Heliyon 9 (2023) e16482

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Neutrophil-to-lymphocyte ratio trend at admission predicts adverse outcome in hospitalized respiratory syncytial virus patients

Eden Shusterman [a,1,*], Lior Prozan [a,1], Jacob Nadav Ablin [a,c], Ahuva Weiss-Meilik [b], Amos Adler [c,d], Guy Choshen [a,d], Orli Kehat [b]

[a] Internal Medicine H, Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel
[b] I-Medata AI Centre, Tel Aviv, Israel
[c] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[d] Infectious Diseases Unit, Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel

ARTICLE INFO

Keywords:
Respiratory syncytial virus
Neutrophil to lymphocyte ratio
Aberrant Imunne Response

ABSTRACT

Background and aims: Severe cases of respiratory syncytial virus (RSV) infection are relatively rare but may lead to serious clinical outcomes, including respiratory failure and death. These infections were shown to be accompanied by immune dysregulation. We aimed to test whether the admission neutrophil-to-leukocyte ratio, a marker of an aberrant immune response, can predict adverse outcome.

Methods: We retrospectively analyzed a cohort of RSV patients admitted to the Tel Aviv Medical Center from January 2010 to October 2020d. Laboratory, demographic and clinical parameters were collected. Two-way analysis of variance was used to test the association between neutrophil-lymphocyte ratio (NLR) values and poor outcomes. Receiver operating characteristic (ROC) curve analysis was applied to test the discrimination ability of NLR.

Results: In total, 482 RSV patients (median age 79 years, 248 [51%] females) were enrolled. There was a significant interaction between a poor clinical outcome and a sequential rise in NLR levels (positive delta NLR). The ROC curve analysis revealed an area under curve (AUC) of poor outcomes for delta NLR of (0.58). Using a cut-off of delta = 0 (the second NLR is equal to the first NLR value), multivariate logistic regression identified a rise in NLR (delta NLR>0) as being a prognostic factor for poor clinical outcome, after adjusting for age, sex and Charlson comorbidity score, with an odds ratio of 1.914 (P = 0.014) and a total AUC of 0.63.

Conclusions: A rise in NLR levels within the first 48 h of hospital admission can serve as a prognostic marker for adverse outcome.

1. Introduction

Respiratory syncytial virus (RSV), a single-stranded RNA virus of the Paramyxoviridae family, is recognized as being an important cause of acute respiratory infection among adults [1–3]. Although most cases of RSV infection follow a mild clinical course, certain

* Corresponding author.
E-mail address: edensh@tlvmc.gov.il (E. Shusterman).
[1] Equal contribution.

https://doi.org/10.1016/j.heliyon.2023.e16482
Received 15 June 2022; Received in revised form 31 March 2023; Accepted 17 May 2023
Available online 19 May 2023

patient populations are prone to suffer a severe, often lethal, disease course when it presents in the form of an upper respiratory tract infection. Adults with comorbidities, long-term care facility residents and immunocompromised hosts appear to be at increased risk for severe disease, complications and mortality [4–6].

The adverse outcome of RSV infection is partly due to an aberrant immune response. An impaired immune activation may facilitate extensive viral replication and invasion. On the other hand, a dysregulated, over-activated immune response may lead to local and systemic injury [7,8]. Early viral invasion is characterised by interleukin- 8 -mediated neutrophilic activation and suppression of lymphocytes. The inability to mount an adaptive lymphocytic response has been shown to underlie a more severe disease ([9].

The neutrophil-to-lymphocyte ratio (NLR) is a constant calculated from a complete blood count used to evaluate the inflammatory status of a patient [10]. NLR levels can serve as a prognostic factor in rheumatic and cardiovascular diseases, as well as in different types of malignancies, such as lung and breast cancer [11–16]. Moreover, recent studies have shown that NLR can serve as a useful marker in predicting outcomes of common infectious diseases [17–19].

