

Original Article

Admission Neutrophil-to-Lymphocyte Ratio Predicts Short- and Long-Term Mortality in Hospitalized Older Adults: A Retrospective Multicenter Study

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ABSTRACT: The neutrophil-to-lymphocyte ratio (NLR) is an inexpensive biomarker of systemic inflammation. Although widely studied in acute and chronic conditions, evidence on long-term outcomes in hospitalized older adults is limited. We assessed whether admission NLR predicts in-hospital and post-discharge all-cause mortality in geriatric patients. We performed a retrospective multicenter cohort study of acute medical admissions across IRCCS INRCA geriatric hospitals in Italy (January 2020–December 2024). Data were retrieved from electronic health records and laboratory databases. We analyzed 16,099 hospitalizations from 10,826 patients aged ≥ 65 years (median 84, 48% male). For long-term outcomes, 9,812 patients discharged alive after their first admission were followed up to 48 months. Admission NLR was calculated from complete blood counts; thresholds were defined by ROC analysis. Outcomes were in-hospital and 48-month mortality. Discrimination was assessed using AUC, Kaplan–Meier curves, and Cox proportional hazards models adjusted for demographics, comorbidities, and laboratory variables. In-hospital mortality occurred in 1,744 cases (11%). An NLR ≥ 5.36 was associated with higher in-hospital mortality (HR: 2.287; 95% CI: 2.025–2.582; $p < 0.001$). For long-term outcomes, an NLR ≥ 5.05 predicted increased 48-month mortality (51.6% vs 26.3% for NLR < 5.05 ; adjusted HR: 1.423; 95% CI: 1.302–1.556; $p < 0.001$). NLR values increased with age and were higher in males ≥ 80 years. A dynamic rise in NLR was observed before in-hospital death, suggesting utility as a marker of

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deterioration. Admission NLR is a strong, independent predictor of short- and long-term mortality in older adults. Its simplicity supports risk stratification, though optimal cut-offs require validation.

Keywords: Neutrophil-to-lymphocyte ratio, mortality, geriatric patients, Aged, 65 and over, biomarkers

INTRODUCTION

The neutrophil-to-lymphocyte ratio (NLR), calculated from routine complete blood counts, is increasingly recognized as a cost-effective inflammatory biomarker with prognostic value in age-related diseases (ARDs) [1]. From the pathophysiological perspective, NLR reflects the complex interplay between the activation of adaptive and innate immune responses, reflecting acute and chronic inflammation [1]. Our group, along with others, has highlighted NLR as a biomarker of inflammaging – a chronic, systemic, and low-grade proinflammatory state that increases with age and is now widely recognized as a key risk factor for the onset and progression of the major ARDs [2, 3].

Growing evidence supports the use of NLR as a prognostic indicator in various infectious diseases, including community-acquired pneumonia [4-6], COVID-19 [3, 7, 8], bacteremia [9], and sepsis [10]. Additionally, NLR has demonstrated prognostic value in several non-infectious conditions, such as acute stroke [11], acute myocardial infarction [12, 13], carotid atherosclerosis [14] heart failure [15], atrial fibrillation [16], intracerebral hemorrhage [17], diabetes [18], and cancer [19-21].

No universal NLR cut-off exists. Reported values in healthy, non-geriatric populations range from 0.78 to 3.92, with variations due to age, sex, comorbidities, and treatments such as steroids or chemotherapy [22, 23]. NLR tends to increase with age and is higher in males and individuals over 85 years [23]. Other factors influencing NLR include exogenous steroid use, endogenous hormonal changes, active hematological disorders, and ongoing chemotherapy treatments [23].

In a recent retrospective study of over 5,000 hospitalized geriatric patients, we identified elevated NLR at admission as an independent predictor of in-hospital mortality, with a cut-off ≥ 7.95 showing good predictive performance [2]. The association between NLR and mortality was confirmed to be significant even after excluding sepsis and pneumonia cases but appeared to be modified by renal function (eGFR < 45 mL/min/1.73 m²). Larger studies including inpatients and outpatients are needed to better define optimal NLR cut-off values for predicting mortality and re-hospitalization. There is increasing interest in the use of administrative health databases to identify prognostic markers in real-world

populations [24]. The Hospital Discharge Record Database collects data on all public hospitalizations in Italy and is now a key resource for clinical and health services research. In the current retrospective study, we combined administrative health databases and routine laboratory data to assess whether NLR predicts both short-term (in-hospital) and long-term (48-month) mortality in older adults. In our opinion, assessing both time horizons in geriatric patients is important, because, with respect to early mortality, NLR may reflect an acute inflammatory status associated to increased vulnerability, while, with respect to long-term mortality, NLR, as putative biomarker of inflammaging, may capture the sustained impact of chronic inflammation in causing negative outcomes in older people.

MATERIALS AND METHODS

Study population

This retrospective study included all hospital admissions of older patients aged 65 years and older at the National Institute on Health and Aging (Istituto Nazionale Ricovero e Cura per Anziani, INRCA) from January 2020 to December 2024, having at least one complete blood count at the time of admission. The study focused on major hospitalizations lasting longer than one day. Patients with a documented history of active hematological malignancies, as identified from electronic medical records, were excluded from the analysis. All analyses, including both in-hospital and long-term mortality, were conducted using each patient's first hospitalization. Therefore, repeated admissions were not treated as independent observations.

