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Monocyte-to-Lymphocyte Ratio as a Prognostic Marker in Patients With Acute Respiratory Distress Syndrome: A Retrospective Observational Study

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Abstract

Background and aims: Acute respiratory distress syndrome (ARDS) is a serious and often fatal inflammatory condition of the lungs. Many factors can help guide disease management, and early prognostic markers play a crucial role in this process. In this study, the monocyte-to-lymphocyte ratio (MLR) was compared with both the neutrophil-to-lymphocyte ratio (NLR) and the Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score for predicting 28-day mortality in ARDS.

Patients and methods: In this retrospective cohort study, 250 adult patients with ARDS admitted to a tertiary intensive care unit (ICU) from September 2022 to July 2024 were analyzed. The MLR and NLR were calculated within 24 hours of admission and on Days 3 and 5. APACHE IV scores were obtained within 24 hours of admission. Outcomes were assessed at 28 days. The study cohort was validated using propensity score matching. Predictive performance was evaluated using receiver operating characteristic (ROC) curve analysis. Logistic regression was used to identify independent predictors of mortality.

Results: The MLR on Day 1 was significantly higher in nonsurvivors (0.93 ± 0.33) than in survivors (0.44 ± 0.33; $p < 0.001$). The APACHE IV score was the best predictor of mortality (area under the curve (AUC) = 0.876), followed by the MLR (AUC = 0.842) and NLR (AUC = 0.823). An MLR ⩾0.74 was independently associated with increased 28-day mortality (adjusted odds ratio (OR) = 5.1, $p < 0.001$). A higher MLR was associated with lower P/F ratios, increased lactate levels, longer duration of mechanical ventilation, post-ARDS lung mechanical recovery, and longer hospital stays.

Conclusions: The MLR is a simple, inexpensive, and independent predictor of 28-day mortality in ARDS, and its predictive value was comparable to that of APACHE IV. The use of the MLR in early risk stratification could help inform clinical decision-making, particularly in low-resource areas.

Categories: Other, Pulmonology, Internal Medicine
Keywords: acute respiratory distress syndrome (ards), apache iv, monocyte-to-lymphocyte ratio (mlr), mortality prediction, neutrophil-to-lymphocyte ratio (nlr)

Introduction

Acute respiratory distress syndrome (ARDS) was first described in 1967 by Ashbaugh and colleagues as a condition characterized by acute-onset tachypnea, hypoxemia, and loss of lung compliance that did not respond to conventional therapy, except for positive end-expiratory pressure (PEEP), which was used to combat hypoxemia and atelectasis [1].

Despite recent advances in treatment regimens, ARDS is associated with high mortality [2,3], making the need for a single marker that can accurately predict prognosis and guide treatment imperative. Risk prediction models lack validation and are extremely complex [4], while biomarkers such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and vascular endothelial growth factor (VEGF) [5], though promising, require specialized samples and testing methods. Our study aims to identify a marker for predicting 28-day mortality in ARDS that can be measured rapidly using bedside techniques.

The pathogenesis of ARDS includes damage to the endothelium and epithelium of the lung alveoli caused by various inflammatory mediators [6-8]. Previous studies have shown that the neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) are novel hematological markers of inflammation [9-13] and potential predictive biomarkers for prognosis in ARDS [2,14,15].

The commonly used intensive care unit (ICU) prognostic scores with established validation, such as Acute Physiology and Chronic Health Evaluation IV (APACHE IV) [16], Sequential Organ Failure Assessment (SOFA) score, and Simplified Acute Physiology Score (SAPS), are not specific to ARDS, involve multiple

organ systems, and have not been evaluated as predictors of other morbidities in patients with ARDS.

MLR and NLR can be calculated from routinely available complete blood counts and may provide accessible indicators of systemic inflammation. Previous studies have examined their prognostic associations in ARDS. Further comparison of these indices with APACHE IV in the same ARDS cohort may help characterize their relative discriminatory performance. The aim of this study is to compare Day 1 MLR, NLR, and APACHE IV scores for predicting 28-day mortality, with exploratory analyses of respiratory support and duration of hospitalization.

Materials And Methods

Study design

The study was conducted as a single-center, investigator-initiated, retrospective observational study, and no funding was acquired. It was conducted over a period of 21 months. The sample size was set at 250 patients, considering a significance level of 5% and a power of 80%. A minimum sample size of approximately 250 patients was required to assess the predictive ability of MLR in the study. Patients aged over 18 years with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of less than 300 who met the Berlin criteria for ARDS [8] were included. Patients with chronic hematological disorders, malignancy, or major comorbidities and those receiving immunosuppressive agents were excluded from the study. Further details on the inclusion and exclusion criteria are provided in Table *1*.

Inclusion Criteria	Exclusion Criteria
1. Age ≥18 years	1. Age <18 years
2. PaO_2/FiO_2 ratio <300 with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 cm H_2O	2. Death within 24 hours of hospital admission
3. Bilateral opacities on chest radiography not fully explained by pleural effusion, lobar/lung collapse, nodules, or heart failure	3. PaO_2/FiO_2 ratio >300
4. Respiratory failure not fully explained by cardiac failure or fluid overload, with no evidence of elevated left atrial pressure on echocardiography	4. Chronic hematological disorders or hematological malignancy
	5. Current use of immunosuppressive agents, vitamin K antagonists, or other anticoagulants
	6. Liver, gastrointestinal, or renal disorders; previous or current heart failure; previous myocardial infarction or myocarditis; ventricular dysfunction; neurological or rheumatological disorders. Patients with stable, asymptomatic minor coronary artery disease were not excluded.
	7. Absence of a complete blood count within 24 hours of ARDS diagnosis and on days 3 and 5
	8. Patient or patient's relative declined consent to participate in the study
	9. Failure to complete the required laboratory investigations/study parameters

TABLE 1: Inclusion and exclusion criteria for study participants

ARDS, acute respiratory distress syndrome; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.

The primary objective of the study is to compare the discriminatory ability of Day 1 MLR, NLR, and APACHE IV for predicting all-cause mortality within 28 days of ARDS diagnosis. The exploratory secondary objectives concern associations with the receipt of invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO), duration of invasive ventilation, and hospital length of stay.

The study was conducted as a single-center, investigator-initiated, retrospective observational study, and no funding was acquired. It was conducted over a period of 21 months.

Sample size

The sample size was limited to 250 patients undergoing treatment for ARDS in the critical care unit.

Justification for sample size

The approximate sample size was calculated using a 5% significance level and 80% statistical power.

$$n = \frac{p(1-p)(z_{\alpha/2})^2}{d^2}$$

where p = prevalence of ARDS among ICU admissions = 10.4%, $z_{\alpha/2}$ = 1.96 at a 5% significance level, and d = precision = 0.0371.

A minimum sample size of approximately 250 patients was required to assess the predictive ability of MLR in the study.

Study duration

The study was conducted from September 2022 to July 2024.

Methods

After enrollment, patient data were obtained from the medical records department. Details of all variables collected are summarized in Table *2*.

Category	Variables Collected
1. Demographic characteristics	Age; sex
2. Comorbidities	Chronic obstructive pulmonary disease; diabetes mellitus; hypertension; coronary artery disease
3. Risk factors for ARDS	Pneumonia; aspiration; non-pulmonary sepsis; other causes
4. Disease severity and ARDS characteristics	ARDS severity (mild, moderate, or severe) according to the Berlin definition[17]; arterial oxygen tension/fraction of inspired oxygen (PaO_2/FiO_2) ratio used for inclusion and ARDS severity categorisation
5. Laboratory parameters	Lactate level within 24 hours of ARDS diagnosis (mmol/L); neutrophil-to-lymphocyte ratio (NLR) on Days 1, 3, and 5; monocyte-to-lymphocyte ratio (MLR) on Days 1, 3, and 5
6. Acute kidney injury	Development of acute kidney injury according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria [18]
7. Disease severity score	Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score within 24 hours of ARDS diagnosis, calculated using an online APACHE IV calculator based on the methodology described by Zimmerman et al. [19]
8. Therapeutic interventions	Invasive mechanical ventilation (yes/no); duration of invasive mechanical ventilation (days); neuromuscular blocker use in patients receiving invasive mechanical ventilation (yes/no); corticosteroid therapy (yes/no), defined as methylprednisolone >0.5 mg/kg/day or an equivalent corticosteroid dose; haemodialysis during the 28-day follow-up period (yes/no); extracorporeal membrane oxygenation (ECMO) requirement (yes/no)
9. Hospital outcomes	Length of hospital stay (days); 28-day mortality
10. Outcome classification	Survivors: patients alive at 28 days from ARDS diagnosis; non-survivors: patients who died within 28 days of ARDS diagnosis

TABLE 2: Variables collected in the study

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; KDIGO, Kidney Disease: Improving Global Outcomes; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PaO_2/FiO_2, arterial oxygen tension to fraction of inspired oxygen ratio.

