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Blood Cell Inflammatory Indices and Intensive Care Admission in Hospitalized Patients with COVID-19

Chun-Lang Su [1,2], Yu-He Li [3], Hsin-Hung Chen [4,5,*] and Wei-Zhe Liang [4,6,*]

1 Department of Nursing, Chung Jen Junior College of Nursing, Health Science and Management, Chiayi City 60077, Taiwan; sutoshiro0903@gmail.com
2 Department of Rehabilitation, Tung Wah Hospital, Zhushan Township, Nantou County 557013, Taiwan
3 Department of Laboratory Medicine, Zuoying Armed Forces General Hospital, Kaohsiung City 813204, Taiwan; colisxp@gmail.com
4 Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung City 813414, Taiwan
5 Department of Physical Therapy, Shu-Zen Junior College of Medicine and Management, Kaohsiung City 82144, Taiwan
6 Department of Pharmacy and Master Program, College of Pharmacy and Health Care, Tajen University, Yanpu Township, Pingtung County 90741, Taiwan
* Correspondence: derekchen@vghks.gov.tw (H.-H.C.); wzliang@vghks.gov.tw (W.-Z.L.); Tel.: +886-7-3422121 (ext. 71564) (H.-H.C.)

Abstract

We examined eight blood cell inflammatory indices in relation to recorded intensive care unit (ICU) admission during patients' first COVID-19 hospitalization in 2021–2025. Among 1128 patients, 691 had a usable blood count and differential pair; 155 (22.4%) had a recorded ICU admission. Pair selection followed export order; specimen timing relative to ICU transfer was unavailable. In 680 patients, marker-only areas under the receiver operating characteristic curve (AUC) were 0.814 for the neutrophil-to-lymphocyte–platelet ratio (NLPR) and 0.804 for the neutrophil-to-lymphocyte ratio (NLR). Their paired difference was 0.010 (95% confidence interval [CI], −0.012 to 0.031). In 678 patients evaluable under both selection rules, first-versus-last NLPR AUCs were 0.819 and 0.682 (difference, 0.137; 95% CI, 0.085–0.188). Each standard deviation increase in log(1 + NLR) was associated with a recorded ICU admission after covariate adjustment (odds ratio, 2.82; 95% CI, 2.23–3.56). In the same 680 patients (149 ICU), five-fold cross-validated AUCs were 0.617 for the clinical model, 0.795 with the NLR and 0.706 with the NLPR. These findings favor the NLR for describing recorded ICU status in this cohort; they do not establish prediction of subsequent ICU transfer.

Keywords: COVID-19; intensive care unit; complete blood count; neutrophil-to-lymphocyte ratio; systemic immune-inflammation index; retrospective study

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1. Introduction

Coronavirus disease 2019 (COVID-19) ranges from self-limiting respiratory illness to hypoxemic respiratory failure, thromboinflammation, multiorgan dysfunction, and death. Severe disease is linked to dysregulated innate and adaptive immune responses, endothelial injury, and coagulation abnormalities. Age, cardiometabolic disease, and evolving treatment over time also influence the clinical course [1,2].

Complete blood count with differential is inexpensive, readily available, and commonly repeated during hospital care. Meta-analyses have found higher neutrophil counts, lower lymphocyte counts, and altered platelet measurements in severe COVID-19 [3–5]. These cell

counts may therefore summarize different aspects of the inflammatory response, although no single biological mechanism can be inferred from the derived indices.

The neutrophil-to-lymphocyte ratio (NLR) is the most extensively studied composite index. Systematic reviews and hospital cohorts have linked higher NLR values to severe disease, intensive care unit (ICU) admission, and mortality [6,7]. A direct multicenter analysis also compared several composite indices for ICU admission [8]. Beyond the NLR, platelet- and monocyte-containing indices may capture partially distinct features of the circulating cellular response. These include the platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte–platelet ratio (NLPR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) [9–15].

Comparing studies is difficult because investigators have used mortality, invasive ventilation, ICU admission, or composite severity outcomes and have sampled blood at different stages of illness [16–19]. Treatment also changed across pandemic waves. The index with the highest discrimination in one cohort may therefore rank differently in another. Discrimination and covariate-adjusted association are distinct measures and should be reported separately.

We selected eight established indices calculable from neutrophil, lymphocyte, monocyte and platelet counts to ask whether the more complex formulas distinguish ICU from non-ICU patients better than the NLR alone. The NLPR divides the NLR by platelet count, whereas SII multiplies it by platelet count. Comparing these formulas in the same patients, using the same blood count pair and ICU outcome, shows how platelet weighting affects discrimination while holding the patient sample constant. For each patient's first recorded COVID-19 hospitalization, we also examined whether adding the NLR or the NLPR to the same clinical model improved cross-validated discrimination and how discrimination varied with the choice of blood count pair. All-cause in-hospital death during that stay was the secondary outcome.

