Association between the Neutrophil-to-Lymphocyte Ratio and Inpatient Mortality in Hospitalized Older Veterans with COVID-19 Infection

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Objectives: Determine the association of high neutrophil-to-lymphocyte ratio (NLR) values with inpatient mortality and other outcomes in older veterans hospitalized with coronavirus disease 2019 (COVID-19).

Methods: This was a retrospective, multicenter, cohort study of hospitalized adults, with laboratory-confirmed COVID-19 infection who were studied for 1 year after discharge or until death. The NLR was categorized into tertiles, and we determined frailty status with the 31-item Veterans Affairs Frailty Index. Multivariate logistic regression and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were performed to assess the association between NLR and clinical outcomes.

Results: The study included 615 hospitalized adult veterans, mean age 66.12 (standard deviation 14.79) years, 93.82% (n = 577) male, 57.56% (n = 354) White, 81.0% (n = 498) non-Hispanic, median body mass index of 30.70 (interquartile range 25.64–34.99, standard deviation 7.13), and median length of stay of 8 days (interquartile range 3–15). Individuals in the middle and upper tertile groups had higher inpatient mortality (8.37%, n = 17 and 18.36%, n = 38, respectively) as compared with the lower tertile (2.93%, n = 6, $P < 0.001$). Compared with the lowest tertile, the middle and upper tertiles had a higher risk of inpatient mortality (aOR 3.75, 95% CI 1.38–10.21, $P = 0.01$, and aOR 8.13, 95% CI 3.18–20.84, $P < 0.001$, respectively). The highest tertile had a higher odds of intensive care unit admission (aOR 4.47, 95% CI 2.33–8.58, $P < 0.001$) and intensive care unit transfer (aOR 3.54, 95% CI 1.84–6.81, $P < 0.001$).

Conclusions: The NLR score is a clinically useful tool to predict in-hospital mortality in older patients with COVID-19.

Key Words: coronavirus disease 2019 (COVID-19), mortality, neutrophil-to-lymphocyte ratio (NLR), veterans

The older adult population is the demographic that is the most vulnerable to the effects of coronavirus disease 2019 (COVID-19) infection.[1] Older adults are at increased risk of developing serious disease leading to hospital admissions that often are associated with higher rates of in-hospital complications and mortality.[2–4] The reasons for such outcomes among hospitalized older adults with COVID-19 may include frailty[5] and a heightened inflammatory response.[6] Two key age-related physiological dysregulations—inflammaging-systemic low-grade inflammation and immunosenescence-adaptive and innate immunity declines—may cause impaired and aberrant inflammatory and immunologic responses resulting in the onset of a cytokine storm.[7] The use of prognosis and risk stratification tools may enable clinicians to both prevent disease progression and support individualized management of patients with early intervention. Since the COVID-19 pandemic began, several tools have

Key Points

- Higher neutrophil-to-lymphocyte ratio (NLR) scores were associated with an increased risk of inpatient death and dying sooner than were low scores. NLR was a good predictor of inpatient death.
- The highest NLR scores were associated with a higher risk of intensive care unit direction admission and intensive care unit transfers.
- The higher scores were not associated with an increased risk of increased length of stay.
- We were the first to show that NLR is not associated with an increased risk of 30-day postdischarge readmission, new postdischarge nursing facility admission, and 6-month and 1-year postdischarge mortality.

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This material is the result of work supported with resources and the use of facilities at the Miami VA Healthcare System GRECC.

J.G.R. has received compensation from Pfizer and the American Board of Internal Medicine. The remaining authors did not report any financial relationships or conflicts of interest.

Accepted June 7, 2023.

0038-4348/0–2000/116-863

DOI: 10.14423/SMJ.0000000000001622

been recommended to aid medical providers in predicting COVID-19 patients with COVID outcomes.[8] Cytokine measurements are expensive and impractical at the point of care. In contrast, routine full blood counts and white cell differentials are widely available across healthcare settings. One such tool, the neutrophil-to-lymphocyte ratio (NLR) is an inexpensive, reliable, and widely available inflammatory biomarker that is a good predictor of clinical risk and outcome in many clinical conditions.[9] Whereas a high neutrophil count reflects the systemic inflammatory innate response characteristic of the cytokine storm, lymphopenia is an indicator of the age-related decline in adaptive immunity.[10]

A meta-analysis of 32 studies with 8120 individuals, including 7482 COVID-19 patients, mean age ranging from 28.4 to 65 years, showed that compared with test-negative individuals, patients with documented COVID-19 infections had significantly higher NLRs.[11] Studies revealed the association of high NLR ratios with serious disease,[11,12] progression to critical illness in patients older than age 60 admitted,[15] in-hospital mortality,[11,13] and an increased risk for 1-month mortality.[14] The data on prolonged length of stay (LOS) were mixed, with two studies finding an association[16,17] whereas others did not.[18,19] Only one study looked at the association of NLR and 30-day postdischarge mortality and found that follow-up, but not initial NLR, was associated with 30-day mortality.[20] Several key questions remain, however. Most studies did not include older adults nor did they examine the association of NLR with posthospital outcomes such as 30-day readmissions, nursing facility placement, and postdischarge mortality.