NLR has been studied in the context of viral infections. Zhang et al. demonstrated that NLR can be a predictive prognostic marker in patients infected with avian influenza [20]. Several very small-scale studies have suggested NLR's application as a diagnostic tool for identifying influenza virus-infected patients (serotypes A and B) among elderly and pediatric populations [21–23].

In contrast, numerous reports have investigated the application of NLR in Coronavirus Disease 2019 (COVID-19), including four large-scale meta-analyses. An increased NLR was found to be an early marker for severe COVID-19 and a prognostic factor for endotracheal intubation and mortality during hospitalization [22,24–29]).

RSV is one of the two major viral pathogens associated with acute lower respiratory infection, and it represents an epidemiologic concern, especially during the winter season [30]. To the best of our knowledge, a possible relation between RSV infection and the NLR parameter has not been previously reported. In the current study, we aim to assess the levels and prognostic value of NLR in adult patients infected with RSV.

2. Methods

2.1. Study design

This retrospective observational study was conducted at the Tel Aviv Sourasky Medical Center, a tertiary academic hospital. We searched the electronic medical records in the microbiology laboratory database for RSV positive reverse transcription polymerase chain reaction (RT-PCR) nasal swabs obtained from 2010 through 2021. For all study procedures The STROBE checklist was followed [31]. The study was reviewed and approved by the Tel Aviv Sourasky Medical Center institutional review board (ethics approval number 056-20-TLV). Requirement for informed consent was waived for this retrospective anonymised study.

2.2. Patients

The study participants were selected according to the following criteria: 1. Positive viral PCR for RSV; 2. Hospital admission from January 1, 2010 to October 1, 2021; 3. Documented complete blood count (CBC) taken at admission; 4. Hospital admission duration over 24 h; 5. At least two consecutive CBCs available within 48 h from admission. Only patients over 18 years of age were included.

2.3. Data collection

Data were extracted from the patients' electronic medical records. Background patient information included sex age, and comorbidities, ranked by the Charlson comorbidity index [32]. Laboratory findings on white blood cell and differential blood counts, estimated glomerular filtration rate, liver function tests, bilirubin, international normalized ratio and C-reactive protein were retrieved for each patient. Blood counts were performed automatically with Beckmann Coulter LH750 or Beckmann Coulter DxH800.

NLR was calculated as followes: neutrophil count at admission divided by the lymphocyte count at admission. Then, Delta NLR values were calculated by subtracting the NLR value of the second test from the first test. The primary outcome measure was defined as a composite score of mortality, death within 30 days of admission, and mechanical ventilation.

2.4. Microbiology

Viral respiratory infection was diagnosed by PCR from combined pharyngeal and nasopharyngeal swabs introduced into UTM tubes and transported to the laboratory. RNA extraction was by the easyMAG® system (BioMérieux, Marcy-l'Étoile, France). RSV was diagnosed by the Simplexa™ Flu A/B & RSV kit (DiaSorin) or the Seeplex® RV7 kit (Seegene).

All positive cultures (blood, sputum, urine and others) from the first seven days of hospitalization were extracted for identification of bacterial or fungal super-infections. The list was reviewed independently by two internal medicine physicians to exclude positive cultures that were considered to be contaminants.

2.5. Statistical analyses

The characteristics of patients with RSV presented as counts and as percentages for categorical variables and as medians and interquartile ranges (IQR) for continues variables and. A repeated measures analysis of variance (ANOVA) was used to compare the

initial trend of NLR values (negative or positive delta NLR) with adverse outcomes. The NLR and delta NLR predictive values for poor clinical outcome were assessed by means of the receiver operating characteristic (ROC) curve analysis. The optimal cutoff value of delta NLR was determined by Youden's index. In order to obtain the odds ratio (OR) of delta NLR and additional factors, multivariate logistic regression was performed. The Chi-square test was applied to compare NLR levels of patients with to those without a superinfection. Statistical calculations were performed using the SPSS 25.0 software (SPSS Inc, Chicago, USA).