2. Materials and Methods

2.1. Study Design and Setting

This retrospective, single-center study used patient admission records and blood count results from Kaohsiung Veterans General Hospital, Taiwan. We screened all hospitalizations with International Classification of Diseases, 10th Revision (ICD-10) code U07.1 during 2021–2025. We linked stays by patient and designated each patient's first chronological admission in that window as the index stay before checking whether a usable blood count and differential were available. A later admission with blood testing or ICU care could not replace the index stay. Each patient contributed at most one observation per analysis.

2.2. Eligibility

Eligibility required a CBC row with white blood cell and platelet counts and a differential row with segmented neutrophil, lymphocyte and monocyte percentages during the index stay. Groups were defined by whether ICU admission was recorded during that stay. The extract recorded the hospital entry route but lacked specimen-collection times, ICU-transfer times and subsequent ward movements. We could not distinguish direct ICU admissions from ward transfers, determine whether a specimen preceded transfer, or apply a common 24–48-h sampling window. Because the extract preserved row order within each admission, we applied the same pairing and selection rule to both groups. The first usable pair in the export could have been collected at any point during the stay.

Within each index stay, we processed CBC rows in export order and matched each to the nearest unused differential row, breaking distance ties in favor of the earlier row. We ranked pairs by the earlier row of the pair and selected the first for the primary analysis and the last for sensitivity analysis. The two record types shared no instrument identifier. Of 691 selected pairs, 615 occupied adjacent rows. Adjacent rows do not necessarily originate from the same specimen and cannot confirm a single laboratory order or the timing of blood draws. White blood cell and platelet counts were recorded in 10^3 cells/μL.

2.3. Inflammatory Indices and Outcomes

Neutrophil percentage was defined as the sum of band and segmented neutrophil percentages; a missing band value was treated as zero. We calculated the absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and absolute monocyte count (AMC) from the white blood cell count and corresponding differential percentages. We expressed the resulting absolute cell counts in 10^3 cells/μL.

The indices were calculated as follows: NLR = ANC/ALC; PLR = platelet count/ALC; LMR = ALC/AMC; MLR = AMC/ALC; NLPR = ANC/(ALC × platelet count); SII = ANC × platelet count/ALC [20]; SIRI = ANC × AMC/ALC [21]; and AISI = ANC × AMC × platelet count/ALC. Values with zero denominators were treated as unavailable.

The primary outcome was any recorded ICU admission during the index stay, referred to as recorded ICU status. This binary outcome does not establish whether ICU admission preceded or followed the selected blood count pair. The secondary outcome was all-cause in-hospital death during that same stay. Records from subsequent hospitalizations were excluded. The extract provided a binary death flag without cause-of-death attribution. Covariates included age, recorded sex and five recorded conditions (cardiovascular disease [CVD], diabetes, hypertension, chronic obstructive pulmonary disease [COPD] and stroke history). Atrial fibrillation (AF) was recorded separately; the supplied CVD flag entered the models without a separate AF term.

The source contained separate acute ischemic stroke (AIS) and stroke-history (STROKE) flags. Only the stroke-history flag entered the covariate set and comorbidity count; AIS was reported descriptively in Table S1. These recorded flags do not establish the date of an acute stroke or its temporal relation to COVID-19 or ICU admission.

2.4. Statistical Analysis

We summarized continuous variables as medians and interquartile ranges and used two-sided Mann–Whitney U tests for group comparisons. For binary characteristics, we used Pearson chi-square tests or Fisher's exact tests when an expected cell count was below five. For the age and comorbidity-count distributions, we tested the Pearson statistic conditional on fixed margins using 20,000 Monte Carlo draws. Reporting followed STROBE and RECORD recommendations [22,23]. For each index, we calculated the area under the receiver operating characteristic (ROC) curve (AUC) and a 95% confidence interval from 1000 outcome-stratified bootstrap samples of individual patients. Exploratory within-sample cutoffs maximized the Youden index; they were not validated clinical decision thresholds. For death, we estimated sensitivity and specificity intervals from 2000 patient bootstrap samples at the original unrounded cutoff.

For the full-sample association analyses, each index entered a separate logistic model as log(1 + index), standardized using the sample standard deviation. The seven nonredundant indices were compared on their shared sample. We adjusted for age, recorded sex, five comorbidities and admission year as a linear term, with HC1 robust standard errors for independent patients. Admission dates were taken from the outpatient, emergency department or direct admission field, in that order. Both patients without an admission

date had a single recorded stay and no usable laboratory pair. The 2023 worksheet supplied their calendar year for selection modeling. All repeat stays had dates, and no patient had tied first dates. We also examined 2021–2022 and 2023–2025 separately using full-sample index scaling and repeated comparisons on the shared eight-index sample.

To compare the NLPR with the NLR and SII, we estimated paired AUC differences from case–control concordance, assigning half credit to ties. Differences in case and control placement influences provided patient-level standard errors for two-sided Wald intervals and p values. These comparisons were exploratory and unadjusted for multiplicity.