Ethics statement

This study was approved by the Ethical Committee of Marche region (Italy), protocol 64/2025. As this investigation was a retrospective study based on routine clinical examination results and the data were analyzed anonymously, informed consent was waived.

Outcomes and covariates

The primary outcome was in-hospital mortality, defined as death occurring during the index hospitalization.

Patients were followed from admission until either in-hospital death or discharge. For long-term outcomes, we evaluated all-cause mortality at 48 months. To ensure analytical consistency and avoid overlap with in-hospital events, only patients discharged alive after their first hospitalization were included in the 48-month survival analysis. Survival time was calculated from the date of discharge to the date of death or end of follow-up.

Covariates included in the multivariable analysis were selected based on clinical relevance and data availability. These included age, sex, Charlson Comorbidity Index (CCI), and admission laboratory parameters such as creatinine, glycemia, hemoglobin, albumin, platelets, white blood cell count, and inflammatory markers including C-reactive protein (CRP). The CCI was computed based on International Classification of Diseases, 9th revision - Clinical Modification (ICD-9-CM) codes following the method proposed by Quan et al. (2011) [25].

Laboratory parameters

Laboratory parameters measured at hospital admission included blood cell counts, creatinine, albumin, hemoglobin, and aspartate aminotransferase/alanine aminotransferase (AST/ALT), and were assessed using standardized procedures. The neutrophil-to-lymphocyte ratio (NLR) was calculated as the ratio of absolute neutrophil count to absolute lymphocyte count, both obtained from the same peripheral blood sample and measured using a Sysmex XN-1000 hematology analyzer. Estimated glomerular filtration rate (eGFR) was calculated using the BIS equation [26]: $BIS1\ eGFR = 3.736 \times SCr^{-0.87} \times age^{-0.95} [\times 0.82\ \text{if female}]$, where SCr = serum creatinine. All INRCA laboratories use standardized analytical procedures based on identical analyzer models and shared reference ranges, ensuring full comparability across centers.

Statistical analysis

Continuous variables were reported as mean \pm standard deviation or median and interquartile range (IQR), depending on their distribution (assessed with the Shapiro–Wilk test). Categorical variables were expressed as absolute numbers and percentages. Between-group comparisons were conducted using Chi-square and Student's t-tests, as appropriate. One-way ANOVA with Bonferroni post hoc correction was used to compare mean NLR levels across diagnostic groups.

To identify the optimal NLR threshold, ROC curve analysis was performed using Youden's Index. Comparisons between ROC curves were assessed using the DeLong test. Non-linear associations between NLR

and outcomes were explored with restricted cubic splines. NLR was then dichotomized based on the identified cut-off and analyzed using Kaplan–Meier survival curves and Cox proportional hazards models. The proportional hazards assumption and linearity of continuous covariates were assessed via Schoenfeld and Martingale residuals, respectively. A two-tailed p-value < 0.05 was considered statistically significant. All analyses were conducted using SPSS software.

RESULTS

In-hospital mortality

A total of 16,099 hospitalizations from 10,826 unique patients were included in the study. The median age at first admission was 84 years (IQR 79–89), 48 % of patients were male. The overall in-hospital mortality rate was 9.4%. Among patients who died during their index hospitalization, 958 out of 1,014 in-hospital deaths (94.5%) occurred within the first 30 days of admission. Patients had a median hospital stay of 9 days (IQR 5–15), accounting for a total of 6,491.2 person-months of hospitalization (Fig. 1).

Supplementary Table 1 presents the demographic and clinical characteristics of all patients based on their first hospitalization, stratified by in-hospital vital status. The CCI score was categorized into three levels (0, 1, and ≥ 2). The mean age was slightly higher among survivors (83.1 ± 7.9 years) compared to deceased patients (83.6 ± 7.9 years; $p < 0.001$). No significant differences were observed in sex distribution between groups ($p = 0.665$). Several comorbidities were significantly more prevalent among deceased patients, including congestive heart failure, dementia, diabetes mellitus, moderate to severe liver disease, metastatic cancer, and AIDS. The distribution of CCI categories did not differ significantly between survivors and non-survivors. Patients who died during hospitalization had significantly lower levels of albumin, hemoglobin, platelet count, and eGFR compared to those discharged alive. Conversely, non-survivors showed significantly higher values of NT-proBNP, AST, ALT, white blood cell count (WBC), C-reactive protein (CRP), glycemia, and creatinine. All differences between the two groups were statistically significant ($p < 0.01$).

The most frequent major diagnostic categories (MDCs) at admission were Circulatory ($n=4,340, 27.0\%$), Respiratory ($n=3,465, 21.5\%$), and Nervous System ($n=1,869, 11.6\%$), representing 60.1% of admissions. Mortality was highest in the Respiratory category (35.9% of deaths), followed by Infectious/Parasitic Diseases (22.6%) and Circulatory (15.1%). Although common, Circulatory cases had a lower mortality rate. Some less common categories, such as Mental Disorders and

Kidney/Urinary Tract, also contributed notably to deaths. Myeloproliferative, Blood/Immunological, and Survival and death distributions differed significantly Endocrine/Metabolic categories (Supplementary Table 2). across most diagnostic groups ($p < 0.05$), except 2).