The primary aim of our study was to examine the association of NLR with inpatient mortality in older military veterans hospitalized with COVID-19. The secondary aims were to determine the associations between NLR scores and prolonged LOS, direct intensive care unit (ICU) admissions and ICU transfers, and posthospital outcomes–postdischarge mortality at 30 days, 6 months, and 1 year. We hypothesized that higher NLR ratio rates would be associated with increased in-hospital mortality and worse postdischarge outcomes.

Methods

This was a retrospective cohort study of military veterans hospitalized with COVID-19 infection at seven VA (Veterans Affairs) Sunshine Healthcare Network (VISN 8) medical centers across Florida and Puerto Rico, between March 1 and August 31, 2020. The inclusion criteria were all of the veterans (18 years old and older) who were admitted to medical wards or ICUs and had a positive COVID-19 antigen or polymerase chain reaction test during admission, even those from long-term care and assisted living facilities admitted for asymptomatic COVID-19 infection. The exclusion criterion was incomplete laboratory tests results for the determination of the NLR. The patients were studied for 1 year after discharge or until death. Staff queried the VA Clinical Data Warehouse, obtaining sociodemographic information, hospitalization information (including admission and discharge dates), date of death, *International Classification of Diseases, Tenth Revision* codes, and relevant laboratory results. Trained research associates verified inclusion criteria and subsequently performed in-depth chart reviews to verify clinical characteristics and outcomes. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cohort studies. A protocol of this study was submitted to and approved by the Miami VA Healthcare System institutional review board. Because this study was a retrospective medical record review and thus presented no more than minimal risk, the institutional review board waived the need for patient informed consent.

Exposures, Outcomes, and Measurements

Sociodemographic Information

We obtained data on age, sex, marital status, race, ethnicity, and body mass index (BMI). The race categories collected were dichotomized into White and non-White (American Indian or Alaska Native, Asian, Black, or African American, Native Hawaiian or Pacific Islander, and Unknown). The ethnicities were Hispanic or Latino, Not Hispanic or Latino, or Unknown.

NLR

Complete blood cell counts, including determination of neutrophils and lymphocytes, were obtained during hospitalization-related blood sampling. We calculated the NLR score by dividing the absolute neutrophil count by the absolute lymphocyte count and categorized patients according to tertiles: lower, middle, and upper (<2.84 lower tertile, 2.84–5.28 middle tertile, and >5.28 upper tertile).

Potential Confounders

We collected data on conditions that place individuals at higher risk for severe COVID-19 infection (Table 1). We collected information on the patient's residence before admission: living at home with no continuous skilled or unskilled services, living in an assisted living facility, or being a nonveteran or living in a veterans nursing facility (Table 1). We also included if patients were self-care patients, which meant that they could perform independent activities of daily living. We also included what type of caregiver(s) the patients had, either nonpaid or paid caregiver services by a nurse or home health aide.

Outcomes

In-Hospital and Postdischarge Mortality

We identified mortality through either VA facilities' electronic health records, death certificates, or National Cemetery Administration data available from the VA Clinical Data Warehouse. For patients surviving hospital admission, we used the date of discharge as time 0, and calculated 30-day, 6-month, and 1-year mortality.

Readmission

We determined readmissions from the date of discharge for COVID-19 hospitalization as day 0 and counted veterans as having any readmission within 30 days following discharge.

