at each timepoint. For NLR, the areas under the curve (AUROC) ranged between 0.59 and 0.81, for PLR, between 0.53 and 0.67. From each ROC curve we computed an optimal cutoff value (e.g. NLR 7 for CPAP for males at admission). NLR performed better than PLR.

Conclusion: our results are in line with other studies that computed NLR and PLR trends and values in disease, especially with those that distinguished between different grades of severity.

Our study is retrospective and single centre, and is limited by selection bias, but includes more than 2000 patients, thus limiting the confounding factors and outliers.

Our cutoffs do not only deal with severity and mortality but allow for a more tailored approach. Future prospect include validating our cutoffs in a prospective cohort and comparing their performance against other Covid19 scores.

Background

Early in the SARS-COV-2 pandemic, Siddiqi et al proposed a model on the natural history of SARS-CoV-2 that comprises a viral and an inflammatory phase and three stages: early infection, which presents with systemic, mild symptoms, pulmonary stage, when pneumonia and local inflammation develops, and systemic hyperinflammation, that concerns only the minority of patients who progress to severe illness with multiorgan involvement¹.

Several markers have been proposed to identify the progression toward this last stage, and C Reactive Protein (CRP), D-dimer, lactate dehydrogenase (LDH), troponin I, leucocytes alterations and thrombocytopenia have already been confirmed of prognostic significance²⁻³. Leucocytes alterations concern mainly the lymphocytes population, with CD4 and CD8 T-cells loss, which has been linked to an amplified inflammatory response. Neutrophilia is also correlated to disease severity, probably because of its immunosuppressive and pro-thrombotic properties⁴.

In this context, the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) could be used as prognostic factors. Thanks to their availability, low cost and reproducibility they already have been proposed as inflammatory and prognostic markers in a variety of specialties (traumatic brain injury, cardiovascular diseases,

hepatic and pancreatic diseases, solid cancer, rheumatic diseases and chronic obstructive pulmonary diseases)⁵⁻⁶⁻⁷⁻⁸⁻⁹⁻¹⁰.

Several studies have shown a similar trend in Covid-19. Three small Chinese studies performed early in the pandemic demonstrated that a high NLR correlated to severity and risk of progression¹¹⁻¹²⁻¹³. Subsequent studies confirmed this finding, adding that an upward trend correlated with mortality, and that peak NLR is also associated to mechanical ventilation¹⁴⁻¹⁵⁻¹⁶. A large meta-analysis including 30 studies and 5570 patients confirmed that NLR accurately determines Covid-19 severity¹⁷.

Similarly, several studies have determined that a baseline low platelet count and a downward trend are associated with severe Covid19¹⁸⁻¹⁹. Studies that focus specifically on PLR are scant, but demonstrate that a high PLR is associated with longer hospital stay and a more severe disease, as is a big PLR increase during treatment²⁰⁻²¹.

Methods

Aim. To describe NLR and PLR trend at different timepoints during the hospital stay of Covid19 patients and to compute an optimal cutoff for each timepoint to predict the risk of four outcomes: use of mechanical non-invasive ventilation (in the form of Continuous Positive Airways Pressure - CPAP), ICU admission, invasive ventilation and death. For each cutoff, we will also produce a Receiver Operating Characteristic (ROC) curve and we will compute the Area Under the Curve (AUROC), the sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV). Finally, we will compare NLR and PLR performance as predictors.

Design and setting. This is a cohort retrospective study, conducted at the Fondazione IRCCS Policlinico San Matteo (Pavia, Italy), an academic hospital. All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Eligibility. All adult patients (older than 18 years old) with a laboratory confirmed SARS-CoV-2 pneumonia who were admitted to the hospital from 21st February 2020 to 18th May 2021 were included in the study. Patients without at least one value of neutrophils, lymphocytes and platelets were excluded. All patients provided informed consent for the use of clinical data for scientific purpose according to hospital policy.