All patients with ARDS in our department were treated according to standardized institutional protocols based on internationally accepted guidelines and literature on ARDS. If a patient was discharged before 28 days after ARDS diagnosis, the patient or a relative was contacted by telephone at home. The remaining patients were followed up until Day 28 after diagnosis.

After data collection, the study population was divided into two cohorts: survivors (patients who were alive at 28 days after diagnosis) and nonsurvivors (patients who died within 28 days after diagnosis).

Statistical analysis

Student's t-test (independent two-sample t-test) was used to assess the significance of differences in baseline demographics between the two groups. The Mann-Whitney U test was used to compare MLR and NLR values between the two groups on different days, as well as baseline age, lactate levels, APACHE IV scores, and P/F ratios.

The Kolmogorov-Smirnov test was used to check whether the data followed a normal distribution. Pearson's chi-square test was used to assess associations between categorical variables, including ARDS severity and ARDS risk factors, between survivors and non-survivors. The chi-square test statistic (χ^2), degrees of freedom (df), p-value, and Cramér's V effect size were reported for each chi-square analysis. A p-value < 0.05 was considered statistically significant. Biserial correlation was used to correlate MLR and NLR with APACHE IV scores and 28-day mortality. Receiver operating characteristic (ROC) analysis was used to measure how well MLR, NLR, and APACHE IV could predict the primary outcome, as well as the requirement for extracorporeal membrane oxygenation (ECMO) and mechanical ventilation, and new cutoff values were calculated. Logistic regression analysis was used to measure the influence of different factors on patient

mortality, first with individual factors (univariate analysis) and then with a group of variables (multivariate analysis). Only variables that were significant in the univariate analysis were included in the multivariate analysis. The independent two-sample z-test for proportions was used to compare interventions and secondary outcomes between the two groups. Propensity score matching was performed at a 1:1 ratio with a caliper width of 0.03 to minimize the imbalance in baseline characteristics and validate the findings. IBM SPSS Statistics for Windows, Version 26 (Released 2018; IBM Corp., Armonk, New York) was used for the analysis.

Results

A total of 250 patients who satisfied the inclusion and exclusion criteria were included in our study. Data were collected from the medical records department and, for some patients, over the phone.

Of the 250 patients admitted to the hospital's intensive care unit, 135 were survivors and 115 were nonsurvivors. The results of the statistical analysis are presented in Table *3*.

Variable	Survivors (n = 135)	Non-survivors (n = 115)	p-value
Age (years)	59.7 ± 6.46	59.7 ± 6.79	0.99
Male sex, n (%); female sex, n (%)	70 (51.9); 65 (48.1)	60 (52.2); 55 (47.8)	0.90; 0.95
Chronic obstructive pulmonary disease (COPD), n (%)	64 (47.4)	44 (38.3)	0.18
Diabetes mellitus, n (%)	90 (66.7)	80 (69.6)	0.72
Hypertension, n (%)	80 (59.3)	65 (56.5)	0.75
Coronary artery disease, n (%)	49 (36.3)	46 (40.0)	0.63
Pneumonia, n (%)	120 (88.9)	100 (87.0)	0.83
Non-pulmonary sepsis, n (%)	7 (5.2)	6 (5.2)	0.83
Aspiration, n (%)	3 (2.2)	5 (4.3)	0.83
Lactate	3.0 ± 0.54	4.4 ± 0.8	<0.001
APACHE IV	15.53±2.97	22.03±4.51	<0.001

TABLE 3: Basic characteristics of study population

Data are presented as mean ± standard deviation or number (percentage).

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; COPD, chronic obstructive pulmonary disease; n, number of patients; p, p-value.

The differences in baseline demographics between the two groups were not statistically significant; however, both lactate levels and APACHE IV scores were higher in the nonsurvivor group (Table *3*). The most common risk factor in the entire study population was pneumonia, followed by sepsis (Figure *1*).

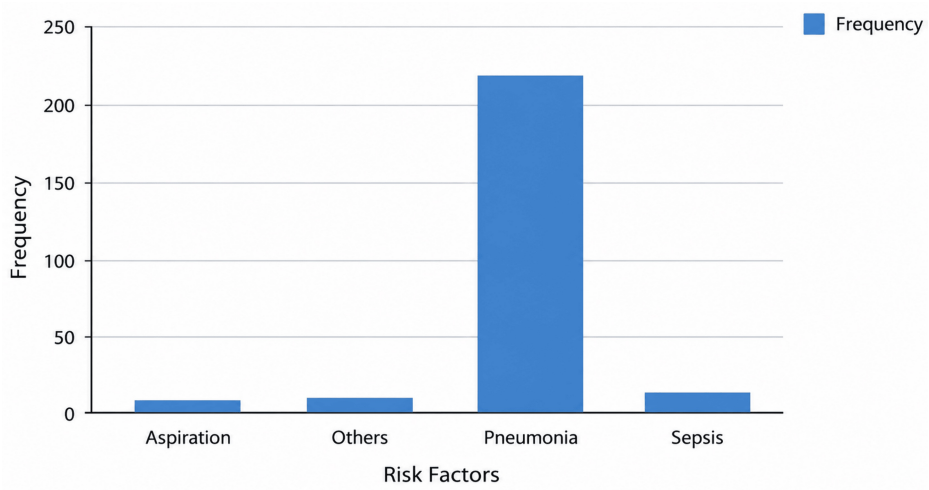


FIGURE 1: Distribution of risk factors in the entire study population

Study parameters

MLR and NLR Values and Primary Outcome (28-Day Mortality)

In our study, NLR and MLR values were obtained within 24 hours of admission and again on Days 3 and 5. We created box plots comparing the MLR (Figure 2) and NLR (Figure 3) values on Days 1, 3, and 5.

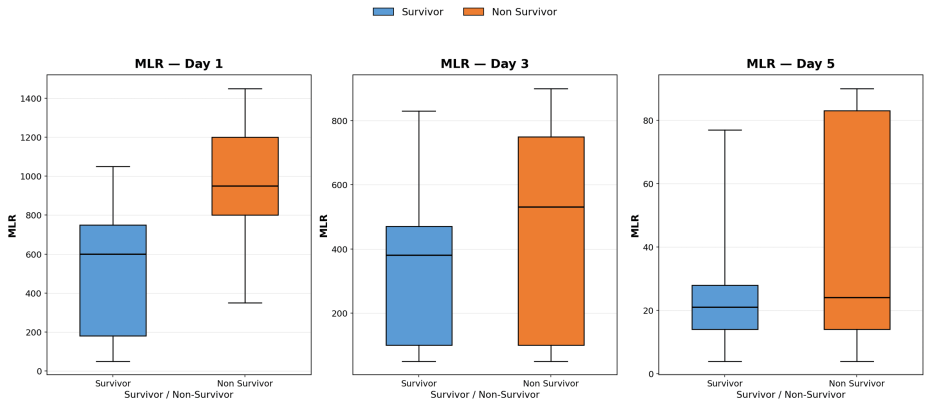


FIGURE 2: Box plots comparing MLR on Days 1, 3, and 5

MLR, monocyte-to-lymphocyte ratio.

As evident from Figure 2, the MLR values showed the greatest difference between survivors and nonsurvivors on Day 1. Figure 3 shows that NLR values also showed the greatest difference between the two groups on Day 1 compared with the other days.