Table 1. Participants' baseline characteristics

Parameter	Lower tertile NLR (n = 205)	Middle tertile NLR (n = 203)	Upper tertile NLR (n = 207)	*P*	Total participants (N = 615)
Age, y, mean (SD)	64.51 (15.49)	65.60 (14.24)	68.24 (14.43)	**0.031**	66.12 (14.79)
Males, n (%)	187 (91.22)	190 (93.60)	200 (96.62)	0.076	577 (93.82)
White race, n (%)	110 (53.66)	118 (58.13)	126 (60.87)	0.328	354 (57.56)
Non-Hispanic, n (%)	175 (85.4)	164 (80.8)	159 (76.8)	0.086	498 (81.0)
BMI, mean (SD)	30.60 (7.50)	31.14 (6.83)	30.36 (7.08)	0.546	30.70 (7.13)
Frail (VAFI), n (%)	106 (51.71)	110 (54.19)	96 (46.38)	0.270	312 (50.73)
No. chronic conditions, median (IQR)	6 (5.75)	5 (5)	5 (6)	0.11	5 (5)
Smoker, n (%)	61 (29.79)	46 (22.66)	39 (18.84)	0.031	146 (23.74)
Substance abuse, n (%)	64 (31.22)	57 (28.08)	48 (23.19)	0.184	169 (27.48)
Diabetes mellitus, n (%)	88 (43.14)	90 (44.33)	89 (43.20)	0.963	267 (43.56)
Cancer, n (%)	33 (16.2)	40 (19.7)	49 (23.8)	0.155	122 (19.9)
CKD, n (%)	59 (28.92)	54 (26.60)	49 (23.79)	0.498	162 (26.43)
Lung disease, n (%)	55 (26.96)	46 (22.66)	56 (27.67)	0.457	158 (25.77)
Dementia, n (%)	51 (25.00)	49 (24.14)	46 (22.33)	0.811	146 (23.82)
CAD, n (%)	47 (23.04)	58 (28.57)	63 (30.58)	0.208	168 (27.41)
HTN, n (%)	157 (76.96)	144 (70.94)	153 (74.27)	0.381	454 (74.06)
CHF, n (%)	38 (18.63)	30 (14.78)	33 (16.02)	0.565	101 (16.48)
Liver disease, (%)	26 (12.75)	22 (10.84)	21 (10.19)	0.697	69 (11.26)
Stroke, n (%)	35 (17.16)	29 (14.29)	28 (13.59)	0.564	92 (15.01)
Self-care, before admission, n (%)	136 (66.34)	148 (72.91)	151 (72.95)	0.239	435 (70.73)
Living at home with nonpaid caregiver, n (%)	17 (8.29)	12 (5.91)	19 (9.18)	0.444	48 (7.80)
Living at home with home services, n (%)	5 (2.44)	9 (4.43)	6 (2.90)	0.493	20 (3.25)
Living in ALF, n (%)	9 (4.39)	16 (7.88)	14 (6.76)	0.335	39 (6.34)
Living in community nursing facility, n (%)	13 (6.34)	8 (3.94)	5 (2.42)	0.137	26 (4.23)
Living in VA nursing facility, n (%)	13 (6.34)	8 (3.94)	6 (2.90)	0.217	27 (4.39)
Living in state Veterans home, n (%)	11 (5.37)	3 (1.48)	4 (1.93)	**0.039**	18 (2.93)

ALF, assisted living facility; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; HTN, hypertension; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation; VAFI, Veterans Affairs Frailty Index.

LOS

The LOS was calculated by subtracting the patient's hospital admission from the date of the patient's discharge. We coded same-day discharges as 0, and leave days were not subtracted from the calculation. We then dichotomized LOS as extended or not, depending on whether LOS was equal to or above the median LOS of 8 days.

ICU Admission and Transfers

ICU admission occurred when critical care physicians admitted patients directly from the emergency department to the ICU. ICU transfers occurred when patients were admitted to a medical ward or step-down unit and then transferred to the ICU.

New Nursing Facility Placement

A new nursing facility placement was defined as an admission to nursing facility units without previous residence at a facility before COVID infection.

Data Analysis

We calculated descriptive statistics on the variables age, sex, marital status, race, ethnicity, smoking history, substance abuse, alcohol abuse, BMI, and other risk factors for severe COVID infection and presented categorical variables as a frequency and percentage within each group of interest and continuous variables as means and standard deviations (SDs). To assess the association between the independent variable, NLR, and our clinical outcomes as the dependent variables, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) using binomial logistic regression and performed a univariate analysis and then a multivariate analysis adjusting for sex, age, marital status, race, ethnicity, BMI, substance abuse, smoking status, posttraumatic stress disorder, bipolar disorder, and schizophrenia. We used multiple imputation for the missing values. We also performed a multivariate survival analysis using Cox proportional hazard regression, with NLR as the independent variable and all-cause inpatient mortality as the dependent. The receiver operating characteristic/area under the curve (AUC) analysis was calculated with 95% CIs to assess the diagnostic accuracy of the NLR score in predicting inpatient mortality. All of the statistical tests were two-tailed, and significance was assumed for $P < 0.05$. We then compared the diagnostic accuracy in predicting in-hospital mortality between the NLR using a receiver operating characteristic/AUC analysis. We used SPSS version 28 (IBM SPSS Statistics, Armonk, NY).

Results

Patient Characteristics

We included 615 veterans hospitalized with COVID-19 infection during our study period. Table 1 shows the participant baseline characteristics. The veterans' mean age was 66.12 (SD 14.79) years, range 22 to 103 years, 93.82% (n = 577) male, 57.56% (n = 354) White, 81.0% (n = 498) non-Hispanic, and a median BMI of 30.70 (interquartile range 25.64–34.99, SD 7.13).

Hospital Outcomes

Inpatient Mortality

A total of 61 (9.92%) inpatients died during follow-up. Veterans in the middle and upper NLR tertiles had a higher proportion of inpatient mortality (8.37%, n = 17, and 18.36%, n = 38, respectively) as compared with the lower NLR tertile (2.93%, n = 6, $P < 0.001$) (Table 2). The middle and upper NLR tertiles were associated with higher inpatient mortality when compared with the lower NLR tertile (adjusted OR [aOR] 3.75, 95% CI 1.38–10.21, and aOR 8.13, 95% CI 3.18–20.84, respectively) (Table 3). During a median LOS of 8 days, the patients in the middle and upper NLR group showed greater in-hospital mortality (adjusted hazard ratio 3.57, 95% CI 1.37–9.29, $P = 0.009$, and adjusted hazard ratio 5.57, 95% CI 2.32–13.46, $P < 0.001$, respectively) (Fig. 1). In terms of diagnostic accuracy, the NLR score was acceptable (AUC 0.737, 95% CI 0.673–0.802, $P < 0.000$) (Fig. 2).