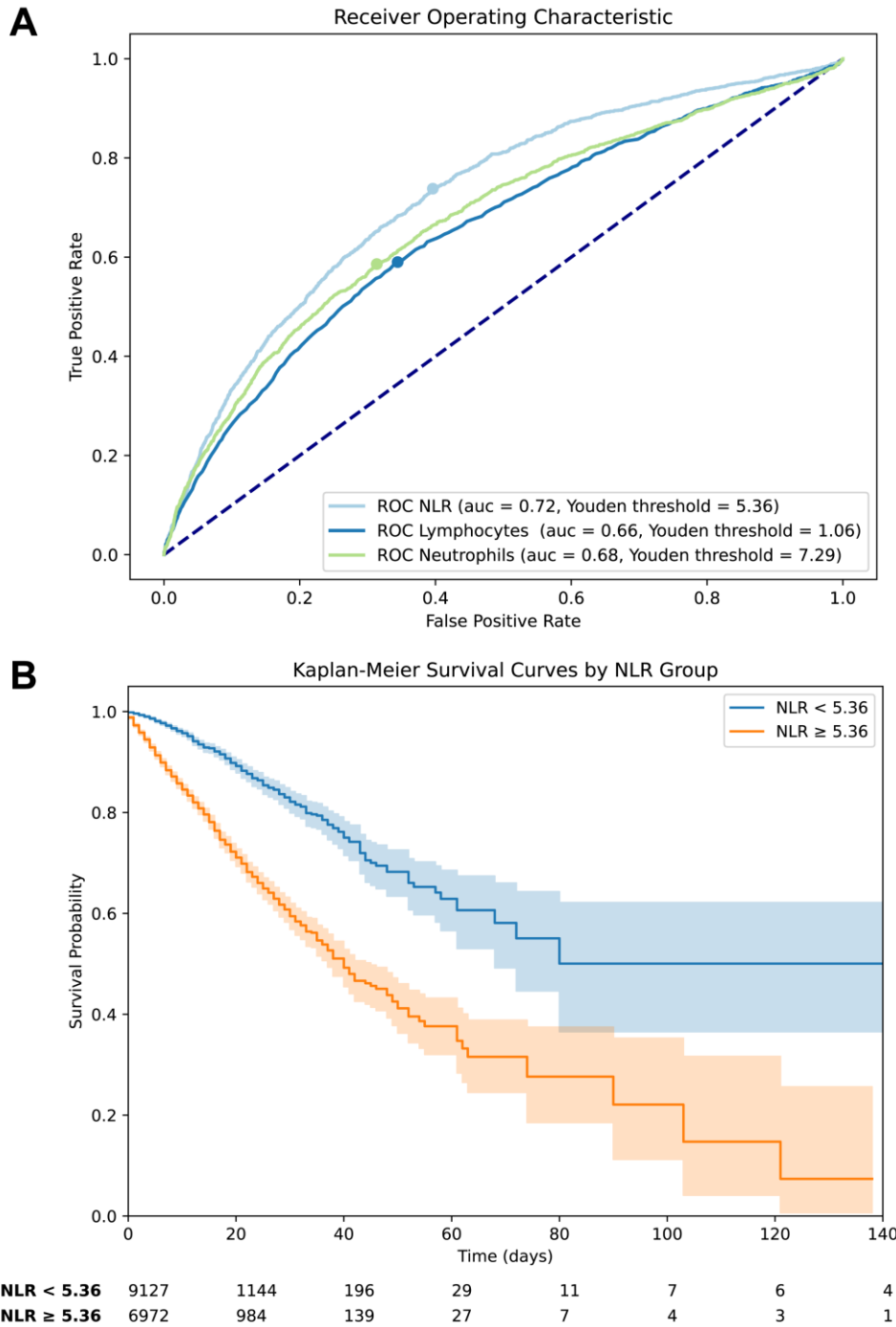


Figure 1. Association of admission NLR with in-hospital mortality. (A) ROC curves for prediction of in-hospital mortality based on neutrophil-to-lymphocyte ratio (NLR), absolute neutrophil count, and absolute lymphocyte count. (B) Kaplan-Meier survival curves for in-hospital mortality stratified by NLR according to the optimal NLR threshold determined by Youden’s Index.

The receiver operating characteristic (ROC) curve analysis showed that the neutrophil-to-lymphocyte ratio (NLR) had an area under the curve (AUC) of 0.72 (95% CI: 0.71–0.74) for in-hospital mortality. The optimal cut-

off value identified using Youden’s Index was 5.36, with a sensitivity of 0.74 and specificity of 0.60. When analyzed as independent predictors, lymphocyte count showed an AUC of 0.66 (95% CI: 0.65–0.67) with a

threshold of 1.06 (sensitivity = 0.59, specificity = 0.66), and neutrophil count had an AUC of 0.68 (95% CI: 0.66–0.69) with a threshold of 7.29 (sensitivity = 0.59, specificity = 0.69). The DeLong test indicated that the

AUC of NLR was significantly higher than those of neutrophil and lymphocyte counts ($p < 0.001$ and $p < 0.001$ respectively).