For the first-versus-last pair sensitivity analysis, we also restricted each index to patients with evaluable values under both rules. We resampled ICU and non-ICU patients separately with replacement 2000 times, retaining both measurements from each sampled patient. The 2.5th and 97.5th percentiles gave 95% confidence intervals for each AUC and the paired difference (first minus last). Thus, patient composition was identical within each paired comparison. First and last refer to export order, not verified sampling chronology.

We additionally restricted the originally selected first pair to patients whose CBC and differential occupied adjacent export rows (absolute row distance of one) without substituting a later pair. For each evaluable index, we estimated marker-only AUCs with 2000 outcome-stratified patient bootstrap samples and refit the year-adjusted ICU model with HC1 robust standard errors. The log-transformed standard deviation from the corresponding full first-pair sample was retained as the odds-ratio unit. This exploratory restriction tests sensitivity to row separation, not specimen identity.

For the selection analysis, we modeled inclusion in the seven-index sample among all 1128 index patients using age, sex, the five comorbidities, admission year, recorded ICU status and in-hospital death. Both outcomes were available for included and excluded patients and were associated with laboratory availability. Including them allowed selection probabilities to reflect this observed outcome-dependent availability. This retrospective selection model was separate from the cross-validation models and was not intended for use before outcomes were known. We refitted the ICU association models using stabilized inverse-probability-of-inclusion weights.

The original weighted HC1 intervals treated estimated weights as fixed. We additionally resampled all 1128 patients with replacement 2000 times, refitting the selection model, recalculating stabilized weights and refitting each weighted outcome model in every replicate. The original seven-index log-transformed standard deviation was retained as the effect unit. Percentile intervals from this bootstrap incorporate weight-estimation uncertainty. Weighting relies on the measured variables adequately accounting for selection and does not correct selection driven by unmeasured determinants of testing or by unobserved index values.

We assessed stabilized-weight percentiles, extremes and effective sample size, calculated as $(\text{sum of weights})^2/\text{sum of squared weights}$. We examined fitted inclusion probabilities in included and excluded patients, their empirical range overlap, and representation across measured covariate levels. To assess how weighting reproduced the full index-patient population, we compared unweighted and weighted included-sample means or proportions with the target population, using absolute mean differences divided by the fixed target-population standard deviation. No weights were trimmed or truncated. These empirical diagnostics cannot establish positivity for every joint covariate pattern or for unmeasured variables.

For internal validation, we compared logistic models containing age, sex, the five comorbidities and calendar year with and without $\log(1 + \text{NLR})$ or $\log(1 + \text{NLPR})$. All three cross-validated models used the same 680 patients with seven evaluable indices, including 149 with recorded ICU admission and 531 without it. The separate 674-patient

sample required all eight indices, including the LMR; it was used only for the common eight-index analysis in Table S6, not cross-validation. Six patients in the 680-patient sample had zero monocyte counts and therefore an undefined LMR; the NLR and NLPR remained evaluable in these patients. All models used the same five folds, stratified by recorded ICU status; each patient contributed one held-out probability. Only fixed, prespecified transformations were applied: age divided by 10, year minus 2023 and log(1 + index). No imputation, data-derived standardization, feature selection or hyperparameter tuning was used in cross-validation. All model coefficients were estimated using the four training folds and applied to the held-out fold. The sample-based standardization used to express association odds ratios was not used in cross-validation. We calculated pooled held-out AUCs, Brier scores and calibration intercepts and slopes. Analyses used Python 3.12.14, NumPy 2.3.5 and pandas 3.0.1.

2.5. Ethics Approval and Informed Consent

The Institutional Review Board of Kaohsiung Veterans General Hospital approved this retrospective study on 28 August 2026 (protocol KSVGH26-CT9-13). The approved retrospective review covered admissions from 2021 through 2025, including the 2025 admissions analyzed in this study. The board waived informed consent for this retrospective study of de-identified data. The study followed the Declaration of Helsinki.

2.6. Use of AI-Assisted Tools

OpenAI ChatGPT (GPT-6; OpenAI, San Francisco, CA, USA) and Codex (GPT-6; OpenAI, San Francisco, CA, USA; accessed 16–23 November 2026) assisted with drafting, language editing, reference organization, formatting, and document checks. Specifically, Codex (GPT-6) assisted with analysis code and manuscript/table revisions (16–17 November 2026), additional analyses and second-round revisions (20 November 2026), and adjacent-row analysis, weighting diagnostics, and third-round revisions (23 November 2026). The original graphical abstract was prepared using SciDraw AI (web application, accessed 3 November 2026), and OpenAI's image generation tool (GPT Image/ChatGPT, accessed 18 November 2026) was used to redraw it.