ICU Admissions and Transfers

Eighty-six veterans (13.98%) were directly admitted to the ICU. The upper NLR tertile had a higher proportion of patients admitted to the ICU (24.15%, $P < 0.001$) compared with the lower and middle tertiles (6.83% and 10.84, respectively) (Table 3). The upper NLR group was associated with a higher risk of direct ICU admission (aOR 4.47, 95% CI 2.33–8.58, $P < 0.001$) compared with the lower tertiles (Table 3). Seventy-eight patients were transferred to the ICU after an initial admission to a general medical or surgical ward. The upper tertile had a higher proportion of patients transferred to the ICU (19.32%, $P < 0.001$) versus the lower and middle NLR tertiles (7.32% and 11.33%, respectively) (Table 2). The upper tertile group was associated with a higher risk of ICU transfers (aOR 3.54, 95% CI 1.84–6.81, $P < 0.001$) compared with the lower and middle tertiles (Table 3).

LOS

The median hospital LOS was 8 days. More than half of the patients had a prolonged stay (n = 311, 50.57%). Veterans in the lower and upper NLR tertiles had a higher proportion of prolonged LOS (50.24%, n = 103, and 56.04%, n = 116) than the middle NLR tertile group (45.32%, n = 92) (Table 2). The middle and upper NLR tertile groups were not associated with a prolonged LOS (aOR 0.79, 95% CI 0.52–1.20, $P = 0.277$, and aOR 1.26, 95% CI 0.82–1.93, $P = 0.287$, respectively) (Table 3).

Nursing Facility Placement

A total of 44 (7.15%) patients were admitted to a nursing facility. Veterans in the middle and upper NLR tertile groups (6.90%, n = 14, and 8.70%, n = 18, respectively) did not have a higher proportion of new nursing facility placements compared with the lower NLR tertile (5.85%, n = 12, $P = 0.527$) (Table 2). The middle and upper NLR tertile groups were not associated with higher risk for nursing facility placement (aOR 1.13, 95% CI 49–2.58, $P = 0.779$, and aOR 1.51, 95% CI 0.68–3.38, $P = 0.311$, respectively) (Table 3).

Postdischarge Outcomes

Readmissions

A total of 89 patients (14.47%) were readmitted within 30 days—36 in the lower (17.56%), 31 in the middle (15.27%), and 22 (10.63%) in the upper NLR tertiles (Table 2). The middle and upper NLR tertile groups were not associated with a greater risk of readmissions (aOR 0.83, 95% CI 0.48–1.45, $P = 0.520$, and aOR 0.66, 95% CI 0.36–1.21, $P = 0.176$) (Table 3).

Mortality within 30 Days

A total of 12 (1.95%) deaths occurred within 30 days from hospital discharge, with four deaths across all three NLR tertile groups—1.95%, 1.97%, and 1.93% in the low, middle, and high tertiles, respectively ($P = 1.000$) (Table 2). The middle and upper NLR tertile groups were not associated with a greater risk of all-cause mortality within 30 days of discharge (aOR 0.73, 95% CI 0.16–3.24, $P = 0.674$, and aOR 0.61, 95% CI 0.14–2.75, $P = 0.523$, respectively) (Table 3).

Mortality within 6 Months

A total of 36 (5.85%) deaths occurred 6 months postdischarge. Veterans within the middle and upper tertiles were not at a greater risk of death within 6 months of discharge (aOR 0.94, 95% CI 0.38–2.30, $P = 0.890$, and aOR 1.16, 95% CI 0.49–2.75, $P = 0.732$, respectively) (Table 3).

Mortality within 1 Year

A total of 51 deaths (8.29%) occurred at 1 year postdischarge. No differences were found in the proportion of deaths in the lower NLR tertile (9.76%, n = 20) compared with the middle and upper

Table 2. Assessment of in-hospital and postdischarge outcomes among NLR groups, adjusted and unadjusted