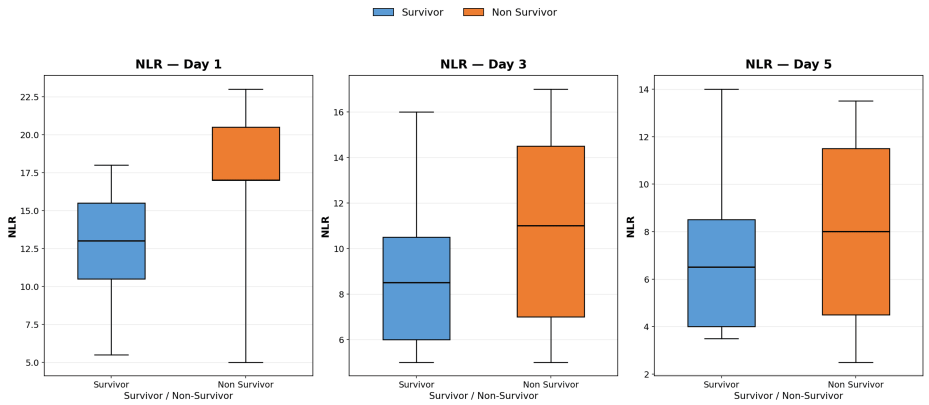


FIGURE 3: Box plots comparing NLR on Days 1, 3, and 5

NLR, neutrophil-to-lymphocyte ratio.

The MLR values on Days 1 and 5 showed statistically significant differences between the two groups ($p < 0.05$). The greatest difference between the two groups was seen on Day 1. NLR values showed significant differences only on Day 1. The MLR and NLR values decreased progressively over time with treatment (Table 4).

Variable	Survivors (n = 135)	Non-survivors (n = 115)	P-value
MLR Day 1	0.4463 ± 0.33	0.93843 ± 0.332	<0.001
MLR Day 3	0.30879 ± 0.23	0.50304 ± 0.28	0.52
MLR Day 5	0.2106 ± 0.17	0.3234 ± 0.25	<0.001
NLR Day 1	12.6285 ± 3.32	17.1154 ± 3.98	<0.001
NLR Day 3	8.389 ± 3.31	11.141 ± 3.81	0.17
NLR Day 5	6.795 ± 3.04	8.361 ± 3.33	0.19

TABLE 4: MLR and NLR values comparison on Days 1, 3, and 5 (mean ± SD)

MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation; n, number of patients; p, p-value.

The Day 1 MLR and NLR values were selected for further analysis.

Comparison of ARDS Severity Categories Between the Two Groups

The distribution of ARDS severity categories (mild, moderate, and severe) differed significantly between survivors and nonsurvivors (Table 5) ($\chi^2 = 16.17$, df = 2, $p < 0.001$; Cramér's V = 0.254). Mild and moderate ARDS were more frequent among survivors, whereas severe ARDS was more frequent among nonsurvivors. The P/F ratios were also significantly different between the two groups, with lower values among nonsurvivors (200 ± 78.3 vs. 165.2 ± 74.5, $p = 0.003$). In the survivors' group, mild and moderate category ARDS patients were higher compared to the non-survivor group. The severe category ARDS patients were higher in the non-survivor group. The P/f ratios were significantly lower in the nonsurvivor group compared with the survivor group. In the overall study population, the highest number of patients had moderate ARDS, followed by mild and severe ARDS (Figure 4).

ARDS	Survivors (n = 135)	Non-survivors (n = 115)	p-value
Mild	60	30	
Moderate	55	45	<0.001
Severe	20	40	
P/F ratio (mean ± SD)	200 ± 78.3	165.2 ± 74.5	0.003

TABLE 5: Comparison between the ARDS categories between the two groups

Pearson's chi-square test: $\chi^2 = 16.17$, df = 2, $p < 0.001$; Cramer's V = 0.254.

ARDS, acute respiratory distress syndrome; P/F, arterial oxygen tension to fraction of inspired oxygen ratio; SD, standard deviation.

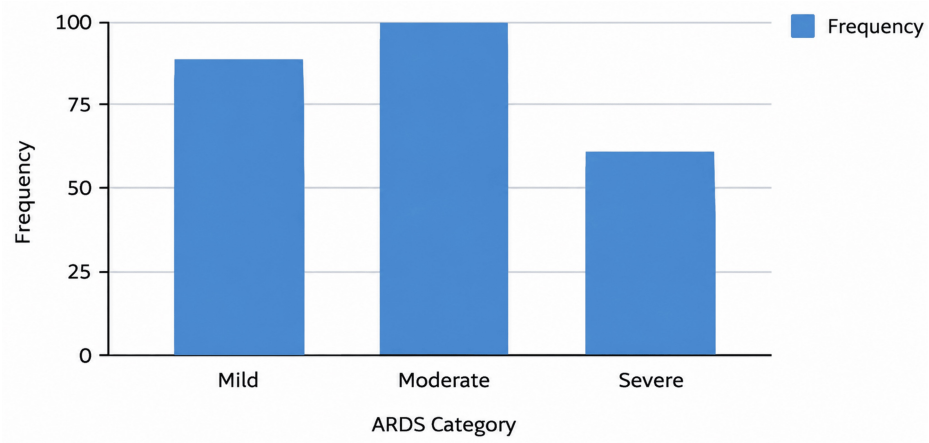


FIGURE 4: Distribution of ARDS categories in the study population

ARDS, acute respiratory distress syndrome.

Comparisons of Interventions and Hospital Stay

The interventions performed (steroid use, muscle relaxant use, HD, ECMO, and invasive mechanical ventilation) were compared between the two groups using the two-sample z-test for proportions. The two groups did not show any significant differences in the interventions, except for the duration of invasive mechanical ventilation and length of hospital stay. The nonsurvivor group required longer periods of invasive mechanical ventilation and had longer hospital stays than the survivor group (Table *6*).

Patient variable	Survivors (n = 135)	Non-survivors (n = 115)	p-value
Steroid (fr)	109	95	0.82
Muscle relaxant (fr)	61	62	0.21
HD (fr)	6	5	0.99
ECMO (fr)	16	17	0.62
Requirement of invasive mechanical ventilation (fr)	75	68	0.65
Duration of invasive ventilation in days (mean ± SD)	4.98 ± 3.56	7.31 ± 3.98	<0.001
Hospital length of stay in days (mean ± SD)	12.38 ± 1.93	13.08 ± 1.89	0.003

TABLE 6: Comparison of interventions and hospital stay between the two groups

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HD, haemodialysis; fr, frequency; SD, standard deviation.

In our study, steroid use was higher, while ECMO use was much lower. In the overall study population, the requirement for invasive mechanical ventilation was higher (Figure *5*).

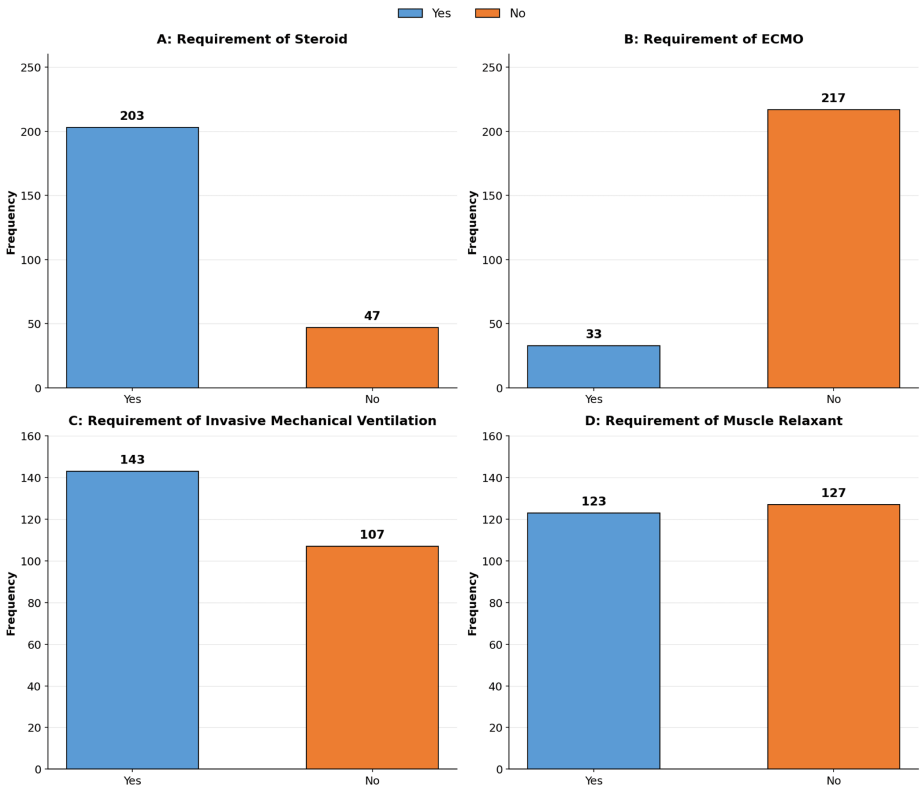


FIGURE 5: Frequency of treatment and supportive interventions in the study cohort (N = 250): (A) steroid use, (B) ECMO requirement, (C) invasive mechanical ventilation requirement, and (D) muscle relaxant requirement

ECMO, extracorporeal membrane oxygenation.