3. Results

3.1. Cohort and Baseline Characteristics

We screened 1184 COVID-19 admissions from 1128 patients. Of these patients, 39 had multiple stays, accounting for 56 subsequent admissions. Of the 1128 index stays, 437 lacked a usable laboratory pair (38.7%). These included 14 patients who had a usable pair only on a later stay. Among the 691 patients with a usable index-stay pair, 155 (22.4%) had a recorded ICU admission and 82 (11.9%) died in hospital (Figure 1).

Median age was 72 years among patients with a recorded ICU admission and 67.5 years among those without ($p = 0.002$). Among 155 ICU patients, 111 (71.6%) were aged 65 years or older, compared with 298 of 536 non-ICU patients (55.6%). Recorded CVD was more frequent in ICU patients (49.7% vs. 38.1%). All 21 patients with recorded AF also had the CVD flag. Table 1 summarizes the distribution of age and comorbidity burden.

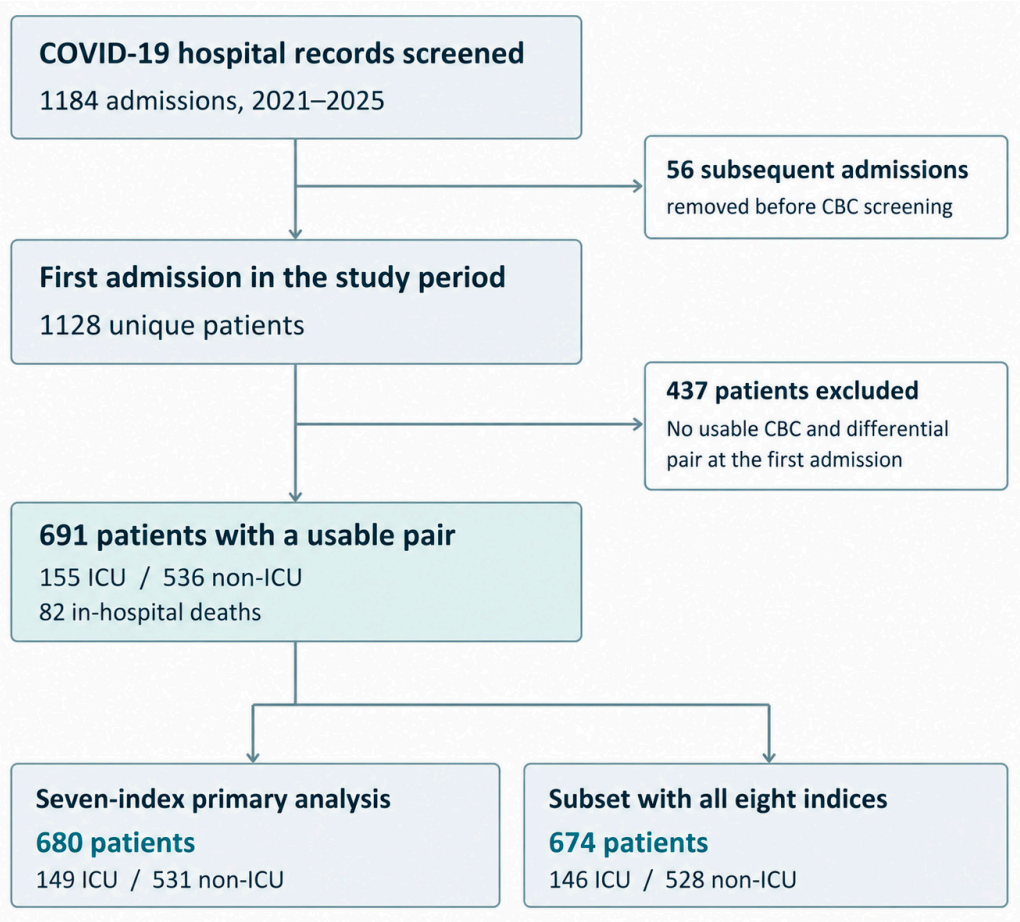

Figure 1. Patient selection from screened COVID-19 hospitalizations. We selected each patient's first admission in the study period before checking for a usable CBC and differential pair. Recorded ICU admission and in-hospital death refer to that same stay. CBC, complete blood count. ICU, intensive care unit.

Table 1. Characteristics of patients with a usable laboratory pair by recorded ICU admission during the index stay.