3. Results

In total, 469 confirmed cases of RSV infection were registered in the database during the study period. They had all been identified by nasal swab RT-PCR findings. Their baseline characteristics, including age, sex and Charlson Comorbidity Index (CCI) are presented in Table 1. The mean age of the cohort was 79 years, and 248 of the patients were female (51%). Comorbidities were presented by the Charlson score, with a mean score of 5.

The mortality rate was 13% (61 cases) among all of the registered RSV patients, and 8% (38 cases) of the patients required mechanical ventilation. For the purposes of analysis, a poor outcome was defined as the presence of any of the two above–mentioned endpoints. As expected, patients with an adverse outcome were significantly older (median 81.5 [range 71–88] Vs. 78 [range 67–85), $p < 0.05$] and had more comorbidities (a median CCI of 6 [range 4–8] Vs. 5 [range 4–7], $p < 0.05$). Patients in the adverse outcome group had significantly higher rates of readmission within 7 days of discharge from the index hospitalization (9.3% Vs. 6.3%, $p < 0.01$).

Table 2 details the patients' laboratory data at presentation, including white blood cell and differential blood counts, liver function tests, bilirubin, international normalized ratio and C-reactive protein. The median NLR at presentation was 6.82 (range 3.9–11.8) and there was no significant difference between NLR levels at admission between patients with or without an adverse outcome (median 6.6 (range 3.8–11.3) Vs. 7.2 (range 4.4–16.6), $p = 0.77$).

All RSV patients in our study had more than two CBCs taken during their hospital stay yielding more than two NLR values, We calculated the delta NLR by subtracting the NLR value of the second test from the first. The median time between the first and second lab tests for NLR was 19 h (IQR 16 h [range 12–28]).

We examined the association between the initial trend of NLR values (delta NLR) and adverse outcomes with a two-way ANOVA. A poor clinical outcome was associated with a sequential rise in NLR levels (positive delta NLR). A repeated measure ANOVA showed a significant test-outcome interaction ($p = 0.008$): patients with adverse clinical outcomes had higher NLR levels in their second test compared to patients with non-adverse clinical (Fig. 1).

Having found the delta NLR as being associated with poor clinical outcome, we further tested the discrimination ability of delta NLR by means of ROC curve analysis (Fig. 2). The area under the curve (AUC) of poor outcomes for NLR was AUC = 0.56 $p = 0.08$ 95% CI [0.49–0.63] and AUC 0.629 $p < 0.001$ 95%CI [0.55–0.69] for delta NLR. The optimal cutoff of delta NLR was obtained from Youden's index: delta of 0.18. Since this cutoff is not a practical number for clinicians, we decided to further analyze our data by using a delta = 0 cutoff (meaning, the second NLR value is equal to the first NLR value). We applied multivariate logistic regression in order to test the discrimination ability of this cutoff as a prognostic factor of poor clinical outcome adjusted for age, sex and CCI score. The results showed an OR of 2.031 for a delta NLR >0 ($p = 0.004$ 95%CI [1.248–3.304]) and a total AUC of 0.64 95% CI [0.57–0.72]. In this model, age, sex and the CCI score emerged as being non-significant in predicting a poor outcome among the RSV patients ($p = 0.091$ (95%CI [0.99–1.03]), $p = 0.817$ (95%CI [0.58–1.53]), P = 0.483 (95%CI [0.28–1.17]), respectively). Fig. 3 demonstrates the similar results of using delta NLR = 0.18 as a cutoff with an OR of 2.209 for a delta NLR >0.18 ($p = 0.001$ (95%CI [1.359–3.592]) and an AUC of 0.645 95% CI [0.58–0.7].

In order to exclude the possibility that the NLR trend was due to a concurrent bacterial or fungal superinfection, we compared the rates of superinfections among patients who had a positive trend with those who had a negative trend and observed that the presence of a superinfection was not associated with a higher NLR trend at admission (χ^2 (1, N = 469) = 0.45, $p = 0.6$) (Fig. 4). Table 3 lists all superinfections among the study participants within the first 7 days from admission. Gram negative infections (n = 67 14% and specifically gram-negative urinary infections (n = 34 7%) were most common. E. Coli was the most frequently isolated pathogen (n =

Table 1
Demographics and outcomes.