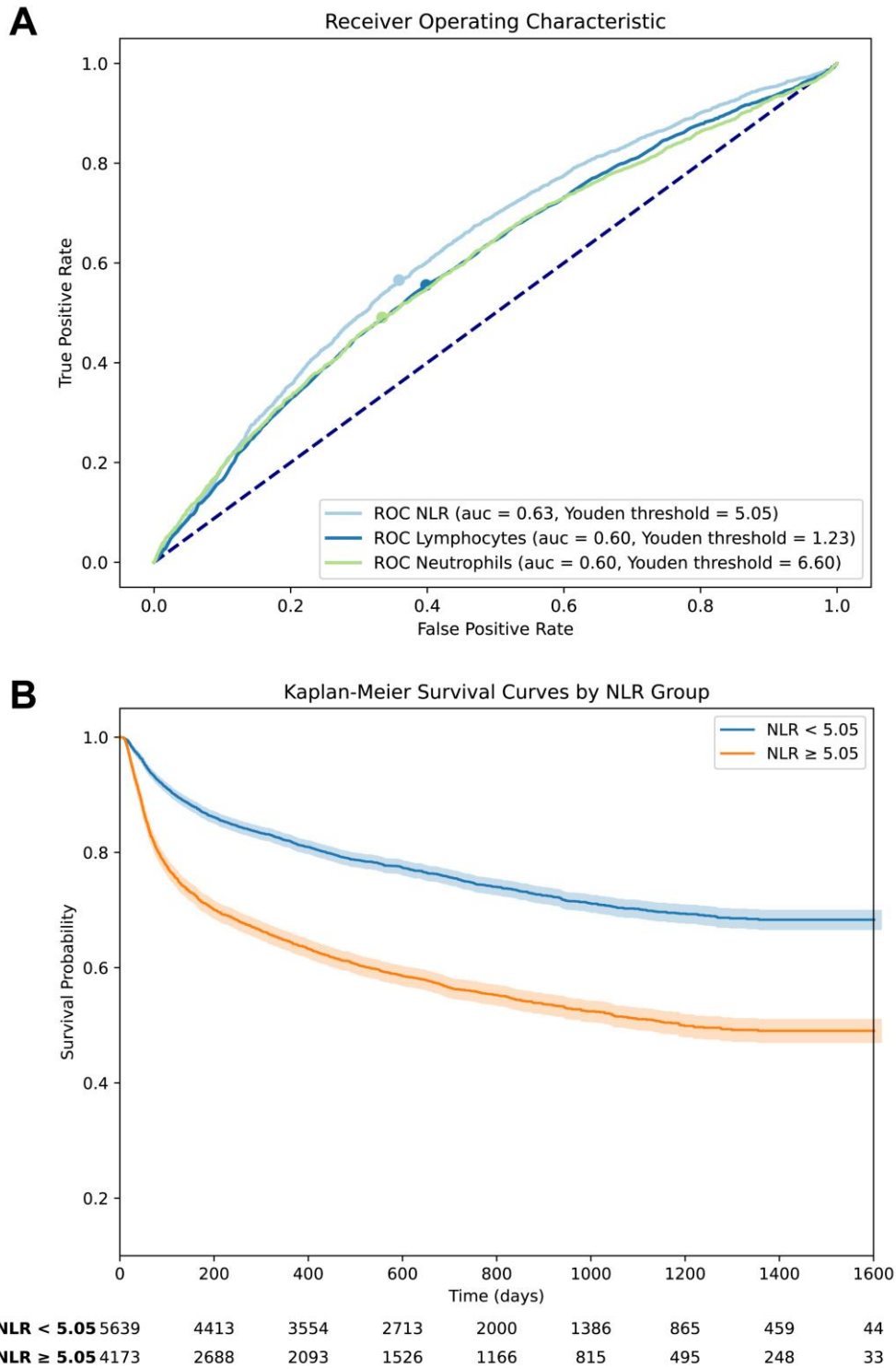


Figure 2. Association of admission NLR with 48-month mortality. (A) ROC curve for prediction of 48-month survival status, (B) Kaplan Meier Curves for prediction of 48-month survival status.

Table 1. Multivariable Cox proportional hazards regression for in-hospital mortality.

Covariates	HR (95% CI)	p-value
NLR \geq 5.36	2.287 (2.025 – 2.582)	<0.001
Age	1.060 (1.051 – 1.070)	<0.001
Sex (male)	0.847 (0.762 – 0.942)	0.002
CCI		
Score = 0	Ref.	
Score = 1	0.995 (0.867 – 1.141)	0.938
Score \geq 2	0.864 (0.756 – 0.987)	0.032
Blood glucose	1.001 (1.001 – 1.002)	<0.001
Hemoglobin	0.972 (0.947 – 0.998)	0.032
Platelets	0.999 (0.999 – 1.000)	0.001
eGFR	0.994 (0.992 – 0.996)	<0.001
MDC at admission		
Respiratory system	1.719 (1.237 – 2.389)	0.001
Infectious and parasitic diseases	1.700 (1.215 – 2.378)	0.002
Mental diseases and disorders	1.518 (0.915 – 2.521)	0.106
Circulatory system	1.050 (0.746 – 1.480)	0.779
Kidney and urinary tract	0.948 (0.639 – 1.407)	0.792
Digestive system	0.888 (0.596 – 1.322)	0.558
Hepatobiliary system and pancreas	0.873 (0.546 – 1.397)	0.572
Nervous system	0.770 (0.535 – 1.107)	0.158
Male reproductive system	0.552 (0.170 – 1.795)	0.324
Musculoskeletal and Connective Tissue	0.173 (0.080 – 0.371)	<0.001

CCI, Charlson Comorbidity Index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio.