Characteristic	Overall	Non-ICU	ICU	*p* Value
Patients, *n*	691	536	155	
Age, years	69 [53, 81]	67.5 [50, 81]	72 [61, 83]	0.002
Male sex, *n* (%)	410/691 (59.3)	322/536 (60.1)	88/155 (56.8)	0.461
Cardiovascular disease, *n* (%)	281/691 (40.7)	204/536 (38.1)	77/155 (49.7)	0.010
Atrial fibrillation, *n* (%)	21/691 (3.0)	13/536 (2.4)	8/155 (5.2)	0.107
Diabetes mellitus, *n* (%)	144/691 (20.8)	113/536 (21.1)	31/155 (20.0)	0.770
Hypertension, *n* (%)	172/691 (24.9)	142/536 (26.5)	30/155 (19.4)	0.070
COPD, *n* (%)	39/691 (5.6)	26/536 (4.9)	13/155 (8.4)	0.093
Stroke history, *n* (%)	57/691 (8.2)	40/536 (7.5)	17/155 (11.0)	0.162
Age group, years				<0.001
<18	2 (0.3)	2 (0.4)	0 (0.0)	
18–64	280 (40.5)	236 (44.0)	44 (28.4)	
65–74	145 (21.0)	96 (17.9)	49 (31.6)	

Table 1. *Cont.*

Characteristic	Overall	Non-ICU	ICU	*p* Value
≥75	264 (38.2)	202 (37.7)	62 (40.0)	
Recorded conditions, *n*				0.008
0	345 (49.9)	282 (52.6)	63 (40.6)	
1	117 (16.9)	79 (14.7)	38 (24.5)	
2	131 (19.0)	96 (17.9)	35 (22.6)	
≥3	98 (14.2)	79 (14.7)	19 (12.3)	

Values are median [interquartile range] or count (percentage within column). The burden count (0–5) sums CVD, diabetes, hypertension, COPD and stroke history. AF was recorded separately and contributed no additional point. For each grouped characteristic, the *p* value is an omnibus comparison of the full distribution. ICU, intensive care unit. COPD, chronic obstructive pulmonary disease.

3.2. Inflammatory Indices and Recorded ICU Status

All seven nonredundant indices were higher in the 149 ICU patients than in the 531 non-ICU patients with complete index values (all $p < 0.001$, Table 2). The median NLR was 9.89 versus 3.24, and the median NLPR was 0.0633 versus 0.0162. The main analyses include the MLR because the LMR is its reciprocal when both counts are positive.

Table 2. Blood cell inflammatory indices by recorded ICU admission during the index stay.

Index	Overall (n = 680)	Non-ICU (n = 531)	ICU (n = 149)	*p* Value
NLR	4.16 [2.08, 9.12]	3.24 [1.82, 6.38]	9.89 [5.81, 19.6]	<0.001
PLR	155 [105, 245]	146 [102, 213]	213 [135, 421]	<0.001
MLR	0.365 [0.222, 0.619]	0.31 [0.205, 0.535]	0.516 [0.38, 1]	<0.001
NLPR	0.023 [0.0103, 0.0564]	0.0162 [0.00883, 0.0371]	0.0633 [0.0341, 0.122]	<0.001
SII	777 [386, 1.66 × 10^3]	650 [342, 1.26 × 10^3]	1.69 × 10^3 [889, 4.45 × 10^3]	<0.001
SIRI	1.88 [0.791, 4.43]	1.39 [0.702, 3.28]	4.45 [2.33, 10.7]	<0.001
AISI	350 [147, 867]	286 [129, 647]	707 [304, 1.93 × 10^3]	<0.001

Values are median [interquartile range]. ICU indicates intensive care unit; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; NLPR, neutrophil-to-lymphocyte–platelet ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; AISI, aggregate index of systemic inflammation. Component white blood cell, platelet, and derived absolute differential counts were expressed in 10^3 cells/μL. All seven rows describe the same 680 patients (149 ICU and 531 non-ICU).

In the same 680 patients, marker-only AUCs were 0.814 for NLPR, 0.804 for the NLR and 0.745 for SII (Table 3). The paired NLPR–NLR difference was 0.010 (95% CI, −0.012 to 0.031, $p = 0.364$), providing no statistically significant evidence that NLPR discriminated recorded ICU status better than the NLR. The NLPR–SII difference was 0.070 (95% CI, 0.027 to 0.113, $p = 0.00153$). At the exploratory NLPR cutoff selected within this cohort (0.0289 rounded), sensitivity was 85.2% and specificity was 68.2%; this cutoff is not a validated clinical decision threshold.

Table 3. Observed discrimination of inflammatory indices for recorded ICU admission during the index stay.

Index	AUC (95% CI)	Cutoff (Rounded)	Sensitivity	Specificity	N (ICU)
NLR	0.804 (0.767–0.840)	≥3.655	0.926	0.550	680 (149)
PLR	0.658 (0.607–0.708)	≥205.0	0.537	0.725	680 (149)
MLR	0.695 (0.645–0.741)	≥0.392	0.745	0.606	680 (149)
NLPR	0.814 (0.777–0.848)	≥0.0289	0.852	0.682	680 (149)
SII	0.745 (0.703–0.792)	≥1409	0.597	0.789	680 (149)

Table 3. *Cont.*

Index	AUC (95% CI)	Cutoff (Rounded)	Sensitivity	Specificity	N (ICU)
SIRI	0.744 (0.698–0.786)	≥1.957	0.805	0.601	680 (149)
AISI	0.695 (0.650–0.745)	≥551.2	0.631	0.706	680 (149)