Propensity score matching and validating the original sample

We used 1:1 propensity score matching as an exploratory tool to compare the two groups. The original cohort was used to detect significant differences in various parameters between the survivor and

nonsurvivor groups. The main objective of propensity score matching was to determine whether the association between Day 1 MLR and mortality was retained after attempting to reduce differences in other variables. Propensity score matching balances two nonequivalent groups based on observed characteristics.

Logistic regression was used to generate propensity scores, and only variables that allowed the model to converge were included in the logistic regression equation. The variables included were Day 1 MLR, P/F ratio, APACHE IV score, lactate level, age in years, and Day 1 NLR, as the other variables did not permit convergence of the model. Thus, the logistic regression model converged and generated propensity scores. This was followed by the k-nearest neighbors algorithm, which was used to match participants with similar propensity scores using a caliper width of 0.03. The matched cohort included 11 participants in each group. Participants were matched based on similar propensity scores. The reduced number of participants after matching was probably because the original cohort was already well separated between the two groups, leaving very little overlap when a narrow caliper width of 0.03 was used. However, even after matching, Day 1 MLR remained significantly higher in the nonsurvivor group, supporting its strong association with mortality (Table 7).

Patient Variable	Original Cohort			Matched Cohort		
	Survivors (n = 135)	Non-survivors (n = 115)	p-value	Survivors (n = 11)	Non-survivors (n = 11)	p-value
Age	59.7±6.46	59.7±6.79	0.99	60.5±5.9	59.7±8.0	0.74
Sex (males) (fr)	70	60	0.9	7	6	0.66
Sex (female) (fr)	65	55	0.95	4	5	0.6
MLR Day 1	0.44 ± 0.33	0.93 ± 0.33	<0.001	0.66 ± 0.10	0.80 ± 0.25	0.02
NLR Day 1	12.62 ± 3.32	17.11 ± 3.98	<0.001	15.75 ± 1.90	15.7 ± 4.02	0.4
APACHE IV	15.53 ± 2.97	22.03 ± 4.51	<0.001	18.5 ± 1.57	17.9 ± 2.5	0.11
COPD (fr)	64	44	0.18	6	6	0.9
DM (fr)	90	80	0.72	10	7	0.12
HTN (fr)	80	65	0.75	7	4	0.69
CAD (fr)	49	46	0.63	4	6	0.39
P/F ratio	200 ± 78.3	165.2 ± 74.5	0.003	177.45 ± 59.06	188.2 ± 52.37	0.21
Lactate	3.0 ± 0.54	4.4 ± 0.8	<0.001	3.7 ± 0.26	3.6 ± 0.38	0.79
Steroid (fr)	109	95	0.82	11	9	0.13
Muscle relaxant (fr)	61	62	0.21	6	6	0.99
HD (fr)	6	5	0.99	1	1	0.89
ECMO (fr)	16	17	0.62	0	1	0.33
AKI	10	8	0.89	2	1	0.8
Requirement for invasive mechanical ventilation	75	68	0.65	7	6	0.66
Duration of ventilation	4.98 ± 3.56	7.31 ± 3.98	<0.001	5.32 ± 1.73	5.3 ± 2.8	0.8
Hospital length of stay	12.38 ± 1.93	13.08 ± 1.89	0.003	12.6 ± 1.43	12.55 ± 1.75	0.89
ARDS: mild	60	30		0	3	
ARDS: moderate	55	45	<0.001	10	7	0.17
ARDS: severe	20	40		1	1	
Aspiration	3	5		0	0	
Others	5	4	0.83	0	0	0.13
Pneumonia	120	100		11	9	
Sepsis	7	6		0	2	

TABLE 7: Original and matched cohorts

AKI, acute kidney injury; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; HD, hemodialysis; HTN, hypertension; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; P/F, arterial oxygen tension to fraction of inspired oxygen ratio; fr, frequency.

Pearson's chi-square test was used for categorical comparisons. Original cohort, ARDS severity: $\chi^2 = 16.17$, df = 2, $p < 0.001$, Cramer's V = 0.254; ARDS risk factors: $\chi^2 = 0.91$, df = 3, p = 0.83, Cramer's V = 0.060. Matched cohort, ARDS severity: $\chi^2 = 3.52$, df = 2, p = 0.17, Cramer's V = 0.400; ARDS risk factors: $\chi^2 = 2.20$, df = 1, p = 0.13, Cramer's V = 0.316.

Quality of prediction of 28-day mortality, requirement of ECMO and

requirement of mechanical ventilation by receiver operating characteristic (ROC) curve

The receiver operating characteristic (ROC) curve is a classification tool. The area under the curve (AUC) measures the overall performance of the markers in correctly classifying survivors and nonsurvivors. The predictive power of the studied parameters, namely MLR, NLR, APACHE IV, and MLR combined with NLR, for 28-day mortality, the requirement for ECMO, and the requirement for invasive mechanical ventilation is depicted by the ROC curves below. MLR and NLR are ratios and are unitless; hence, their simple average was used to combine them into a third parameter, namely MLR+NLR.

28-Day Mortality

The ROC curve for 28-day mortality (Figure *6* and Table *8*) showed that Day 1 MLR had a sensitivity of 78% and a specificity of 76% for predicting mortality. The APACHE IV score had the highest AUC and thus the best predictive performance, while MLR combined with NLR had a higher AUC than NLR alone. MLR had the second-highest AUC and was therefore a good predictor of mortality compared with NLR and MLR combined with NLR.

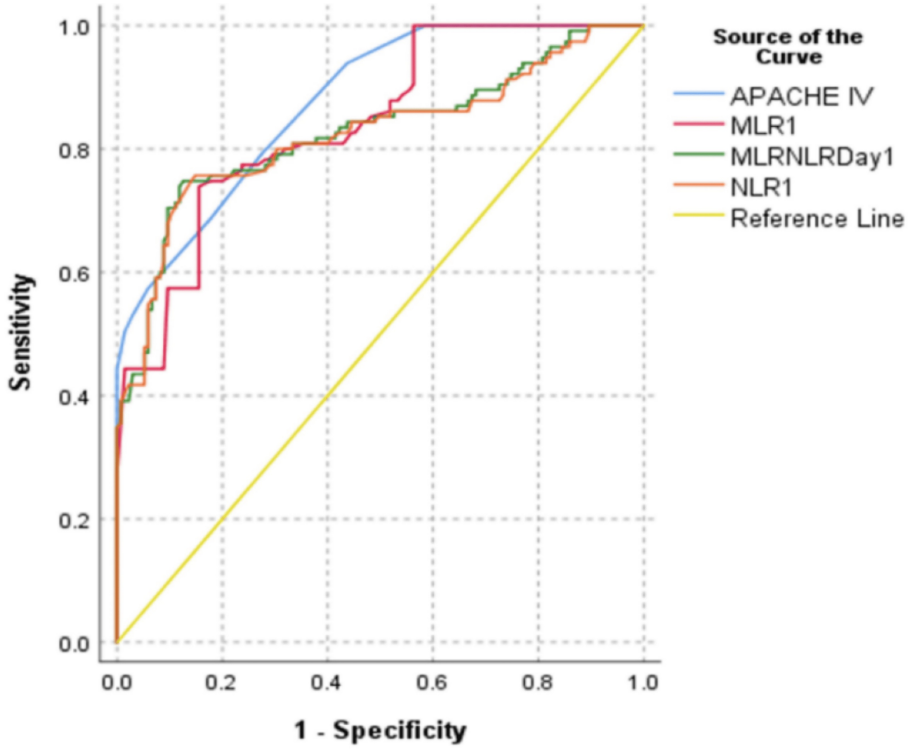


FIGURE 6: ROC curve showing 28-day mortality

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristic.