Data and variables. Administrative data about our hospital's Covid-19 patients are collected in a registry (SMACORE), approved by the Fondazione IRCCS Policlinico San Matteo's ethics committee with protocol number 20200046877, within the framework of the PERISCOPE (Pan-European Response to the ImpactS of COVID-19 and future Pandemics and Epidemics) European project, funded by Horizon 2020 (grant agreement: 101016233). Data extracted from the database include epidemiological data (age and gender), duration of hospital stay and wards of stay. Data were anonymized before use. No missing data were detected in all the extracted variables.

Outcome data include ICU stay, death, use of intubation/tracheostomy/invasive ventilation and non invasive mechanical ventilation (CPAP). ICD9 codes were used to identify patients who underwent intubation (96.04, 96.05), tracheostomy (31.1), invasive ventilation (96.70, 96.71, 96.72) and non invasive mechanical ventilation (93.90). In the context of this study, intubation, tracheostomy and invasive ventilation are considered under a single outcome called "invasive ventilation".

Laboratory data, extracted from patients' records, include neutrophil, lymphocyte and platelet count. Laboratory data were extracted at four timepoints: admission (0-24 hours), 48 hours (24-72 hours), 7 days (120-216 hours), discharge (within the last 48 hours before discharge). If more than one value of neutrophils, lymphocytes and platelets were present for each timepoint, the mean value was used to compute NLR and PLR.

Statistical analyses. Categorical data are presented as absolute frequencies and proportions. Continuous data are presented by mean and 95% confidence interval.

To study the ability of NLR and PLR to distinguish the patients' outcomes at each timepoint, a non-parametric (U-Mann-Whitney) test was used (univariate analysis).

ROC curves were built for NLR and PLR at each timepoint (minus discharge) for males and females in order to identify a cutoff to distinguish severe and non severe disease. We defined our optimal cutoff as the NLR or PLR value with the highest sensibility and a minimum specificity of 0.5, in order to have the smallest possible number of false negatives. The statistical significance of the cutoff values was assessed with the Chi-square test.

We also compared NLR and PLR ROC curves to define which is the best predictor of each outcome at the four timepoints with DeLong's test.

All statistical tests were two-sided and a p value of 0.05 was used.

Data preprocessing, descriptive analysis and univariate analyses were handled with Python 3.7.

ROC curves and multivariate analyses were performed on R 4.0.5.

Results

Population. We found 2204 eligible patients. Readmissions were excluded, generating a total of 2169 patients. The mean age at admission was 68 ± 16 years; 1317 were males (60.7%). Figure 1 correlates the number of patients with age at admission and gender.

Distribution of length of stay (LOS) is shown in Figure 2. The mean LOS was 12 ± 13 days, the maximum was 141.

The number of patients with available NLR and PLR at each timepoint is described in Table 1.

Outcomes. The prevalence of each outcome (CPAP, ICU admission, invasive ventilation and death) in the population, reported also by gender, is shown in Table 2.

NLR and PLR trend. The mean NLR and PLR trends at the four timepoints are shown in Figure 3. Both NLR and PLR are higher in males than in females, but while NLR decreases during hospitalization in both genders, PLR decreases in males but remains stable in females.

The trends at the four timepoints for each outcome are shown in Figure 4. The red lines show the trend of patients who had severe Covid-19 (patients who underwent invasive or non-invasive ventilation, patients who were admitted to the ICU and patients who died), while the blue lines show the trend of patients who had non-severe Covid-19.

Both NLR and PLR are always higher in severe Covid-19 at all the timepoints, with a gap that gets bigger the more severe the disease is. From admission, both NLR and PLR show a progressive increase reaching a peak at 7 days. This trend is steeper for more severe outcomes. There are two exceptions to this: NLR and PLR trends for the CPAP

outcome, which increase from admission to 48 hours, decreases slightly from 48 hours to 7 days and plummets to the discharge. This could be explained by the fact that CPAP therapy is usually implemented in the first hours after admission and rarely as late as the seventh day of hospitalization. The second exception is the NLR trend for the death outcome: the red line continually increases, diverging from the blue line that shows the normalization of NLR of patients who survived.