AUC indicates area under the receiver operating characteristic curve; CI, confidence interval; N, number of patients; ICU, intensive care unit; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; NLPR, neutrophil-to-lymphocyte–platelet ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; AISI, aggregate index of systemic inflammation. Component white blood cell, platelet, and derived absolute differential counts were expressed in 10^3 cells/μL. Higher values indicate recorded ICU status. Cutoffs are exploratory, selected within this cohort and rounded for display; they are not validated clinical decision thresholds. Sensitivity and specificity were calculated at the unrounded thresholds. Each row includes the same 680 patients (149 ICU). Each 95% CI for the AUC used outcome-stratified patient resampling.

3.3. Adjusted Associations and Secondary Outcome

Among the 680 patients with seven evaluable indices, 149 had recorded ICU admission. A one-standard-deviation increase in log(1 + NLR) was associated with higher odds of recorded ICU admission after adjustment for calendar year, demographics and comorbidities (adjusted OR, 2.82, 95% CI, 2.23–3.56). Table 4 reports each index separately.

Table 4. Adjusted associations between blood cell inflammatory indices and recorded ICU admission during the index stay.

Index	N	ICU, *n*	Adjusted OR (95% CI)	*p* Value
NLR	680	149	2.82 (2.23–3.56)	<0.001
PLR	680	149	1.65 (1.32–2.08)	<0.001
MLR	680	149	1.76 (1.42–2.18)	<0.001
NLPR	680	149	1.76 (1.07–2.90)	0.026
SII	680	149	2.38 (1.84–3.07)	<0.001
SIRI	680	149	2.31 (1.86–2.88)	<0.001
AISI	680	149	1.94 (1.45–2.59)	<0.001

OR, adjusted odds ratio. CI, confidence interval. Each index entered a separate logistic model in the same 680 patients. Covariates were age, recorded sex, CVD, diabetes, hypertension, COPD, stroke history and admission year. ORs represent a one-standard-deviation increase in log(1 + index). Wald intervals and *p* values use HC1-robust standard errors.

During the index stay, 82 patients died from any cause (Table S1). Marker-only AUCs for death were 0.781 for the NLPR and 0.759 for the NLR (Table S2). These are descriptive estimates: no formal paired comparison of mortality AUCs was performed, so the numerical difference does not establish superior mortality discrimination by the NLPR. Adjusted ORs were 2.13 (1.67–2.71) for the NLR and 1.39 (0.97–1.99) for the NLPR (Table S3).

The mortality models used the same covariates and HC1 standard errors as the ICU models. Seven indices were evaluable in 680 patients (79 deaths), and the LMR was evaluable in 684 patients (81 deaths).

3.4. Sensitivity Analyses

Patients with a usable pair on the index stay ($n = 691$) were older than those without one ($n = 437$) (median age, 69 vs. 66 years). Recorded CVD was more common in the paired group (40.7% vs. 30.9%). Recorded ICU admission (22.4% vs. 5.5%) and in-hospital death (11.9% vs. 5.9%) were more frequent in the paired group (Table S4A). In the rule-specific samples, the NLPR AUC was 0.814 (95% CI, 0.777–0.848) with the first usable pair and 0.681 (0.626–0.736) with the last pair in export order; these analyses included 680 and 687 patients, respectively (Table S4B, panel A).

In the 678 patients evaluable under both rules (148 ICU patients), the NLPR AUC was 0.819 (95% CI, 0.783–0.852) for the first pair and 0.682 (0.628–0.733) for the last, with a paired difference of 0.137 (0.085–0.188). For the NLR in the same patients, the corresponding AUCs were 0.811 (0.774–0.846) and 0.681 (0.633–0.728), with a paired difference of 0.130 (0.077–0.180). Table S4B, panel B reports all eight indices with index-specific sample sizes and ICU counts.

The adjacent-row restriction retained 615 patients (131 ICU); 605 (126 ICU) had evaluable values for the seven primary indices. In these 605 patients, the NLR and NLPR AUCs were 0.812 (95% CI, 0.773–0.849) and 0.825 (0.788–0.858), respectively. The paired NLPR–NLR difference was 0.013 (−0.010 to 0.036; $p = 0.269$). Adjusted ORs were 3.05 (2.37–3.92) for the NLR and 2.67 (1.58–4.54) for the NLPR. The LMR was evaluable in 610 patients (128 ICU). Table S4C reports all eight indices. The direction of association was preserved, but adjacency did not verify specimen identity.

The adjusted NLR OR was 3.07 (2.17–4.36) in 2021–2022 and 2.54 (1.85–3.49) in 2023–2025. After selection weighting, it was 2.65, with a fixed-weight HC1 interval of 2.10–3.34 and a re-estimated-weight bootstrap interval of 2.19–3.55 (Table S5). All 2000 bootstrap replicates converged. For NLPR, the weighted OR was 1.54; its fixed-weight interval included one (0.97–2.45), whereas its bootstrap interval did not (1.19–2.89). This interval-method sensitivity warrants caution.