Patient Variable	AUC	95% CI	p-value	Sensitivity (%)	Specificity (%)	Optimal Cutoff
MLR Day 1	0.842	0.79-0.88	<0.001	78%	76%	0.74
NLR Day 1	0.823	0.76-0.87	<0.001	77.00%	71%	15.2
APACHE IV	0.876	0.83-0.91	<0.001	79%	73%	17.5
MLR Day 1 + NLR Day 1	0.826	0.77-0.88	<0.001	80.90%	68%	7.7

TABLE 8: Receiver operating characteristic analysis of MLR Day 1, NLR Day 1, APACHE IV score, and combined MLR and NLR Day 1 for prediction of 28-day mortality in patients with ARDS

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ARDS, acute respiratory distress syndrome; AUC, area under the curve; CI, confidence interval; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Requirement of ECMO

In predicting the requirement for ECMO, MLR had the highest AUC, making it the best predictor of ECMO requirement. NLR and MLR combined with NLR had the second-highest AUC. The APACHE IV score performed the worst, with the lowest AUC (Figure 7 and Table 9). All parameters except APACHE IV showed 100% sensitivity.

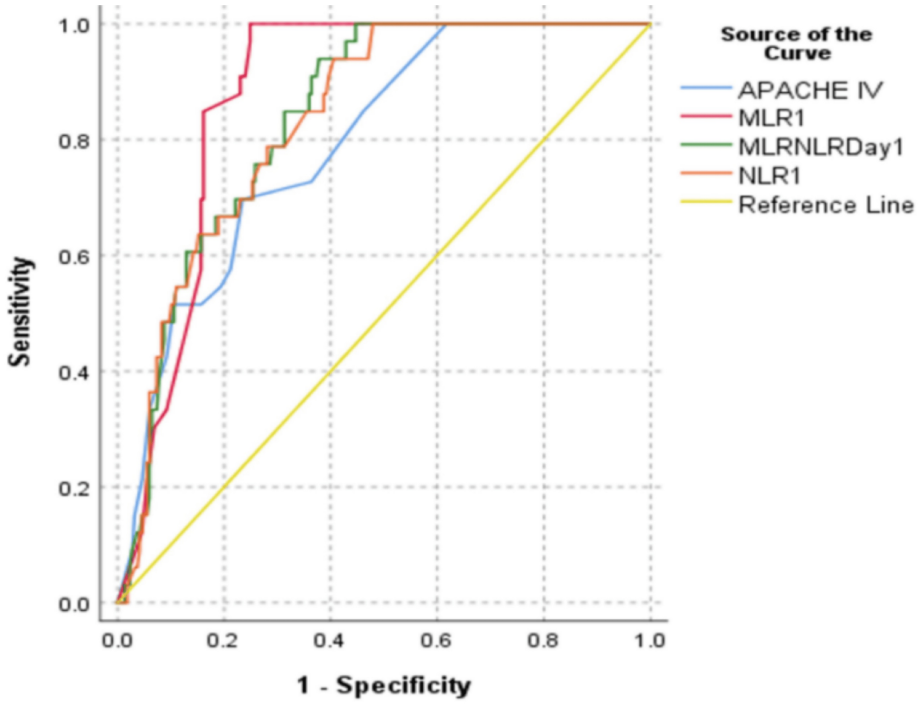


FIGURE 7: ROC curve showing requirement of ECMO

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ECMO, extracorporeal membrane oxygenation; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristic.

Patient Variables	AUC	95% CI	p-value	Sensitivity (%)	Specificity (%)	Optimal Cutoff
Apache IV	0.79	0.72-0.86	<0.001	84%	54%	17.5
MLR Day 1	0.87	0.83-0.91	<0.001	100%	55%	0.68
NLR Day 1	0.83	0.77-0.89	<0.001	100%	20%	10.5
MLR Day 1 + NLR Day 1	0.83	0.78-0.89	<0.001	100%	21%	5.03

TABLE 9: Receiver operating characteristic analysis of MLR Day 1, NLR Day 1, APACHE IV score, and combined MLR and NLR Day 1 for requirement of ECMO in patients with ARDS

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ARDS, acute respiratory distress syndrome; AUC, area under the curve; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Requirement of Invasive Mechanical Ventilation

In our study, while comparing the predictive values of the study parameters for the requirement for invasive mechanical ventilation, it was observed that MLR again had the highest AUC, making it the best predictor of the requirement for invasive mechanical ventilation. The second-best predictor was MLR combined with NLR, closely followed by NLR and the APACHE IV score (Figure *8* and Table *10*).

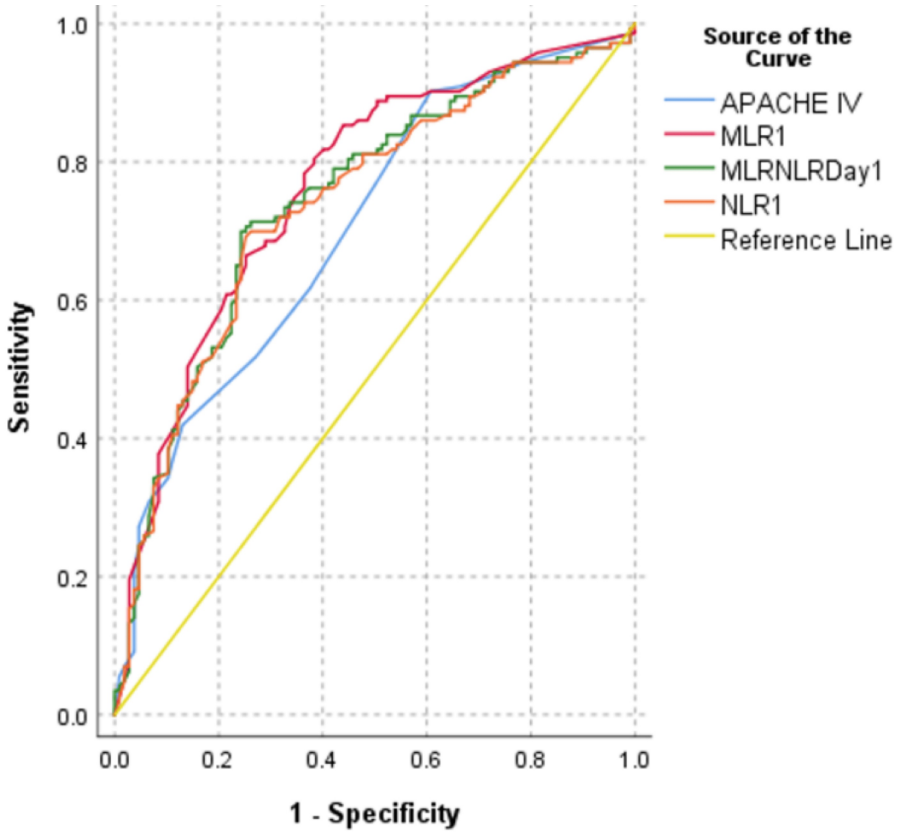


FIGURE 8: ROC curve showing requirement of invasive ventilation

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristic.

Patient Variables	AUC	95% CI	p-value	Sensitivity (%)	Specificity (%)	Optimal cutoff
Apache IV	0.704	0.64-0.76	<0.001	90.20%	40%	15.5
MLR Day 1	0.762	0.70-0.82	<0.001	67.10%	73%	0.71
NLR Day 1	0.737	0.67-0.80	<0.001	90.20%	30%	10.7
MLR Day1 + NLR Day 1	0.744	0.68-0.80	<0.001	71.30%	70%	7.7

TABLE 10: Receiver operating characteristic analysis of MLR Day 1, NLR Day 1, APACHE IV score, and combined MLR and NLR Day 1 for requirement of invasive mechanical ventilation in patients with ARDS

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ARDS, acute respiratory distress syndrome; AUC, area under the curve; CI, confidence interval; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Relationship between the study parameters and length of hospital stay, duration of mechanical ventilation, and P/F ratio

Correlation analysis is a statistical tool used to measure the extent of the linear relationship between variables. Correlation analyses were performed to study the associations of Day 1 MLR, Day 1 NLR, and APACHE IV scores with patient mortality, duration of mechanical ventilation, length of hospital stay, and P/F ratio.

Correlation analysis was performed for the continuous secondary outcomes. Day 1 MLR, Day 1 NLR, and APACHE IV scores all showed strong positive correlations with the length of hospital stay (Figure *9*).