Univariate analyses. NLR and PLR values for the first three timepoints were able to distinguish between the outcomes at each timepoints, with the exception of PLR at admission that cannot predict ICU admission. NLR and PLR at discharge distinguishes between patients who died and patients who survived. The results are shown in Table 3.

Cut-off analyses (ROC curves). The results of ROC curves' analyses for NLR and PLR values for males and females are shown in Tables 4 and 5, while Figure 5 show composite ROC curves with Area Under the Curve (AUROC) values, where a higher number shows a better predictive performance. NLR performed better than PLR and males performed better than females. For NLR, the lowest AUROC is 0.59 for CPAP and ICU admission at the admission timepoint for males, while the highest is 0.81 for both genders for death at 7 days. For PLR, the lowest AUROC is 0.53 for death at admission for males, while the highest is 0.67 for CPAP at 48 hours for females and for invasive ventilation at 7 days for males.

From each ROC curve we computed an optimal cut-off value (tables 4 and 5). Each cut-off value is presented with sensitivity, specificity, accuracy, positive and negative predictive values (PPV and NPV respectively). For example, the cutoff for CPAP use at admission is 7.0 for males and 6.36 for NLR, and 239.22 for males and 233 for females for PLR. The cut-offs have been plotted in Figure 6 and 7, with their sensitivity, putting the outcomes in order of severity.

NLR and PLR comparison. The comparison of NLR and PLR ROC curves (figure 8) showed that NLR generally performs better, with comparable curves only in the CPAP outcome at admission and 7 days, and better NLR AUROC in all the other outcomes and timepoints.

Discussion

We showed that NLR and PLR are able to distinguish between the patients with mild/moderate Covid-19 and patients who had a severe disease (with need of non-invasive ventilation, ICU admission or invasive ventilation or patients who died). In fact, both ratio show higher values in the population with severe disease. A NLR that is continually increasing at successive timepoints, in particular, is able to predict death.

We also computed cut-offs for males and females for the four outcomes at each timepoint. Males NLR cutoff is higher than females of at least 1 point. Sensitivity is also higher in males. At each timepoint an "easy to remember" value (e.g. 6.3 and 7.0 at admission for females and males respectively, or 5.3 and 7.3 at 48 hours for males and females respectively) could be quite good at predicting all the outcomes, with a sensitivity that increases progressively at successive timepoints (the minimum is 0.61 for females at admission for ICU admission, the maximum 0.91 for males at 7 days for invasive ventilation). The positive predictive value are low, but the negative predictive values range from 0.73 to 0.98, making our cutoffs efficacious in excluding patients at risk if their NLR is lower. The same can be said for PLR cutoffs, even though, differently from NLR, they start out similar for males and females. Moreover, at a single timepoint, PLR cutoffs for the various outcomes can be quite different (e.g. 250 vs. 293 for males at 48 hours for CPAP and death respectively), possibly making it easier to distinguish different grades of severity.

Finally, we showed that NLR is generally better than PLR at predicting severity.

A Chinese study aimed at finding NLR and PLR reference values for healthy subjects showed that both are sex and age dependent²²; successive studies confirmed that this distinction is maintained in disease²³, in line with our findings.

Four Chinese studies plotted NLR and PLR from admission to post-discharge and obtained trends similar to ours, with lower and stable values for non-severe patients and higher and increasing values for severe patients¹⁴⁻²⁰⁻²⁴⁻²⁵.