Outcomes	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Hospital outcomes				
In-hospital mortality				
Lower tertile		1 (*Reference*)		
Middle NLR tertile	3.03 (1.17–7.85)	**0.022**	3.75 (1.38–10.21)	**0.010**
Upper NLR tertile	7.46 (3.08 –18.07)	**<0.001**	8.13 (3.18–20.84)	**<0.001**
LOS (prolonged)				
Lower tertile		1 (*Reference*)		
Middle NLR tertile	0.82 (0.56–1.21)	0.320	0.79 (0.52–1.20)	0.277
Upper NLR tertile	1.26 (0.86–1.86)	0.239	1.26 (0.82–1.93)	0.287
ICU admission, direct				
Lower tertile		1 (*Reference*)		
Middle NLR tertile	1.66 (0.82–3.34)	0.157	1.60 (0.79–3.26)	0.194
Upper NLR tertile	4.34 (2.32–8.15)	**<0.001**	4.47 (2.33–8.58)	**<0.001**
ICU admission, transfer from floor				
Lower tertile		1 (*Reference*)		
Middle NLR tertile	1.78 (0.91–3.48)	0.093	1.83 (0.92–3.64)	0.086
Upper NLR tertile	3.32 (1.78–6.20)	**<0.001**	3.54 (1.84–6.81)	**<0.001**
New nursing facility placement				
Lower tertile		1 (*Reference*)		
Middle NLR tertile	1.19 (0.54–2.64)	0.667	1.13 (0.49–2.58)	0.779
Upper NLR tertile	1.53 (0.72–3.27)	0.270	1.51 (0.68–3.38)	0.311
Postdischarge outcomes				
30-d readmission				
Lower tertile		1 (*Reference*)		
Middle NLR tertile	0.85 (0.50–1.43)	0.533	.83 (.48–1.45)	0.520
Upper NLR tertile	0.56 (0.32–0.99)	0.045	.66 (.36–1.21)	0.176
Mortality within 30 d of discharge				
Lower tertile		1 (*Reference*)		
Middle NLR tertile	1.01 (0.25–4.09)	0.989	0.73 (0.16–3.24)	0.674
Upper NLR tertile	0.99 (0.24–4.01)	0.989	0.61 (0.14–2.75)	0.523
Mortality within 6 mo of discharge				
Lower tertile		1 (*Reference*)		
Middle NLR tertile	1.01 (0.43–2.39)	0.981	0.94 (0.38–2.30)	0.890
Upper NLR tertile	1.28 (0.57–2.89)	0.553	1.16 (0.49–2.75)	0.732
Mortality within 1 y of discharge				
Lower tertile		1 (*Reference*)		
Middle NLR tertile	0.74 (0.37–1.49)	0.395	0.69 (0.33–1.44)	0.320
Upper NLR tertile	0.77 (0.39–1.54)	0.467	0.65 (0.31–1.37)	0.260

Boldface type indicates statistical significance. CI, confidence interval; ICU, intensive care unit; LOS, length of stay; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio.

tertiles (7.39%, n = 15, and 7.73%, n = 16, $P = 0.644$, respectively) (Table 2). No associations were seen in the middle and upper tertiles with a greater risk of death 1 year after discharge (aOR 0.69, 95% CI 0.33–1.44, $P = 0.320$, and aOR 0.65, 95% CI 0.31–1.37, $P = 0.260$, respectively) (Table 3).

Discussion

In this retrospective cohort study, we investigated the association between the NLR and in-hospital outcomes such as inpatient mortality and postdischarge outcomes in military veterans who were admitted with a confirmed diagnosis of COVID-19 infection. As predicted, after adjusting for multiple covariates, higher NLR scores were associated with an increased risk of all-cause in-hospital mortality. The NLR demonstrated an acceptable diagnostic accuracy for inpatient mortality. The highest NLR tertiles also were associated with an increased risk of ICU admissions and transfers. Our study did not, however, find an association between higher NLR scores and prolonged LOS; new nursing

Table 3. Participants' clinical outcomes per NLR tertiles

Outcome	Lower NLR tertile (n=205)	Middle NLR tertile (n=203)	Upper NLR tertile (n=207)	*P*	Total (N = 615)
Corticosteroid use, n (%)	72 (35.1)	88 (43.3)	119 (57.5)	**<0.01**	279 (45.4)
In-hospital mortality, (n%)	6 (2.93)	17 (8.37)	38 (18.36)	**<0.001**	61 (9.92)
Prolonged LOS, n (%)	103 (50.24)	92 (45.32)	116 (56.04)	0.094	311 (50.57)
<30-d readmission, n (%)	36 (17.56)	31 (15.27)	22 (10.63)	0.125	89 (14.47)
New nursing facility placement, n (%)	12 (5.85)	14 (6.90)	18 (8.70)	0.527	44 (7.15)
Direct ICU admission, n (%)	14 (6.83)	22 (10.84)	50 (24.15)	**<0.001**	86 (13.98)
ICU transfer, n (%)	15 (7.32)	25 (12.32)	43 (20.77)	**<0.001**	83 (13.50)
30-d mortality, n (%)	4 (1.95)	4 (1.97)	4 (1.93)	1.000	12 (1.95)
6-mo mortality, n (%)	11 (5.37)	11 (5.42)	14 (6.76)	0.791	36 (5.85)
1-y mortality, n (%)	20 (9.76)	15 (7.39)	16 (7.73)	0.644	51 (8.29)

Boldface type indicates statistical significance. ICU, intensive care unit; LOS, length of stay; NLR, neutrophil-to-lymphocyte ratio.

facility placement; 30-day postdischarge readmissions; and 30-day, 6-month, and 1-year postdischarge all-cause mortality.