	All	Adverse Outcome	No Adverse Outcome	*p* values
N	469	86	383	–
age (median + IQR)	79 (68–86)	81.5 (71–88)	78 (67–85)	$p < 0.05$[a]
Females (%)	248 (52.9%)	46 (53.5%)	202 (52.7%)	NS[a]
Charlson Index (median + IQR)	5 (4–7)	6 (4–8)	5 (4–7)	$p < 0.05$[a]
Complications				
Readmission in 7 days (%)	32 (6.8%)	8 (9.3%)	24 (6.3%)	$p < 0.01$[b]
Long length of stay (%)	148 (31.6%)	41 (47.7%)	107 (27.9%)	NS[b]
Outcomes:				
Ventilation (%)	37 (7.8%)			
Mortality within 30 days (%)	61 (13%)			
Adverse outcome (ventilation or mortality) (%)	86 (18%)			

[a] Mann Whitney.
[b] Chi Square.

Table 2
Laboratory tests at presentation of patients diagnosed with RSV.

Lab Test upon admission (N)	All (IQR)	Adverse Outcome (IQR)	No Adverse Outcome (IQR)	*p* value[a]
Hemoglobin (469) (g/dL)	12.3 (10.6–13.6)	12.3 (10.7–13.5)	12.15 (10.425–2310)	NS
WBC (469) (10e3/μL)	9.3 (6.9–12.8)	8.9 (6.7–12.5)	10.9 (8.275–14.4)	$p < 0.01$
Neutrophils (469) (10e3/μL)	7.2 (5.1–10.1)	6.9 (4.9–9.9)	8.5 (6.4–11)	$p < 0.01$
Lymphocytes (469) (10e3/μL)	1 (0.7–1.6)	1 (0.7–1.5)	1 (0.6–1.625)	NS
NLR (469)	6.8 (3.9–11.8)	6.6 (3.8–11.3)	7.2 (4.4–16.6)	NS
PLT (469) (10e3/μL)	200 (155–255)	199 (153–255)	210.5 (166.75–258.5)	NS
INR (402)	1.07 (1–1.1)	1.07 (1–1.1)	1.1 (1–1.3)	$p < 0.01$
ALT (460) (U/L)	20 (14–30)	19.5 (14–28.75)	22 (13.25–35)	NS
AST (381) (U/L)	26 (19–36.5)	25 (18–34)	30.5 (22–52.5)	NS
GGT (401) (U/L)	29 (18–63.5)	28 (18–59.75)	32 (19.5–76)	NS
ALK (456) (U/L)	76 (60–99)	74 (60–97)	83 (65–117)	$p < 0.05$
Bilirubin (459) (mg/dL)	0.37 (0.2–0.6)	0.38 (0.2–0.6)	0.315 (0.2–0.6)	NS
CRP (461) (mg/L)	50.41 (19.9–112.4)	47.84 (19.1–109.5)	63.465 (22.4–122.1)	NS

Continuous variables are presented as medians and inter-quartile ranges.
RSV-Respiratory Syncytial Virus *WBC*-white blood cells, *PLT*-platlets *ALT* Alanine transaminase, *AST* Aspartate transaminase *GGT* Gamma-glutamyltransferase *ALKP* Alkaline phosphatase *INR* international normalized ratio, *CRP* C-reactive protein *NLR* neutrophil-to-lymphocyte ratio. [a] Mann Whitney.