Regarding the predictive value of the ratios and their cut-off, several studies plotted ROC curves for NLR and PLR, finding that they perform well in predicting severity and death, with NLR performing better than PLR in those studies that compared them¹²⁻¹⁴⁻¹⁵⁻²¹⁻²⁵⁻²⁶⁻²⁷. A Turkish study on 306 patients found that at admission NLR (but not PLR) significantly predicted Covid-19 pneumonia, and they computed a cutoff of 1.73²⁶. A similar study on 69 patients found a cutoff for severe disease of 3.3 for NLR and 180 for PLR, and another on 61 patients used 3.13 for NLR¹¹⁻²¹. All of these studies, however, did not aim at distinguishing severe from non-severe patients, but patients with or without pneumonia, which could explain the difference between their cut-offs and ours, that are much higher. In fact, a study which tried to distinguish different grades of severity (common cases, severe non-ICU patients and severe-ICU patients) found values of NLR and PLR that increase with severity, although they did not compute any cutoffs²⁵. A cutoff was actually computed by Ye et al, who found a NLR cutoff of 7.13 for death and 7.28 for invasive ventilation, both values that are very similar to our own²⁴. An Indian study limited to severe patients found a cutoff of 5.1 for mortality, but it did not specify at which point during hospitalization the NLR was extracted²⁵. Finally, Yldiz et al computed a 5.94 NLR cutoff on a derivation cohort for mortality and subsequently validated in a successive cohort²⁷.

All these studies have the limitation of being retrospective and limited to a single centre with no more than a few hundreds of patients. Our study presents the same limitations, but dealt with more than 2000 patients, thus limiting the confounding factors and outliers. We also divided our results for males and females, which we consider a strength as it takes into consideration the physiologic differences of NLR and PLR and adds a further level of stratification. Moreover, our cutoffs do not only deal with severity and mortality but allow for a more tailored approach, dividing severe patients in who can still be treated in an ordinary ward, possibly with the implementation of CPAP, and those who need early referral to the ICU.

Another limitation is selection bias, since we selected our patients and stratified them in severity grades based on ICD9 codes, which can be inaccurate.

Finally, another confounder could be the use of anti inflammatory or myelotoxic drugs, but this effect should be corrected by the number and the periodicity of observations. In fact, the greatest usefulness of the cutoffs lies in the admission and 48 hours timepoints, where the steroid-induced neutrophilia is not yet present.

Conclusion

Our study show that NLR and PLR can distinguish mortality, need for ventilation (non-invasive and invasive), and ICU admission, and their trend correlates with disease severity. We also computed male and female cutoffs (with good sensitivity and negative predictive values) for the various stages of severity at different timepoints during hospitalization. Our score is extremely handy and easy to compute, while many other proposed tools are difficult to measure or vary at different timepoints, which might explain their conflicting results. In fact, future prospect include validating our cutoffs in a prospective, possibly multi-centric cohort and comparing their performance against scores like the Quick Covid-19 Severity Index (qCSI), and the 4C Mortality Score.

Abbreviations

NLR: neutrophil to lymphocytes ratio

PLR: platelet to lymphocytes ratio

CPAP: continuous Positive airways pressure

ICU: intensive care unit

ROC: receiver operating characteristic

AUROC: area under the ROC curve

CRP: C reactive protein

LDH: laccate dehydrogenase

PPV: positive predictive value

NPV: negative predictive value

PERISCOPE: Pan-European Response to the ImpactS of COVID-19 and future Pandemics and Epidemics

IRB: internal review board

LOS: length of stay

qCS: Quick Covid-19 Severity Index

Declarations

Ethics approval and consent to participate. All patients provided informed consent for the use of clinical data for scientific purpose according to hospital policy. Collection of data under the SMACORE database was approved by the Fondazione IRCCS Policlinico San Matteo's ethics committee (protocol number 20200046877).

Consent for publication. Not applicable.

Availability of data or materials. The published article includes all datasets generated or analyzed during the study. Data sharing is available from the corresponding author upon reasonable request.

Competing interests. The authors declare that they have no competing interests.