Patients were stratified into two groups based on the optimal NLR cut-off value of 5.36, as identified through ROC analysis. As shown in Figure 2A, individuals with $\text{NLR} \geq 5.36$ had significantly lower survival probabilities during hospitalization compared to those with $\text{NLR} < 5.36$, with the log-rank test confirming a statistically significant difference between the groups ($p < 0.001$). In terms of event distribution (Fig. 2B), 5.0% of patients with $\text{NLR} < 5.36$ experienced in-hospital death, while 95.0% were censored. Conversely, among those with $\text{NLR} \geq 5.36$, 18.5% died during hospitalization and 81.5% were censored. In the overall population of 16,099 hospitalizations, 1,744 in-hospital deaths were recorded, resulting in an event-free proportion of 89.2%.

In the multivariable Cox proportional hazards regression model, an NLR value ≥ 5.36 remained independently associated with an increased risk of in-hospital mortality, with a hazard ratio (HR) of 2.287 (95% CI: 2.025–2.582, $p < 0.001$), even after adjusting for age, sex, comorbidities, diagnosis at admission, and routine parameters (Table 1).

To account for the potential confounding impact of COVID-19, we conducted a sensitivity analysis excluding 739 hospitalizations with a discharge diagnosis of COVID-19 (ICD-9-CM codes 043.11, 043.12, 043.21, 043.22, 043.31, 043.32, 480.41, 480.42, 518.91, 518.92, 519.71, and 519.72). The analysis was repeated in the remaining 15,360 non-COVID hospitalizations and confirmed that an $\text{NLR} \geq 5.36$ remained independently

associated with in-hospital mortality (HR: 2.459; 95% CI: 2.153–2.808; $p < 0.001$). Other predictors such as age, sex, eGFR, glycemia, hemoglobin, and diagnostic categories (MDCs) retained similar effect sizes and statistical significance (Supplementary Table 3).

Long-Term Mortality Analysis

After evaluating in-hospital mortality, we extended our analysis to assess long-term mortality at 48 months. For this purpose, we included 9,812 unique patients, considering only their first hospitalization. The median follow-up duration was 494 days (IQR, 146 – 946), with a mean of 591 days. Overall, the cohort contributed a total of 190,552 person-months of observation.

At 48 months, ROC analysis showed that NLR maintained a moderate discriminative ability for all-cause mortality, with an AUC of 0.67 (95% IC: 0.66 - 0.68). The optimal NLR threshold determined by Youden's Index was 5.05, with a sensitivity of 0.63 and a specificity of 0.64. Lymphocyte and neutrophil counts had lower AUCs (0.63 for both) (Fig. 2A). Kaplan-Meier curves demonstrated a persistent and significant difference in survival between patients with $\text{NLR} \geq 5.05$ and those with $\text{NLR} < 5.05$ (Fig. 2B). At 48 months, mortality occurred in 2,578 of 4,996 patients (51.6%) with high NLR, compared to 1,535 of 5,830 (26.3%) with lower NLR values ($p < 0.001$). The survival rate was 73.7% in the low-NLR group, versus 48.4% in the high-NLR group.

Table 2. Multivariable Cox regression for long-term mortality in patients surviving their index hospital admission.

Covariates	HR (95% CI)	p-value
NLR ≥ 5.05	1.423 (1.302 – 1.556)	<0.001
Age	1.081 (1.074 – 1.088)	<0.001
Sex (male)	0.810 (0.743 – 0.882)	<0.001
CCI		
Score = 0	Ref.	
Score = 1	1.364 (1.209 – 1.539)	<0.001
Score ≥ 2	1.632 (1.4460 – 1.824)	<0.001
Fasting glucose (mg/dL)	1.000 (1.000 – 1.001)	0.363
Hemoglobin (g/dL)	0.916 (0.897 – 0.936)	<0.001
Platelets ($\times 10^3/\text{mm}^3$)	1.001 (1.000 – 1.001)	0.004
eGFR (mL/min)	0.999 (0.997 – 1.000)	0.092
CRP (mg/dL)	1.013 (1.007 – 1.018)	<0.001

CCI, Charlson Comorbidity Index; CRP, C-reactive protein; eGFR, Estimated glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio.