Our findings are consistent with previous studies demonstrating an association between higher NLR scores and an increase in in-hospital mortality[11,13] and critical illness requiring ICU admission or transfer.[15] Our study was consistent with some but not all that higher NLR scores were not associated with LOS.[16–19] The studies supporting NLR association with longer hospital LOS were shown with NLR scores greater than even the high tertile group of our study.[16,17] Our study was consistent with a prior study that showed admission NLR did not predict 30-day postdischarge mortality.[20] In terms of 30-day readmissions and 6-month and 1-year mortality, there were no studies of hospitalized COVID-19 patients to compare with ours. Before the pandemic, however, NLR was neither a consistent predictor of 30-day readmissions[21–23] nor 1-year mortality in other populations.[24,25] Studies that have found associations between NLR and 30-day readmission had higher NLR scores than the upper tertile group of our study.[24] In addition, admission NLR scores may not be associated with LOS, 30-day readmission, and postdischarge mortality unless the ratio is very large because the decrease in lymphocytes is a late phenomenon during admission.[26,27] Measuring NLR later in the hospitalization can better predict the LOS and 30-day mortality.[19,20]

The dynamics early in the pandemic may explain the absence of an association between NLR scores and hospital readmissions, LOS, and new nursing facility placement. In terms of hospital readmissions, one of the most common reasons for readmission was retesting positive regardless of clinical status.[27] Because these patients did not suffer from a serious illness, their NLRs may have been indistinguishable from test-negative patients.[28] During the early part of the pandemic, highly negative news coverage of nursing facilities[29] may have influenced patients' and families' decisions to keep patients at home rather than at a healthcare

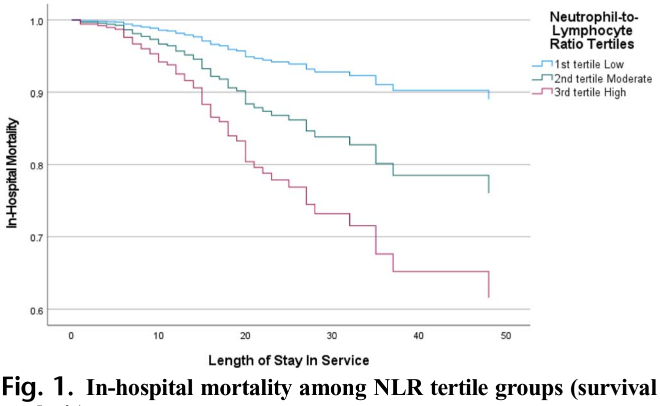

Fig. 1. In-hospital mortality among NLR tertile groups (survival analysis).

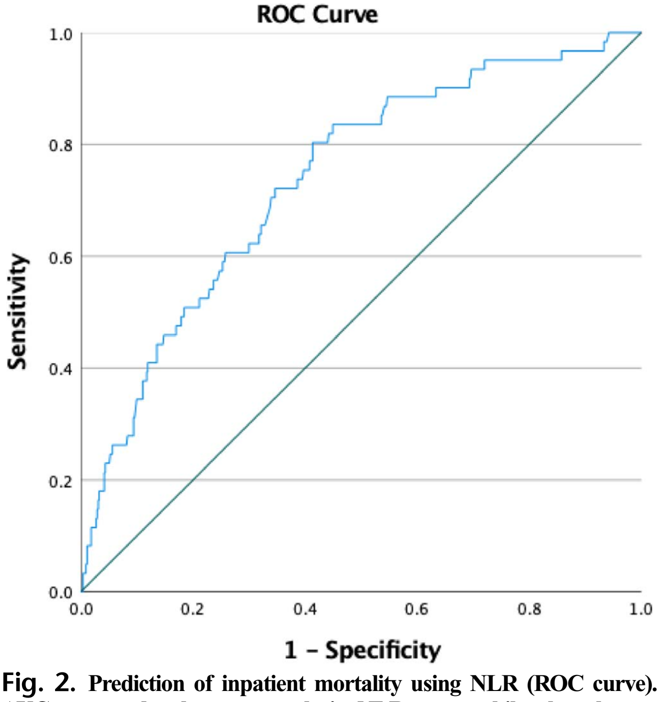

Fig. 2. Prediction of inpatient mortality using NLR (ROC curve). AUC, area under the curve analysis; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristic.

institution.[30] In combination with the fact that frail individuals have not had a high risk of new nursing facility placement from COVID-19,[5] whereas before COVID-19 they did[31,32] suggests that patients with COVID-19 were actively choosing against nursing facility placement, resulting in higher readmission rates.[25] We also did not have the statistical power to detect differences in postdischarge outcomes because of the small number of events and sample size.

The strengths of this study were the capture of comprehensive sociodemographic and clinical information from electronic health records complemented with in-depth chart reviews, an evaluation of the wide range of clinical and utilization outcomes previously seen in studies of NLR and COVID-19 outcomes, well-defined outcomes, and exposures and statistical adjustments of several potential confounders.