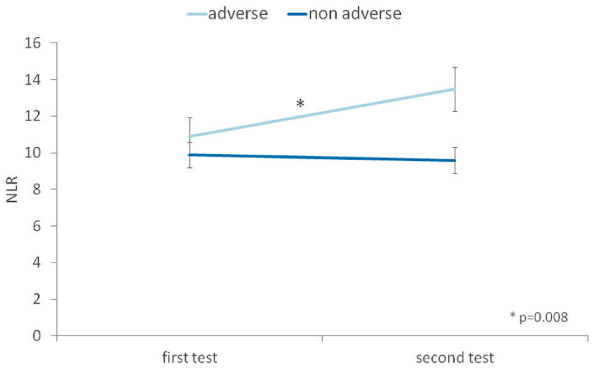

Fig. 1. Repeated measure ANOVA showed a significant test – outcome interaction (N = 469 $p = 0.008$): patients with adverse clinical outcomes had higher levels of Neutrophil to Lymphocyte Ratio (NLR) compared to non-adverse patients in the second test, but not in the first one.

29 6%).

4. Discussion

Severe cases of RSV, although relatively rare, can have severe outcomes, such as respiratory failure and death. These cases have been shown to be accompanied by immune dysregulation. The current study findings demonstrated that a rise in the neutrophil-to-leukocyte ratio, a well-known marker of an aberrant immune response, during the first 48 h of hospitalization, is associated with an adverse outcome. Hospitalizations of patients aged 5–50 years due to RSV are rare and generally involve such patients who have underlying comorbidities. However, RSV is an important cause of mortality and carries the same hospitalization burden as Influenza A in a vaccinated population of older adults [33–35].

We retrospectively retrieved a cohort of nearly 500 RSV cases admitted to our institute over a decade between 2010 and 2021. The mean age of our patients was 79 years, which is higher compared to other studies in which an age range of 65–76 years was reported [2–4]. Interestingly, in our study, age was not an independent risk factor when adjusted for comorbidities, sex and NLR trend. This finding may be explained by the initial advanced age of the admitted patients in our study. The mortality rate of our study patients was 13% and mechanical ventilation rate was 8%, both of which are relatively high but in accordance with the reports of others in which mortality and requirement of mechanical ventilation rates ranged between 8-19% and 3–17%, respectively [2–4,33,34]. Early identification of high-risk patients emerges as being crucial given such substantial morbidity.

The findings of a recent study by our group in which the prognostic value of NLR in COVID-19, influenza and RSV patients were compared showed that NLR at admission was not a useful prognostic marker in RSV patients despite pathophysiological reasoning [36]. In our current work, we tested the independent prognostic value of the NLR trend within the first 48 h, which was defined as a delta NLR (second NLR minus first NLR) larger than zero. A positive NLR trend (delta NLR >0) emerged as an independent risk factor for death or need for mechanical ventilation adjusted for sex, age and comorbidities. Indeed, after using delta NLR and including sex, age and comorbidities, the AUC of this model was only 0.63. This low (albeit significant) AUC is not surprising, considering the diverse

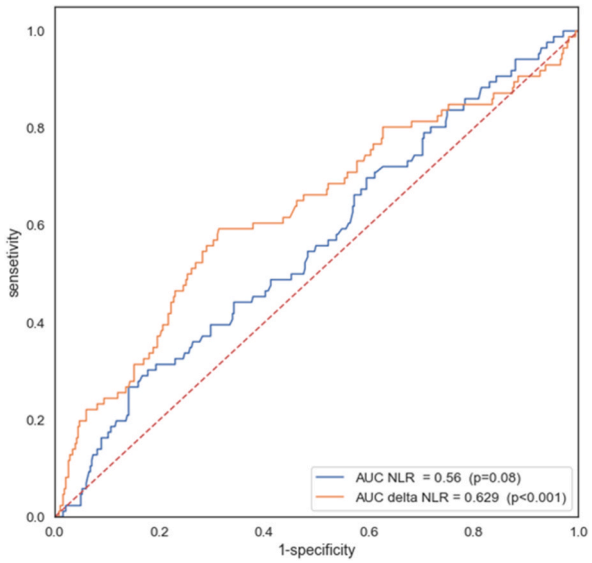

Fig. 2. Receiver operating characteristic (ROC) curves analyses for predicting poor outcomes (death within 30 days or mechanical ventilation) for RSV patients (N = 469) using NLR (AUC = 0.56 P = 0.08 (CI (0.49–0.63)) or delta NLR (AUC 0.629 $p < 0.001$ CI (0.55–0.69)). *NLR* neutrophil-to-lymphocyte ratio, *RSV* respiratory syncytial virus, *AUC* area under the curve. *Delta NLR* (NLR in the second blood test after admission-NLR in the first test at admission) *CI* confidence interval.