At 48-month follow-up, several biochemical and hematological parameters remained significantly different between survivors and deceased patients (Supplementary Table 4). Deceased individuals had lower levels of albumin (3.30 vs 3.66 g/dL), hemoglobin (11.37 vs 12.20 g/dL), and eGFR (52.8 vs 64.5 mL/min/1.73 m²), and higher levels of creatinine (1.48 vs 1.20 mg/dL), glycemia (122.4 vs 115.4 mg/dL), NT-proBNP (7516.2 vs 3625.9 pg/mL), PCR (7.14 vs 5.49 mg/L), transaminases, and white blood cell count (10.1 vs 8.7 $\times 10^3/\mu\text{L}$). All comparisons were statistically significant ($p < 0.001$). In the multivariable Cox proportional hazards model (Table 2), NLR ≥ 5.05 was independently associated with increased 48-month mortality (HR: 1.423; 95% CI: 1.302–1.556; $p < 0.001$), after adjustment for age, sex, comorbidity burden, and routine laboratory parameters. Among the covariates, age, male sex, CCI score, CRP, platelets, and hemoglobin were also significantly associated with mortality (Table 2).

Age- and gender- related NLR distribution

NLR values progressively increased with advancing age, with the highest median NLR values observed in the oldest group (>95 years: median 6.6, IQR 3.8–10.9), and the lowest found in the youngest group (65–69 years: median 3.2, IQR 2.1–5.5) (Supplementary Table 5). Post-hoc pairwise comparisons with Bonferroni correction showed statistically significant differences between most age groups (Supplementary Table 6). Further stratification by sex revealed higher NLR values in males

aged ≥ 80 and <95 years compared to females, while no sex-related differences were observed in patients aged >95 years. Figure 3A illustrates the age- and sex-related distribution of NLR, and Supplementary Table 5 summarizes the median and interquartile ranges by age and sex categories. When stratified by sex, a moderate but significant positive correlation between NLR and age was observed in both males ($r = 0.179$, $p < 0.001$) and females ($r = 0.150$, $p < 0.001$) (Pearson correlation). These results suggest that both age and sex influence the inflammatory status reflected by NLR in older adults.

Temporal trend of NLR

The temporal trend analysis of the neutrophil-to-lymphocyte ratio (NLR), aligned to the last hospitalization or death (day 0), revealed markedly divergent patterns between survivors and non-survivors (Fig. 3B). Among deceased patients, the moving median NLR remained relatively elevated and stable around 5.5–6.0 until approximately 30–40 days prior to death, after which it began to rise sharply. In the final 10 days, the NLR increased steeply, reaching values above 10 shortly before death. This dynamic upward trend is consistent with a worsening systemic inflammatory response preceding fatal outcomes. Conversely, survivors maintained consistently lower NLR values, with the moving median ranging between approximately 4.0 and 4.5 throughout the 100-day observational window, with only minor fluctuations and no evident upward trend approaching day 0. These findings suggest that a dynamic increase in NLR may reflect clinical deterioration and could potentially serve as a marker for adverse outcomes during hospitalization.

DISCUSSION

In this study, we evaluated the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in a large cohort of older adults – comprising 16,099 hospitalizations from 10,826 unique patients – admitted for acute medical conditions to IRCCS INRCA hospitals between January 2020 and December 2024, with a follow-up of up to 48 months. Our results demonstrate that an elevated NLR at hospital admission is an independent predictor of both in-hospital and long-term mortality, even after adjusting for age, sex, comorbidity burden, and routine laboratory parameters. Specifically, an NLR threshold of ≥ 5.36 was associated with an increased risk of in-hospital mortality, while a cut-off of ≥ 5.05 predicted long-term mortality at 48 months. Previous work by our group in a cohort of over 5,000 geriatric inpatients identified an NLR > 7.95 as a strong predictor of in-hospital mortality [2]. Several additional reports highlight the remarkable heterogeneity

of NLR thresholds across clinical settings. In community- or outpatient-based cohorts, proposed cut-offs are often lower (around 3–4), whereas studies conducted in acute care environments typically identify higher values. For instance, optimal cut-offs around 6–7 have been reported in acute heart failure patients depending on the underlying trigger of decompensation [27], in critically ill unselected ICU populations where median NLR values approach 9 [28], in older adults presenting to the emergency department where non-survivors often exhibit NLR >8 [29], and in disease-specific settings such as cardiovascular disease [30–32], hematological

malignancies [33], and trauma [34, 35], where even higher thresholds have been described. This wide variability likely reflects differences in patient acuity, inflammatory burden, comorbidity load, and methodological approaches to defining risk thresholds. Consequently, while our cut-offs fall within the range reported for older hospitalized populations, the existing evidence collectively suggests that NLR may be more appropriately interpreted as a continuous marker rather than relying on any fixed universal cut-off.