The present study does have limitations worth mentioning, such as the retrospective cohort study design that includes the possibility of bias, such as missing data that may limit control of confounding, misclassification of comorbid conditions or diagnostic measures, and selection bias. Generalizability may be limited because of the number of males to females that is typical of VA studies and subjects only treated at VA facilities in VISN 8, although veterans may have received hospital care at non-VA facilities.[33] Other limitations include the lack of chart review into immune-mediated conditions besides cancer, other co-infections, and timing of dexamethasone before laboratory values were taken. The acuity and severity of veterans admitted for COVID-19 to non-VA hospitals may have been different from those admitted to a VA facility. Evidence shows that the quality of inpatient care at VA hospitals may be better than at non-VA hospitals, potentially influencing study outcomes.[34,35] The introduction of COVID-19 vaccines and therapeutic interventions may have altered the associations of the NLR with the outcomes. We need more prospective studies in healthcare systems inside and outside VA, with more diverse populations who received COVID-19 vaccines and therapeutics to confirm the association of NLR scores with these clinical outcomes.

Regarding the ramifications for clinical care, the NLR may be a practical tool for hospitalists, emergency department doctors, and intensivists to determine prognosis and to risk stratify patients, which may in turn guide clinical management, potentially improving clinical outcomes. With the knowledge of their patients' mortality risk and other outcomes, these physicians can tailor the care of individual patients. They also may use the NLR as a starting point to frame the discussions regarding preferences for treatment modalities.[36] Patients with middle and upper NLR scores admitted with COVID also may benefit from the involvement of interprofessional geriatric teams and inpatient comprehensive geriatric assessment that may lead to better clinical and cost outcomes for hospitalized older adults.[37] Geriatricians also are likely to recommend geriatrics models of care proven to help older adult inpatients, such as the Hospital Elder Life Program, which has reduced the incidence of delirium and falls, the number of days in the hospital, and delay institutionalization.[38]

Conclusions

Our results reveal that the NLR was associated with serious illness incidence in patients with COVID-19 infection. The early application of NLR may serve to determine prognosis and for the risk stratification of patients hospitalized with serious COVID-19 infections.

Acknowledgments

The authors thank our older veterans in Florida and Puerto Rico; Dominique Tosi, Valerie Hart-Quezada, Orly Hadar, Gabriela Falcon, Sanaa Badour, Ezekiel Ijaopo, and Eken Ahmed for their initial chart reviews that contributed to this work; and Fei Tang for guidance on the statistical analysis.

References

1. Lithander FE, Neumann S, Tenison E, et al. COVID-19 in older people: a rapid clinical review. *Age Ageing*, 2020;49:501–515.
2. Becerra-Muñoz VM, Núñez-Gil IJ, Eid CM, et al. Clinical profile and predictors of in-hospital mortality among older patients hospitalised for COVID-19. *Age Ageing* 2021;50:326–334.
3. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm. Published March 27, 2020. Accessed December 17, 2022.
4. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020;41:145–151.
5. Dumitrascu F, Branje KE, Hladkowicz ES, et al. Association of frailty with outcomes in individuals with COVID-19: a living review and meta-analysis. *J Am Geriatr Soc* 2021;69:2419–2429.
6. Hu B, Huang S, Yin L, et al. The cytokine storm and COVID-19. *J Med Virol* 2021;93:250–256.
7. Wang Y, Pang SC, Yang Y, et al. A potential association between immunosenescence and high COVID-19 related mortality among elderly patients with cardiovascular diseases. *Immun Ageing* 2021;18:25.
8. Thomas B, Goodacre S, Lee E, et al. Prognostic accuracy of emergency department triage tools for adults with suspected COVID-19: the PRIEST observational cohort study. *Emerg Med J* 2021;38:587–593.
9. Zahorec R. "Neutrophil-to-lymphocyte ratio, past, present and future perspectives." *Bratisl Lek Listy* 2021;122:474–488.
10. Blomaard LC, Speksnijder C, Lucke JA, et al. Geriatric screening, triage urgency, and 30-day mortality in older emergency department patients. *J Am Geriatr Soc* 2020;68:1755–1762.
11. Alkhatip AAAMM, Kamel MG, Hamza MK, et al. The diagnostic and prognostic role of neutrophil-to-lymphocyte ratio in COVID-19: a systematic review and meta-analysis. *Expert Rev Mol Diagn* 2021;21:505–514.
12. Ozdin M, Hakan K, Gulact U, et al. The diagnostic value of neutrophil to lymphocyte ratio in determining the severity of COVID-19. *IMC J Med Sci* 2021;16:1–7.
13. Li Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect 2020;81:e6–e12.
14. Moradi EV, Teimouri A, Rezaee R, et al. Increased age, neutrophil-to-lymphocyte ratio (NLR) and white blood cells count are associated with higher COVID-19 mortality. *Am J Emerg Med* 2021;40:11–14.
15. Lian J, Jin C, Hao S, et al. High neutrophil-to-lymphocyte ratio associated with progression to critical illness in older patients with COVID-19: a multicenter retrospective study. *Aging (Albany NY)* 2020;12:13849–13859.