Selection diagnostics compared the 680 included patients with the remaining 448 of 1128 index patients. Stabilized weights had a median of 1.021 (interquartile range, 0.845–1.146), a range of 0.641–1.547 and an effective sample size of 655.3 (96.4% of 680); no weight exceeded 2. Fitted inclusion probabilities ranged from 0.390 to 0.941 in the included patients and 0.400 to 0.910 in the excluded patients. Ten included patients lay outside the empirical overlap of these ranges. Absolute standardized differences from the full target population were at most 0.008 after weighting (Table S5, panels C–E).

Among 691 first pairs, 11 had zero lymphocytes and 7 had zero monocytes. All eight indices were evaluable in 674 patients, including 146 with a recorded ICU admission (Table S6). This sample excluded six patients with zero monocyte counts from the 680-patient seven-index sample; three of these six had recorded ICU admission.

Internal validation used 680 patients (149 ICU) for each of the base, base + NLR and base + NLPR models. Their cross-validated AUCs were 0.617, 0.795 and 0.706, respectively, with calibration slopes of 0.73, 0.88 and 0.75. Held-out folds contained 137, 136, 136, 136 and 135 patients, with 30, 30, 30, 30 and 29 ICU events, respectively. Table S7 reports the sample and event counts for each model and fold.

4. Discussion

Among patients with evaluable blood counts during the index stay, the NLPR and NLR distinguished those with and without recorded ICU admission. Their marker-only paired AUC difference was small and its confidence interval included zero; these results do not establish superiority of the NLPR. A higher NLR remained associated with recorded ICU admission after adjustment for calendar year, demographics and recorded comorbidities. Restricting first-versus-last comparisons to the same 678 patients still yielded a lower NLPR AUC for the last pair in export order (0.819 versus 0.682). Thus, differing patient composition alone does not explain the observed decrease.

The NLR findings are consistent with systematic reviews reporting higher NLRs in cases of severe or fatal COVID-19 [6,7,24]. The present NLR AUC of 0.804 is numerically close to the summary AUC of 0.82 for disease severity reported by Sarkar and colleagues [24]. Their pooled endpoint differed from index-stay ICU admission. Differences in populations, treatment periods and measurement times also limit direct comparison.

Earlier cohorts identified older age and organ dysfunction as correlates of mortality, and a multicenter US ICU cohort also identified patient- and hospital-level risk factors [25,26]. These reports support considering clinical context when interpreting inflammatory measures; neither validates the index ranking nor cutoff in the present cohort.

Our findings can be considered alongside earlier laboratory evidence. Soraya and Ulhaq reported higher leukocyte and neutrophil counts and lower lymphocyte and platelet counts in severe COVID-19 [3]. We examined combinations of these cell counts and compared eight formulas against a defined ICU outcome in a single cohort.

Hamad and colleagues compared composite inflammatory indices in a multicenter cohort and found higher values among ICU patients. Their adjusted analysis included acute clinical variables such as oxygen support, C-reactive protein, and D-dimer [8]. Our primary ICU models adjusted for age, recorded sex, five comorbidities and admission year. Differences in timing, case mix, and adjustment variables can affect the apparent ranking of indices; they do not establish the universal superiority of any index.

Associations for SII, SIRI and AISI were consistent in direction with earlier reports [9–15]. Many earlier studies combined ICU care with death, ventilation or other definitions of severity. Here, marker-only AUCs describe the ranking of patients by recorded ICU status, while adjusted odds ratios quantify associations conditional on the recorded covariates.

The NLPR divides the NLR by platelet count, while the SII multiplies the NLR by platelet count. The paired comparison provided little evidence that division by platelet count improved discrimination over the NLR alone. the LMR and MLR are reciprocals when both counts are positive. Their direction-adjusted AUCs were both 0.708 in the same 674 patients (Table S6).

Internal validation suggested that the NLR added information to demographic and comorbidity data for classifying recorded ICU status. Its held-out AUC was numerically higher than that of the model extended with the NLPR; no formal statistical comparison of these cross-validated model AUCs was performed. Oxygenation, respiratory rate, renal function, C-reactive protein and other bedside measures were unavailable for comparison. The incremental value of the NLR beyond clinical acuity at presentation therefore remains unknown. Calibration slopes below one in held-out patients also caution against transporting these models to other hospitals.

Measurement timing is particularly important. Serial-index studies have described changes during illness, and a study of circulating plasma cells found that these cells typically appeared after severe disease had developed [16,27]. These observations illustrate why a marker measured during severe illness cannot be assumed to predict that illness. The substantial reduction in NLPR discrimination under alternative source-row selection reinforces this concern in the present data.