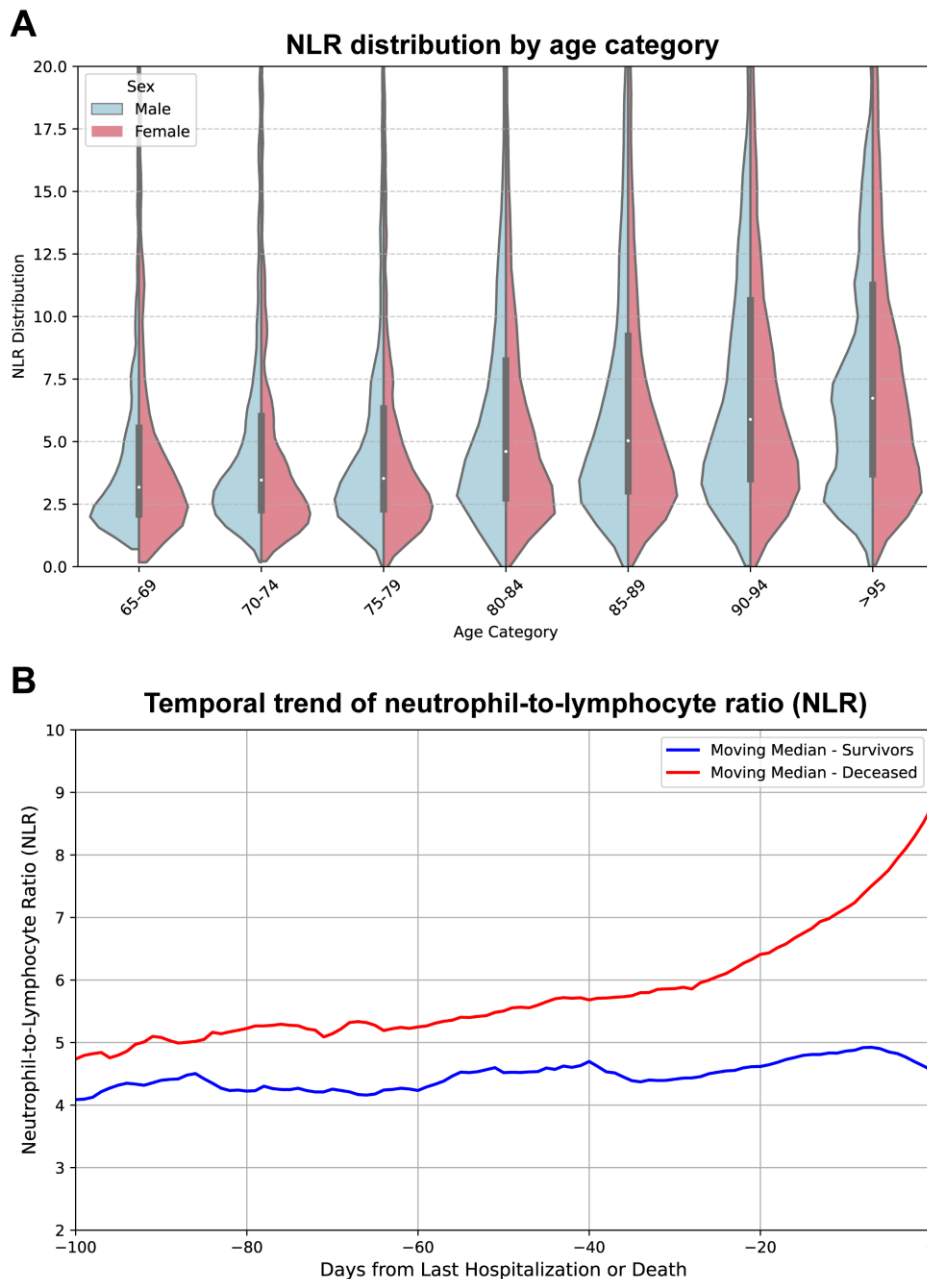


Figure 3. Age- and sex-related distribution of NLR and temporal trend before death or discharge. (A) Violin plots show the distribution of NLR values stratified by age categories (x-axis) and sex (blue: male; pink: female). The black lines within each violin represent the interquartile range and median. **(B)** Temporal trend of neutrophil-to-lymphocyte ratio (NLR) in survivors (blue) and deceased patients (red), aligned to last hospitalization or death (Day 0).

The progressive rise in NLR observed in the days preceding in-hospital death is consistent with the systemic inflammatory surge that often accompanies terminal physiological decline. Similar temporal patterns have been described in other acute settings: in critically ill trauma patients, an increasing NLR trajectory over the first 48 hours predicted organ failure and worse outcomes [36], and in adults hospitalized with respiratory syncytial virus (RSV) infection, a rise in NLR within the first 48 hours was independently associated with adverse events including mechanical ventilation and death [37]. These observations support the idea that NLR dynamics reflect evolving inflammatory instability. From a clinical point of view, such trends could be useful to flag individuals who might benefit from closer monitoring or a more cautious approach to discharge planning.

More broadly, because NLR is routinely measured on admission and during hospitalization, it could be incorporated pragmatically into existing workflows. Elevated or rising NLR values may complement early warning scores at the bedside and support risk stratification in the first days of care. Similarly, the admission NLR, together with its in-hospital trajectory, could be considered alongside functional status and comorbidity burden during geriatric assessment. In this context, NLR might also complement established frailty-oriented tools such as the Clinical Frailty Scale (CFS), which integrate functional, cognitive, and comorbidity dimensions. While these instruments capture global vulnerability and partly reflect the downstream consequences of chronic inflammation, they indeed do not directly quantify systemic inflammatory status, differently from NLR. In other words, from our perspective, as solid biomarker of systemic inflammation, NLR might improve the accuracy of frailty assessment and risk of death in hospitalized frail older people. This intriguing idea is indeed supported by community-based evidence showing that higher NLR levels predict both prevalent and incident frailty over time [38], but data on the association between NLR and age-related frailty in the context of hospitalization are still lacking. Therefore, the incorporation of NLR in the assessment of frailty in hospitalized older people will be eventually validated by future large scale prospective studies.