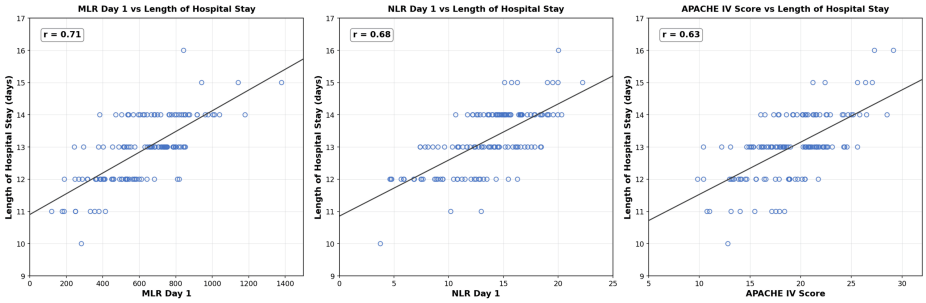


FIGURE 9: Scatterplots with fitted regression lines showing the correlation between length of hospital stay and MLR Day 1 (r = 0.71), NLR Day 1 (r = 0.68), and APACHE IV score(r = 0.63). All three variables showed a positive correlation with the duration of hospital stay

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Similar to the length of hospital stay, Day 1 MLR, Day 1 NLR, and APACHE IV scores all showed strong positive correlations with the duration of mechanical ventilation (Figure *10*).

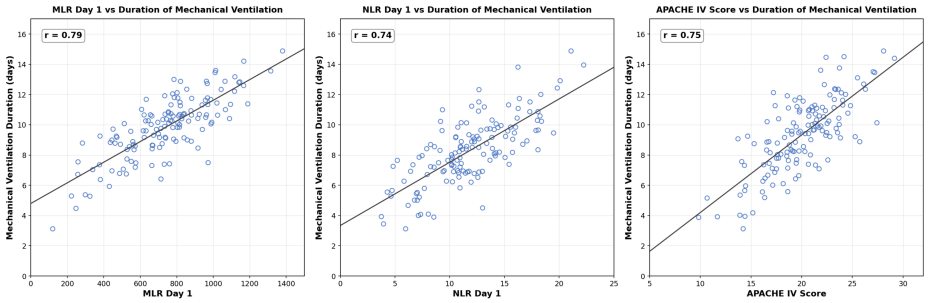


FIGURE 10: Scatterplots with fitted regression lines showing the correlation between duration of mechanical ventilation and MLR Day 1 (r = 0.79), NLR Day 1 (r = 0.74), and APACHE IV score (r = 0.75). All three parameters showed a positive correlation with the duration of mechanical ventilation

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

All parameters, i.e., MLR, NLR, and APACHE IV scores, showed inverse correlations with the P/F ratio (Figure *11*).

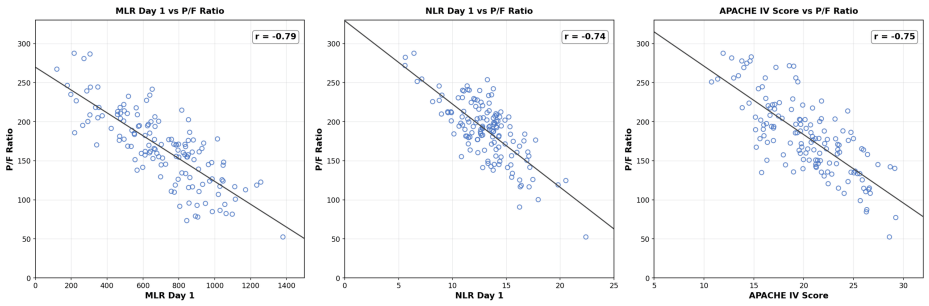


FIGURE 11: Scatterplots with fitted regression lines showing correlation between the P/F ratio and MLR Day 1 (r = -0.79), NLR Day 1 (r = -0.74), and APACHE IV score (r = -0.75). All three parameters showed an inverse correlation with the P/F ratio.

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; P/F, arterial oxygen tension to fraction of inspired oxygen ratio.

Relationship between the study parameters and ECMO, requirement for invasive mechanical ventilation, steroid use, and muscle relaxant use

Our study showed significant associations with the administration of ECMO, the requirement for invasive mechanical ventilation, steroid use, and muscle relaxant use. Higher MLR, NLR, and APACHE IV scores were associated with greater use of muscle relaxants and steroids and a higher requirement for invasive mechanical ventilation and ECMO (Table *11*).

Intervention	Patient Variable	Yes, Mean ± SD	No, Mean ± SD	p-value
ECMO	MLR Day 1	1.09 ± 0.22	0.60 ± 0.39	<0.001
	NLR Day 1	18.8 ± 2.58	14.06 ± 4.12	<0.001
	APACHE IV	23.15 ± 4.7	17.82 ± 4.6	<0.001
Invasive mechanical ventilation	MLR Day 1	0.83 ± 0.37	0.45 ± 0.36	<0.001
	NLR Day 1	16.13 ± 3.99	12.7 ± 3.86	<0.001
	APACHE IV	20.07 ± 5.0	16.46 ± 4.10	<0.001
Steroid use	MLR Day 1	0.71 ± 0.40	0.47 ± 0.39	<0.001
	NLR Day 1	15.12 ± 4.18	12.78 ± 4.15	0.001
	APACHE IV	19.08 ± 4.97	16.04 ± 4.13	<0.001
Muscle relaxant use	MLR Day 1	0.86 ± 0.35	0.49 ± 0.37	<0.001
	NLR Day 1	16.43 ± 3.8	13.0 ± 4.02	<0.001
	APACHE IV	20.3 ± 4.91	16.8 ± 4.37	<0.001

TABLE 11: Association between MLR, NLR, and APACHE IV scores and the requirement for ECMO, invasive mechanical ventilation, steroids, and muscle relaxants in patients with ARDS

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation.

Correlation between Day 1 MLR, Day 1 NLR, and APACHE IV scores and 28-day mortality

Biserial correlation was used to measure the correlations, particularly because one variable was continuous and the other was categorical. All the study parameters showed positive correlations with 28-day mortality (Table *12*).

28-Day Mortality	Biserial Correlation
MLR Day 1	0.59
NLR Day 1	0.52
APACHE IV	0.65
MLR Day 1 + NLR Day 1	0.53

TABLE 12: Biserial correlation of MLR, NLR, APACHE IV score, and combined MLR and NLR with 28-day mortality in patients with ARDS

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ARDS, acute respiratory distress syndrome; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Univariate and multivariate analysis

We performed regression analysis to determine which variables significantly influenced mortality. Initially, univariate analysis was carried out on each variable separately using logistic regression. The variables that were significant in the univariate analysis ($p < 0.05$) were included in the multivariate analysis, and logistic regression was used for both the univariate and multivariate analyses. The multivariate analysis showed that Day 1 MLR, P/F ratio, APACHE IV score, and lactate levels were variables that had a significant influence on patient mortality. Day 1 NLR in the original cohort may have differed significantly between survivors and nonsurvivors, but the matched cohort, calculated to validate the findings from the original cohort, did not show any significant difference in Day 1 NLR between the survivor and nonsurvivor groups, which had equal

numbers of participants. It was also observed in the univariate regression analysis that Day 1 NLR did not have any significant influence on patient mortality. Based on these observations, it can be concluded that Day 1 NLR did not have much influence on patient mortality in this particular study, so Day 1 NLR may not be a very good predictor of mortality compared with Day 1 MLR or APACHE IV. Day 1 MLR, APACHE IV score, P/F ratio, and lactate levels are probably independent predictors of mortality (Table *13*).

Patient Variables	Univariate Analysis			Multivariate Analysis	
	OR (95% CI)	p-Value		OR (95% CI)	p-value
Age	1.05 (0.90-1.21)	0.5			
ARDS (P/f ratio)	1.055 (1.03-1.08)	<0.001	ARDS (P/F ratio)	1.055 (1.03-1.07)	<0.001
MLR Day 1	1607.5 (3.44-749281.9)	0.019	MLR Day 1	2005.9 (23.87-168505.2)	0.001
NLR Day 1	1.03 (0.68-1.54)	0.88	APACHE IV	2.81 (1.65-4.77)	<0.001
APACHE IV	3.3 (1.70-6.45)	<0.001	Lactate	30.2 (5.28-173.5)	<0.001
HD	0.41 (0.005-38.50)	0.7			
Lactate	27.8 (4.60-167.7)	<0.001			
Steroid	0.42 (0.046-3.98)	0.45			
Muscle relaxant	1.38 (0.82-2.33)	0.21			
ECMO	1.12 (0.52-2.42)	0.75			

TABLE 13: Univariate and multivariate logistic regression analysis of factors associated with 28-day mortality in patients with ARDS

ARDS, acute respiratory distress syndrome; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; HD, hemodialysis; ECMO, extracorporeal membrane oxygenation; OR, odds ratio; CI, confidence interval.