16. Pillai J, Mistry PPK, Le Roux DA, et al. Laboratory parameters associated with prolonged hospital length of stay in COVID-19 patients in Johannesburg, South Africa. *S Afr Med J* 2022;112:201–208.
17. Liu G, Zhang S, Hu H, et al. The role of neutrophil-lymphocyte ratio and lymphocyte–monocyte ratio in the prognosis of type 2 diabetics with COVID-19. *Scott Med J* 2020;65:154–160.
18. Kashefizadeh A, Ohadi L, Golmohammadi M, et al. Clinical features, and short-term outcomes of COVID-19 in Tehran, Iran: an analysis of mortality and hospital stay. *Acta Biomed* 2020;91:e2020147.
19. Jeraiby MA, Hakamy MI, Albarqi MB, et al. Routine laboratory parameters predict serious outcome as well as length of hospital stay in COVID-19. *Saudi Med J* 2021;42:1165–1172.
20. Chelariu AC, Coman AE, Lionte C, et al. The value of early and follow-up elevated scores based on peripheral complete blood cell count for predicting adverse outcomes in COVID-19 patients. *J Pers Med* 2022;12:2037.
21. Haran C, Gimpel D, Clark H, et al. Preoperative neutrophil and lymphocyte ratio as a predictor of mortality and morbidity after cardiac surgery. *Heart Lung Circ* 2021;30:414–418.
22. Da Silva M, Cleghorn MC, Elnahas A, et al. Postoperative day one neutrophil-to-lymphocyte ratio as a predictor of 30-day outcomes in bariatric surgery patients. *Surg Endosc* 2017;31:2645–2650.
23. Uthamalingam S, Patvardhan EA, Subramanian S, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. *Am J Cardiol* 2011;107:433–438.
24. Ergin ÖN, Bayram S, Anarat FB, et al. Prognostic factors affecting survival of patients with intertrochanteric femoral fractures over 90 years treated with proximal femoral nailing. *Eur J Trauma Emerg Surg* 2020;46: 663–669.
25. Seropian IM, Romeo FJ, Pizarro R, et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as predictors of survival after heart transplantation. *ESC Heart Fail* 2018;5:149–156.
26. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther* 2020;5:61.
27. Sotoodeh Ghorbani S, Taherpour N, Bayat S, et al. Epidemiologic characteristics of cases with reinfection, recurrence, and hospital readmission due to COVID-19: a systematic review and meta-analysis. *J Med Virol* 2022;94:44–53.
28. Kimura LF, Sant'Anna MB, Andrade SA, et al. COVID-19 induces proatherogenic alterations in moderate to severe non-comorbid patients: a single-center observational study. *Blood Cells Mol Dis* 2021;92:102604.
29. Miller EA, Simpson E, Nadash P, et al. Thrust into the spotlight: COVID-19 focuses media attention on nursing homes. *J Gerontol B Psychol Sci Soc Sci* 2021;76:e213–e218.
30. Lai YF, Lim YW, Kuan WS, et al. Asian attitudes and perceptions toward hospital-at-home: a cross-sectional study. *Front Public Health* 2021;9:704465.
31. Kojima G. Frailty as a predictor of nursing home placement among community-dwelling older adults: a systematic review and meta-analysis. *J Geriatr Phys Ther* 2018;41:42–48.
32. Hao Q, Zhou L, Dong B, et al. The role of frailty in predicting mortality and readmission in older adults in acute care wards: a prospective study. *Sci Rep* 2019;9:1207.
33. Sherman RL, Judon KM, Koufacos NS, et al. Utilizing a health information exchange to facilitate COVID-19 VA primary care follow-up for veterans diagnosed in the community. *JAMIA Open* 2021;4:ooab020.
34. Nuti SV, Qin L, Rumsfeld JS, et al. Association of admission to Veterans Affairs hospitals vs non-Veterans Affairs hospitals with mortality and readmission rates among older men hospitalized with acute myocardial infarction, heart failure, or pneumonia. *JAMA* 2016;315:582–592.
35. Anhang Price R, Sloss EM, Cefalu M, et al. Comparing quality of care in Veterans Affairs and non-Veterans Affairs settings. *J Gen Intern Med* 2018;33:1631–1638.
36. Austin CA, Mohottige D, Sudore RL, et al. Tools to promote shared decision making in serious illness: a systematic review. *JAMA Intern Med* 2015;175: 1213–1221.
37. Ellis G, Langhorne P. Comprehensive geriatric assessment for older hospital patients. *Br Med Bull* 2005;71:45–59.
38. Hshieh TT, Yang T, Gartaganis SL, et al. Hospital Elder Life Program: systematic review and meta-analysis of effectiveness. *Am J Geriatr Psychiatry* 2018;26: 1015–1033.