Funding. This research was granted by the Pan-European Response to the ImpactS of COVID-19 and future Pandemics and Epidemics (PERISCOPE) H2020-SC1-PHE-CORONAVIRUS-2020-2 PERISCOPE Project (Grant agreement: 101016233).

Authors' contribution. Conceptualization, VZ, FMe, AL, AP and PS; Methodology, VZ, PS and EA; Formal Analysis, GA; Investigation, MS, TCP, MCa, MCo and LM; Resources, RB; Data Curation, GA; Writing – Original Draft Preparation, GA and EA; Writing – Review & Editing, VZ, PS, FMe, FMo and RB; Visualization, GA; Supervision, PS, FMo and RB. All authors read and approved the final manuscript.

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Tables

Table 1: number of patients with at least one available NLR and PLR value.

Timepoint	Number of patients
Admission	1948
48 hours	1981
7 days	1623
Discharge	1326

Table 2: prevalence of outcome in the population, divided in males and females.

Outcome	Total population	Males	Females
CPAP or NIV	0.285	0.334	0.21
ICU admission	0.167	0.22	0.084
Invasive ventilation	0.104	0.14	0.048
Death	0.253	0.264	0.234

Table 3: univariate tests on NLR and PLR values for each outcome at the four timepoints. P value is significant <0.05.

Timepoints	Outcome	pvalue for NLR	pvalue for PLR
Admission	CPAP or NIV	<0.001	<0.001
	ICU admission	0.021	0.081
	Invasive ventilation	<0.001	0.032
	Death	<0.001	<0.001
48 hours	CPAP or NIV	<0.001	<0.001
	ICU admission	<0.001	<0.001
	Invasive ventilation	<0.001	<0.001
	Death	<0.001	<0.001
7 days	CPAP or NIV	<0.001	<0.001
	ICU admission	<0.001	<0.001
	Invasive ventilation	<0.001	<0.001
	Death	<0.001	<0.001
Discharge	CPAP or NIV	0.35	<0.001
	ICU admission	0.95	0.071
	Invasive ventilation	<0.001	0.23
	Death	<0.001	<0.001

Table 4: results of the ROC curve analyses for NLR for males and females.

	Timestep	Outcome	Cut-off	Sensitivity	Specificity	Accuracy	AUROC	PPV
Males	Admission	CPAP or NIV	7	0.65	0.51	0.55	0.59	0.41
		ICU admission	7.2	0.64	0.50	0.53	0.59	0.27
		Invasive ventilation	7.29	0.67	0.50	0.53	0.62	0.19
		Death	7	0.66	0.50	0.55	0.60	0.33
	48h	CPAP or NIV	7.33	0.69	0.50	0.57	0.63	0.42
		ICU admission	7.47	0.77	0.51	0.57	0.68	0.33
		Invasive ventilation	7.66	0.84	0.50	0.55	0.71	0.23
		Death	7.27	0.77	0.50	0.57	0.70	0.35
	7days	CPAP or NIV	6.17	0.67	0.50	0.56	0.61	0.42
		ICU admission	5.67	0.85	0.50	0.59	0.73	0.38
		Invasive ventilation	6.03	0.91	0.50	0.57	0.78	0.28
		Death	6.03	0.88	0.51	0.59	0.81	0.33
Females	Admission	CPAP or NIV	6.36	0.62	0.51	0.53	0.60	0.27
		ICU admission	6.61	0.61	0.50	0.51	0.60	0.11
		Invasive ventilation	7	0.67	0.55	0.55	0.63	0.07
		Death	6.28	0.66	0.51	0.55	0.62	0.31
	48h	CPAP or NIV	5.57	0.72	0.50	0.55	0.66	0.30
		ICU admission	5.87	0.82	0.50	0.53	0.68	0.14
		Invasive ventilation	6.05	0.76	0.51	0.52	0.69	0.08
		Death	5.35	0.77	0.5	0.56	0.71	0.31
	7days	CPAP or NIV	4.82	0.72	0.50	0.56	0.65	0.31
		ICU admission	5.15	0.81	0.53	0.56	0.71	0.19
		Invasive ventilation	5.38	0.87	0.54	0.56	0.75	0.12
		Death	4.61	0.92	0.5	0.57	0.81	0.29

Table 5: results of the ROC curve analyses for PLR for males and females.