Rearrangement of the original cohort according to the cutoff values of the study parameters from the ROC curve of mortality

Considering the good sensitivity and specificity of the ROC curves for 28-day mortality for all the study parameters, we divided the entire cohort based on their respective cutoff values. We concluded that a Day 1 MLR value greater than 0.74, a Day 1 NLR value greater than 15.2, and an APACHE IV score greater than 17.5 were significantly associated with lower P/F ratios, higher arterial lactate levels, greater use of steroids and muscle relaxants, a higher requirement for ECMO and invasive mechanical ventilation, longer durations of mechanical ventilation, and prolonged hospital stays.

Discussion

An efficient marker for prognosis in patients with ARDS has been difficult to identify for decades. The search for such a marker has been hindered by numerous factors, such as the heterogeneity of the disease, lack of proper identification of patients suffering from the condition, controversies, and ever-changing management protocols for the disease. A few markers have been identified, but as discussed previously, they are either not routinely tested, expensive, difficult to obtain samples for, or lack consistent results across all ARDS subphenotypes.

In our study, we attempted to include the earliest components of the pathophysiology of ARDS and investigate their efficiency as tools for predicting outcomes in ARDS. We retrospectively enrolled 250 patients, of whom 135 were survivors and 115 were nonsurvivors. As evident from Table *1*, the baseline demographics, including age, sex, comorbidities, and risk factors for ARDS, showed no significant differences between the two groups.

In line with the pathogenesis of ARDS, MLR values showed the greatest difference between the two groups on Day 1 (Figure *2* and Table *4*). In the study conducted by Yang et al. [2], they had similar results, finding that the most significant differences were on Days 1 and 3, while the difference on Day 5 was not statistically significant. In contrast, our study results showed no significant difference on Day 3 but significant differences on Days 1 and 5, although the gap between the mean values was not as large on any other day as it was on Day 1. This could implicate the role of monocyte-derived macrophages in inducing

lung fibrosis and associated poor outcomes.

The NLR values in our study showed significant differences only on Day 1 (Figure *3* and Table *4*), while in the study conducted by Yang et al. [2], the differences in NLR values were significant between the two groups on both Days 1 and 3. However, in studies conducted by Wang et al. [14] and Song et al. [15], the NLR values were measured only on Day 1 (i.e., within 24 hours of admission). This could implicate the pathophysiological basis of ARDS, in which the main event is neutrophil and monocyte recruitment. In other studies of different conditions, such as those conducted by Mirna et al. [13] on myocarditis, Cheng et al. [12] on stroke-associated pneumonia, and Djordjevic et al. [11] on patients with trauma and sepsis, the NLR and MLR values at the time of enrollment showed the greatest predictive efficiency, similar to our study.

The ARDS severity categories and P/F ratios differed significantly between the two groups in our study (Table *5*). As expected, mild and moderate ARDS were more frequent among survivors, who had higher P/F ratios, while severe ARDS was more frequent among nonsurvivors, who had lower P/F ratios. This result was similar to the findings of Yang et al. [2], Wang et al. [14], and Song et al. [15]. In the study conducted by Ruan et al. [20], it was concluded that the P/F ratio was inversely associated with death in patients with ARDS who had been mechanically ventilated for more than 12 hours with PEEP ⩾5 cm H_2O, which is similar to our study. However, in our study, we measured P/F ratios at admission, and even though our study showed that lower P/F ratios were associated with higher mortality, they were not good predictors of outcomes due to differences in ARDS subtypes, different modes of ventilation, etc., causing changes in P/F ratios among patients with ARDS [21]. The other baseline variables, lactate levels and APACHE IV scores, were significantly higher in the nonsurvivor group (Table *2*).

In our study, there was a statistically significant difference in the lactate levels between the two groups. This could be due to the high proportion of patients with sepsis-induced ARDS in our study (pneumonia and non-respiratory sepsis; Figure *1*), which is in line with the findings by Zhang et al. [22], who used serial lactate measurements and group-based trajectory modeling to conclude that higher lactate levels in ARDS patients are associated with higher mortality rates. In our study, we have seen that higher lactate levels are possibly associated with higher mortality rates in ARDS patients, and since 85% of patients with ARDS have sepsis (pulmonary and non-pulmonary) as risk factors, this particular avenue might require further large-scale studies [8].

The APACHE IV score also showed a significant difference between the two groups, with the inference being that higher APACHE IV scores are associated with higher mortality. The APACHE IV score is an improvement over the APACHE III score in terms of newer calibration and the addition of new relevant variables. The results of our study are in line with the findings by Zimmerman et al. [18], where it was evident that APACHE IV scores were higher in survivors and associated with worse outcomes.

The interventions investigated in our study, which were steroid usage, muscle relaxant usage, use of hemodialysis, and administration of ECMO, showed no significant difference between the survivor and non-survivor groups (Table *6*). This was in line with the study conducted by Yang et al. [2], where there was no difference between the survivors and non-survivors in terms of steroid administration, use of hemodialysis, and ECMO. This probably echoes what was shown by the trial conducted by Combes et al. [23] (the EOLIA trial) in 2018 on severe ARDS patients. In the EOLIA trial, administration of ECMO did not improve outcomes, even with a 28% crossover from the conventional management group to the ECMO group, and should be used as a rescue measure. In our study, we included muscle relaxant usage as part of the interventions considered, which was in contrast to previous studies on MLR and NLR as prognostic markers for ARDS [2,13,14]. We didn't find any significant difference in the usage of muscle relaxants between the survivor and non-survivor groups (Table *6*). These findings are similar to the results from the study conducted by the National Heart, Lung, and Blood Institute PETAL Clinical Trials Network [24] (PETAL study) in 2019, where the use of muscle relaxant did not create a difference in mortality in severe ARDS patients.

Auriemma et al. [25] studied attributable mortality in sepsis-related ARDS patients. In that study, they concluded that higher mortality rates are associated with the requirement of prolonged mechanical ventilation and also increased length of stay in the hospital. However, the duration of mechanical ventilation is a poorly defined parameter when the type and other factors of mechanical ventilation (i.e., delta pressure, plateau pressure, etc.) are not considered. This is a possible major drawback in our study. Nonetheless the duration of invasive mechanical ventilation and hospital length of stay, both were significantly prolonged in the non-survivor group in our study. However, the requirement for invasive mechanical ventilation is not significantly different between the two groups. It has been shown in the study conducted by Wang et al. [26] that pulmonary cause of ARDS is associated with a greater requirement for mechanical ventilation. Hence, in our study, the slightly higher percentage of pulmonary cause of ARDS patients in the survivor group (88.8%) compared to the non-survivor group (86.9%) might have caused this result.

The predictive value of MLR taken within 24 hours of admission for mortality at 28 days, requirement of invasive mechanical ventilation, and requirement of ECMO was quite promising. However, in the case of

predicting 28-day mortality, MLR on day 1 was superseded by the APACHE IV score (AUC: 0.842 and 0.876, respectively) (Figure *6*, Table *8*). Previously, in a study conducted by Dan et al. [27] on trauma-related ARDS, the results showed that MLR is an excellent predictor of prognosis in ARDS patients with an AUC of 0.818. Another study conducted by Peng et al. [28] showed that both MLR and NLR had high sensitivity with lower specificity for the diagnosis of ARDS in COVID-19 patients, while both had high AUC values (0.785 and 0.722, respectively). Similarly, the ROC curves in our study show that MLR has high sensitivity (78 %) with high specificity (76%) (Figure *6* and Table *8*) for 28-day mortality. Nevertheless, this contrasts with the study conducted by Yang et al. [2], where the specificity of MLR was much higher than the sensitivity (81. % and 55.3%, respectively), and this may be attributed to differences in exclusion criteria and the heterogeneity of ARDS management. The study conducted by Yang et al. [2] also showed that the AUC for MLR was highest compared to the APACHE II score, which was opposite to our study. This could be due to the fact that in our study, we used the APACHE IV score.

However, in our study, the AUC of MLR (0.842) was only second to the APACHE IV score (0.876), thus making it a better predictor of mortality than the rest (Table *8*). The predictive efficacy of NLR and MLR combined with NLR was almost the same, with AUC values of 0.823 and 0.826, respectively, but NLR was the worst. In the study by Sun et al. [29] and Yang et al. [2], combining MLR and NLR values resulted in improved prediction of the diagnosis of COVID-19 in patients and mortality at 28 days in ARDS patients, respectively, with higher AUC than MLR alone. In contrast to that, our study combining MLR and NLR only improved the sensitivity while AUC remained lower than MLR day 1 alone (78% vs 80.9%) as shown in Table *8*. This is probably because the sensitivity and specificity of MLR day 1 and NLR day 1 are not very different from each other.