In summary, in the context of hospitalization, adding a simple inflammatory marker such as NLR may help refine the short-term prognostic classification and support decisions related to monitoring intensity, discharge readiness, and post-acute care planning of older patients,

While the role of NLR in predicting short-term outcomes in older patients had been already well established, our findings extend its utility to long-term mortality risk, underscoring its role as a marker of inflammaging regardless from acute variations. The

association between NLR and long-term mortality remained robust after excluding COVID-19-related hospitalizations, further supporting the general applicability of NLR as a prognostic biomarker in older hospitalized adults. Interestingly, our results are consistent with from the general population: in a large U.S. cohort, NLR was significantly associated with all-cause mortality up to 93 months of follow-up [39].

Beyond mortality prediction, NLR has been proposed as a marker of “healthy aging”, reflecting the balance between neutrophil-driven inflammation and adaptive immunity [40]. NLR captures immunological alterations driven by disease, lifestyle, and environmental exposures, and has been identified as a predictor of all-cause mortality and multimorbidity in older individuals [41]. NLR is also linked to age-related functional decline, including muscle weakness and sarcopenia [42], with recent studies confirming its association with adverse outcomes in longitudinal cohorts such as InCHIANTI. [43].

Recent observations from COVID-19 cohorts further support the link between systemic inflammation and vascular aging. In patients with COVID-19, inflammation-driven arterial stiffening was shown to persist beyond the acute phase and to correlate with microvascular damage in both retinal and renal districts [44, 45]. These findings fit within the broader concept that chronic, low-grade inflammation contributes to the progression of atherosclerosis over the life course, often remaining clinically silent for years. Notably, in older asymptomatic adults, NLR has been identified as a reliable marker of carotid atherosclerotic plaques [14]. Taken together, these data reinforce the biological plausibility and clinical relevance of our findings, strengthening the role of NLR as a prognostic biomarker of long-term outcomes in older patients beyond the acute setting.

The progressive increase of NLR with advancing age observed in our study strengthens the already mentioned link between NLR and the chronic, low-grade inflammation known as inflammaging in the context of immunosenescence. Alterations in lymphocyte counts and subtypes, together with a decline in adaptive immunity, are recognized hallmarks of immune system aging [46]. Interestingly, we observed that males aged 80–95 years exhibited higher NLR values compared to females, in line with previous studies [23]. However, this sex-related difference appeared to diminish in the oldest-old subgroup (age >95 years), suggesting a convergence of immune profiles at extreme ages.

In addition to NLR, innovative neutrophil-based indexes are currently under investigation as diseases outcomes predictor. The neutrophil-to-high-density lipoprotein cholesterol ratio (NHR) has emerged as a

potential biomarker for chronic disease outcomes, underscoring the importance of integrating these indexes into mortality risk evaluations, offering a potential strategy for early intervention in aging populations [47]. Neutrophil-to-albumin ratio (NAR) and neutrophil-to-bilirubin ratio (NBR) are emerging as promising biomarkers in the diagnosis and prediction of response to therapies [48]. These emerging markers may offer complementary information to NLR, enhancing the assessment of inflammatory status and improving risk stratification in aging populations.

Nevertheless, this study has limitations. The retrospective design may be subject to residual confounding despite multivariable adjustment. Moreover, while our cohort is large, it reflects an Italian population of hospitalized older adults, and findings may not be directly generalizable to other populations or outpatient settings. Future prospective studies should validate these thresholds across diverse settings and assess the clinical impact of incorporating NLR into standard risk assessment tools.

Conclusions

In this large multicenter cohort of hospitalized older adults, admission NLR emerged as an independent predictor of both in-hospital and long-term mortality. Its prognostic value remained consistent after adjustment for demographics, comorbidities, and routine laboratory parameters, underscoring its role as a simple, low-cost, and widely accessible biomarker of systemic inflammation. The observed associations with age and sex highlight the importance of age-adjusted interpretation in geriatric care. Although fixed cut-offs are not yet established, integrating NLR into routine assessments may improve early risk stratification and support clinical decision-making. Prospective studies are needed to validate context-specific thresholds, assess the added value of NLR trajectories, and explore its integration with emerging inflammatory indexes to refine prognostic models in aging populations.

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Authors' contributions

Conceptualization: F.O., L.S. Data curation: L.A., M.D.R.; Formal analysis: L.A., J.S., M.D.R.; Funding acquisition: F.L., F.O.; Investigation: L.A., N.F.; Project

Administration: L.S., A.G.; Validation: J.S., M.D.R., A.G.; Visualization: L.A., J.S., L.B., A.G.; Writing – original draft: L.A., J.S., L.B., A.G., L.S., F.O.; Data curation: A.R.B., A.M.L.; Writing – review & editing: G.M., C.G., M.M., M.F., L.S., M.C., L.P., L.M., F.T., F.P. Y.R., M.B., S.I., R.S., A.C. Supervision: L.S., F.O.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Marche region (Italy), protocol 64/2025.

Competing interests

The authors report no potential conflicts of interest.

Supplementary Materials

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2025.1209.

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