	Timestep	Outcome	Cut-off	Sensitivity	Specificity	Accuracy	AUROC	PPV	NPV
Males	Admission	CPAP or NIV	239.22	0.61	0.50	0.54	0.58	0.39	0.71
		ICU admission	245.86	0.61	0.50	0.53	0.56	0.26	0.82
		Invasive ventilation	248	0.61	0.50	0.52	0.57	0.17	0.88
		Death	250.39	0.55	0.51	0.52	0.53	0.30	0.75
	48h	CPAP or NIV	250.05	0.72	0.50	0.58	0.64	0.43	0.78
		ICU admission	281.24	0.70	0.50	0.55	0.62	0.30	0.85
		Invasive ventilation	288.62	0.72	0.50	0.54	0.63	0.20	0.91
		Death	292.85	0.59	0.50	0.52	0.58	0.29	0.78
	7days	CPAP or NIV	261.35	0.73	0.50	0.58	0.63	0.44	0.78
		ICU admission	268.72	0.73	0.50	0.56	0.65	0.35	0.83
		Invasive ventilation	278.74	0.75	0.50	0.55	0.67	0.24	0.91
		Death	276	0.72	0.50	0.55	0.65	0.28	0.87
Females	Admission	CPAP or NIV	233	0.65	0.5	0.53	0.60	0.27	0.83
		ICU admission	245.90	0.56	0.51	0.52	0.58	0.10	0.92
		Invasive ventilation	246.45	0.56	0.51	0.51	0.58	0.06	0.96
		Death	241.54	0.56	0.51	0.53	0.55	0.27	0.78
	48h	CPAP or NIV	231.53	0.75	0.50	0.56	0.67	0.30	0.87
		ICU admission	248.73	0.70	0.51	0.53	0.64	0.12	0.95
		Invasive ventilation	250.27	0.68	0.51	0.52	0.62	0.07	0.97
		Death	246.19	0.59	0.51	0.53	0.58	0.26	0.81
	7days	CPAP or NIV	241	0.69	0.50	0.55	0.62	0.31	0.83
		ICU admission	257.59	0.61	0.53	0.54	0.61	0.15	0.91
		Invasive ventilation	258.23	0.62	0.52	0.53	0.58	0.08	0.95

Death	247,05	0.66	0.50	0.53	0.59	0.23	0.86

Figures

Figure 1

histogram shows the number of admitted patients for age group, divided by gender.

Figure 2

histogram showing the distribution of patients' length of stay (LOS).

Figure 3A:

Figure 3B:

Figure 3C:

Figure 3D:

Figure 3

3A: mean NLR trend at the four timepoints, shown with 95% confidence interval

3B: mean NLR trend at the four timepoints divided by gender

3C: mean PLR trend at the four timepoints, shown with 95% confidence interval

3D: mean NLR trend at the four timepoints divided by gender

Figure 4

ratios trends for each outcome at the four timesteps. NLR (A) and PLR (B) mean trends (with 95% CI) for patients with respiratory failure in orange and mean trends (with 95% CI) for patients without respiratory failure. The p-values expressing the significance of the difference in the NLR or PLR values for each time point are shown in the box.

Figure 5

ROC curves for NLR (A) and PLR (B) cutoffs, with respective AUROCs.

Figure 6

NLR cut-off values for males and females, plotted in order of timepoints and severity, shown with their sensitivity.

Figure 7

NLR cut-off values for males and females, plotted in order of timepoints and severity, shown with their sensitivity.

Figure 8

comparison of NLR and PLR ROC curves for each outcome at each timepoint.

Supplementary Files

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- [GraphicalAbstract.jpg](#)