In our study, we thus infer that MLR is a very good predictor for mortality at 28 days in ARDS patients compared to NLR, while if we consider MLR and NLR in combination, the sensitivity improves without too much compromising the specificity. In our study, the best predictor of 28-day mortality was the APACHE IV score, followed by MLR day 1 values, then MLR and NLR combined, followed by NLR day 1 values.

The APACHE IV score, as already shown in studies conducted by Zimmerman et al. [19], was the predictor of mortality with the highest AUC, but had similar sensitivity to MLR.

The NLR on day 1 showed both high sensitivity and specificity (77% and 71 %, respectively) for mortality at 28 days (Table *8*). A study conducted by Song et al. [15] also showed similar results, where the sensitivity and specificity of the lymphocyte-to-neutrophil ratio for predicting mortality in ARDS patients were 83.8% and 80.2%, respectively. In the study conducted by Wang et al. [14], NLR values greater than 14 correctly predicted mortality at 90 days and the need for invasive mechanical ventilation (as shown by their Kaplan-Meier curve and regression analysis). Similarly, in our study, the optimal cutoff for NLR was 15.2 for predicting mortality at 28 days. This was also in line with the NLR model published in 2021 by Zahorec et al. [30], where NLR values greater than 11 were associated with severe inflammation and stress.

The prediction of other outcomes, i.e., the requirement of ECMO and the requirement of invasive mechanical ventilation, was also analyzed in our study. The ROC curves (Figures *7*, *8* and Tables *9*, *10*) show that MLR measured on day 1 has the highest AUC, making it the best predictor for the requirement of invasive mechanical ventilation and the requirement of ECMO. MLR day 1 values had 100 % sensitivity for the requirement of ECMO in our study (Table *9*).

In a study by Yang et al. [31], NLR values were combined with factors that influenced the need for invasive mechanical ventilation (i.e., P/f ratio, hemoglobin levels, lactate levels, use of vasoactive drugs) and plotted on an ROC curve. The resultant AUC was 0.768 and showed good levels in both sensitivity and specificity. In contrast, our study showed an AUC of NLR on day 1 for the requirement of invasive mechanical ventilation of 0.737 (Table *10*), with very high sensitivity (90.2%) and low specificity (30%). This is probably another major drawback of our study, as we have not considered the other factors that might have influenced the requirement of invasive mechanical ventilation.

However, our results are in line with the basic pathophysiology of ARDS, which shows that, even though in the exudative phase both neutrophil recruitment and monocyte recruitment are the heralding factors, the later part of the pathophysiology is mainly continued by monocytes, paving the pathway for the proliferative phase and the fibrotic phase [8,32]. In both cases, combining MLR with NLR did not show much improvement over MLR day 1 values as a predictor for the requirement of ECMO.

The secondary outcomes that had continuous variables were analyzed using correlation. In our study, MLR day 1 and NLR day 1 values showed a high positive correlation with length of stay in the hospital and duration of invasive mechanical ventilation (Figures *9*, *10*). This was again similar to the study done by Yang et al. [2], where higher MLR and NLR were associated with prolonged hospital stay in ARDS patients. In the study by Yang et al. [30], high NLR levels were associated with more days in the hospital and a longer duration of invasive mechanical ventilation, which again was similar to our study.

Furthermore, both NLR and MLR showed high negative correlations with the P/f ratio of the patients (Figure

11). In the study conducted by Song et al. [15], similar results were seen, where the lymphocyte-to-neutrophil ratio showed a moderate correlation with P/f ratio in ARDS patients.

APACHE IV score also showed a high positive correlation with duration of invasive mechanical ventilation and hospital length of stay, and a high negative correlation with P/f ratios. In our study, there was a significant association between high MLR, NLR, and APACHE IV scores and high usage of steroids and muscle relaxants. This also indicates that high MLR and NLR are probably associated with higher inflammatory responses and lower P/f ratios (Figure *11*).

In the studies conducted by Yang et al. [2], Song et al. [15], Yang et al. [31] on ARDS patients, Djordjevic et al. [11] on sepsis patients, and Mirna et al. [13] on myocarditis patients, all showed that high NLR and high MLR values are associated with higher mortality rates. This finding was similar to our study, where higher MLR and NLR values showed a high positive correlation with mortality. (Table *12*)

The regression analysis in our study showed MLR at day 1, APACHE IV score, P/f ratio, and lactate to be independently associated with mortality. Previous studies on MLR as a prognostic factor in critical illness, such as the one by Yang et al. [2] on ARDS patients and the one by Wen et al. [10] on peritoneal dialysis patients, showed that MLR is an independent predictor of mortality. However, our regression analysis model demonstrates an independent association of MLR on day 1 with mortality, but the magnitude of association remains uncertain when compared with other mortality indicators, leading to wide confidence intervals. These wide confidence intervals and the high odds ratio can also be attributed to the fact that the original cohort is, in itself, well separated, with less intergroup overlap and significant intragroup overlap between the considered variables, leading to large coefficient generation, and also to the fact that the numerical scale for MLR is 0.1, whereas the odds ratio scale is 1, which should be considered.

In studies conducted on NLR, such as those by Wang et al. [14] and Song et al. [15] in ARDS patients, NLR was an independent predictor of mortality. This was in contrast with our study, where, even though NLR showed a positive correlation with mortality, it did not show to be a significant predictive factor of mortality in our regression analysis. The possible cause of this difference is that, in our study, we excluded patients with major comorbidities such as liver disease, renal disease, and cardiac diseases, and we also observed higher use of invasive mechanical ventilation and lower use of ECMO as a rescue device (Figure *5*). However, in our study, comparing the AUCs of NLR and MLR on day 1, as well as the fact that NLR is a weaker predictor of outcome compared to MLR, is quite similar to the findings of Mirna et al. [13] and Wang et al. [14]. In both studies, NLR was a poorer marker of outcome when compared with MLR. This raises a bigger question, considering that there is a significant difference between MLR on Day1 and again on Day 5 between the two groups, with the MLR being higher in the non-survivor group compared to the survivor group (Table *4*), and the pathophysiology of ARDS and the fact that invasive mechanical ventilation was used in higher proportions in the non-survivor group, might indicate that higher MLR values are associated with poor lung ventilator interactions causing post-ARDS fibrosis. This may be a research question for further investigation.

Furthermore, in our study, we found that MLR day 1 values greater than 0.74, NLR day 1 values greater than 15.2, and APACHE IV scores greater than 17.5 are associated with worse prognosis and also with more aggressive management of ARDS (Table 14). The cut-off points for MLR and NLR found in our study are similar to those found in the study conducted by Wang et al. [14] and Yang et al. [2].

Our study has several drawbacks; for example, our study population size is small, the study is retrospective, and it was a single-center study. There are methodological limitations with the propensity score matching and the regression models, which warrant further large-scale studies. We used the Berlin criteria for ARDS, which has major drawbacks [21]. We also excluded patients with major comorbidities, which is different from real-life scenarios. We also did not consider the ventilation specifics, prone positioning, and other factors that might have influenced outcomes in our study.

Conclusions

We conclude that, in our study, MLR was an independent predictor of mortality in ARDS, but the magnitude of this association requires further study. The NLR value shows strong association with poorer outcomes but it might not be a good predictor of mortality, and also, APACHE IV score is almost equal in performance to MLR in prediction of outcomes in ARDS patients. The literature on the role of MLR as a prognostic factor in ARDS and in lung-ventilator interactions and post-ARDS fibrosis is scarce, and it is justified to pursue further investigations into the same.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Clinical Research Ethics Committee, Medica Superspecialty Hospital, Kolkata issued approval CERC Ref: CERC/2012/AUG/1(v). The study was reviewed and approved by the Clinical Research Ethics Committee (CERC) of Medica Superspecialty Hospital, Kolkata (now Manipal Hospital, EM Bypass), following approval by the institutional ethics committee and Scientific Review Committee, and was conducted in accordance with the principles of the Declaration of Helsinki. Patient confidentiality was strictly maintained throughout the study. No identifying information, such as patient names or hospital identification numbers, was recorded, and all data were anonymized before analysis. The study posed no additional risk to participants, and no compensation was applicable. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to appropriate institutional and ethical considerations. The data are stored as de-identified participant data.

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