Clinical case mix and treatment also require consideration. Diabetes and metabolic syndrome have been associated with adverse COVID-19 outcomes [28,29]. Cohort studies have documented changes in treatment and outcomes across surges, as well as differences in inflammatory measures and treatment use between patient groups [30,31]. Randomized evidence for dexamethasone further shows that treatment can influence outcomes [32]. The present extract did not provide vaccination, variant, antiviral or corticosteroid exposure, or other acute severity measures; residual and time-dependent confounding therefore remain plausible.

Observational and randomized studies of statins have also investigated inflammation and COVID-19 outcomes, but treatment effects cannot be inferred from the blood-cell associations reported here [33,34]. Work on updating COVID-19 prediction models over time further emphasizes that performance can change as clinical populations and care

evolve [35]. Any future use of these indices for triage would require a clearly defined pre-decision sample, comparison with clinical predictors, calibration, and independent temporal or external validation.

Dexamethasone can increase circulating neutrophils and reduce circulating lymphocytes within hours [36]. A high NLR at an unknown point during admission could therefore reflect both illness and treatment. Calendar year and broad periods cannot resolve individual vaccination, prior SARS-CoV-2 infection or hybrid immunity, circulating variant, obesity, changing ICU admission practices or treatment timing. These factors could influence both the cell counts and ICU use.

We evaluated eight indices within a single cohort and selected each patient's first admission before reviewing blood counts or outcomes. We modeled each index separately because the formulas share blood-cell components. AUCs and adjusted odds ratios describe discrimination and conditional association, respectively. The analysis of all-cause death and the comparison of source-order pairs examined how findings varied with outcome and record selection.

The order of the blood count records in the export does not establish when blood was drawn relative to ICU admission. A ward-to-ICU transfer could be paired with blood collected earlier on the ward or after clinical deterioration. Symptom-onset dates were unavailable, so we could not calculate the interval from symptom onset to hospital admission or to blood sampling. Changes in inflammation during illness, corticosteroid exposure, bacterial superinfection and erroneous pairing could all contribute to the sensitivity to record selection. The paired analysis holds patient composition constant but cannot separate these explanations or identify a biological trajectory. The adjacent-row sensitivity analysis retained the direction of association, but neighboring rows can still represent different specimens or orders and do not resolve timing relative to ICU transfer. The between-group comparisons describe patients as sampled during hospitalization. If ICU patients were tested later in illness or after treatment escalation, the observed differences and index ranking could change at a common sampling time. Cross-validation within this cohort preserves that timing uncertainty and does not validate the prediction of subsequent ICU transfer.

The outcome-inclusive selection model addresses differences captured by the measured variables; it cannot remove bias from unmeasured reasons for testing, such as changing oxygen needs, treatment escalation or undocumented clinical severity. Resampling the full selection population accounts for estimated-weight uncertainty but does not remedy misspecification of that model or unmeasured selection. Although fitted probabilities and weight magnitudes showed no near-zero inclusion probabilities or large weights under the specified model, empirical overlap was incomplete and these diagnostics do not prove positivity across all joint covariate patterns. The weighted analyses are therefore sensitivity analyses, not proof that selection bias has been eliminated.

5. Conclusions

In this cohort, the marker-only comparison did not establish superior discrimination of recorded ICU status by the NLPR over the NLR. The NLPR estimate remained sensitive to the choice of blood count pair when the same patients were compared. Adding the NLR to the clinical model yielded a larger numerical increase in cross-validated AUC than adding the NLPR. These findings favor the NLR for describing recorded ICU status under the sampling conditions of this cohort. They do not establish prognostic performance for subsequent ICU transfer. Prospective evaluation requires blood drawn at a common pre-decision time and comparison with bedside severity measures.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/pathogens15121237/s1: Table S1. Baseline characteristics and inflammatory indices by all-cause in-hospital death during the index stay. Table S2. Exploratory ROC analysis for all-cause in-hospital death during the index stay. Table S3. Adjusted associations between inflammatory indices and all-cause death during the index stay. Table S4A. Patients with and without a usable CBC and differential pair during their index stay. Table S4B. First versus last usable blood count pair in export order: panel A, rule-specific analyses; Panel B: paired first-versus-last AUC comparisons. Table S4C. Sensitivity analysis restricted to adjacent CBC and differential rows. Table S5. Recorded ICU associations: panel A, calendar adjustment, period and selection weighting; Panel B: uncertainty after re-estimating selection weights; Panel C: stabilized-weight distribution; Panel D: fitted inclusion-probability overlap; Panel E: included-sample balance against the full target population. Table S6. All eight indices in the same patients. Table S7. Internal validation for recorded ICU status: panel A, model performance; Panel B: shared cross-validation fold sizes.

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Informed Consent Statement: The Institutional Review Board waived the requirement for informed consent because the study used retrospectively collected, de-identified data. No directly identifying patient information is reported.

Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to institutional and ethical restrictions.

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