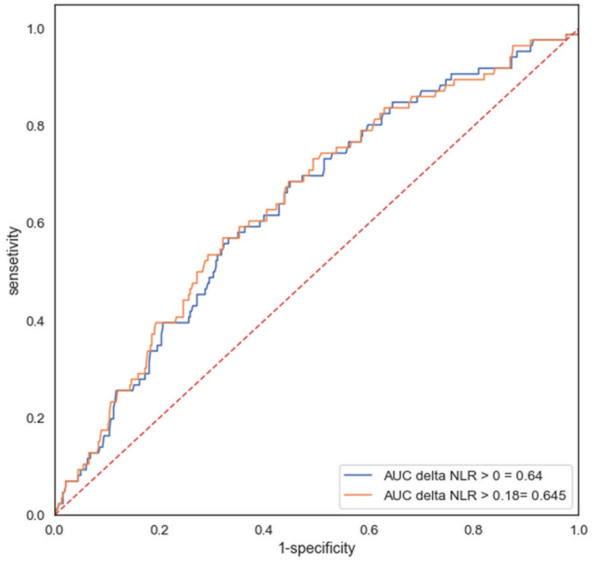

Fig. 3. Receiver operating characteristic (ROC) curve for logistic regression model used to test the discrimination ability of delta NLR (above or below 0.18 or above or below 0) as a prognostic factor of poor clinical outcome adjusted to age, sex and CCI among RSV patients (N = 469).AUC $_{\text{delta NLR}>0.18} = 0.645$ CI (0.58–0.7) AUC $_{\text{delta NLR}>0} = 0.64$ CI(0.57–0.72). *NLR* neutrophil-to-lymphocyte ratio, *RSV* Respiratory syncytial virus, *AUC* area under the curve, *CCI* Charlson comorbidity index. *Delta NLR* (NLR in the second blood test after admission-NLR in the first test at admission) *CI* confidence interval.

backgrounds and presentations of these patients. Compiling a model with a higher discriminative ability is possible, but it would include many more variables and be cumbersome to be used clinically.

An NLR trend has been shown to be associated with adverse outcome in various clinical scenarios [37,38]. A temporal rise of the NLR during the first five days was associated with death rather than survival in abdominal septic shock [39]. Interestingly, those authors observed that a higher admission NLR was associated with a better prognosis in the first five days, suggesting that an NLR at admission and an NLR trend do not always bear the same prognostic value. In our study, a positive NLR trend within the first 48 h, but not the NLR at admission, was associated with a poor prognosis. This finding may derive in part from the temporal pattern of

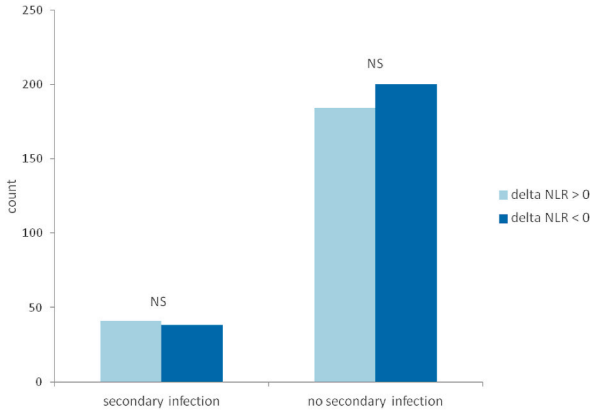

Fig. 4. Frequency of superinfections among patients with a positive NLR trend (N = 41) compared to patients with no increase in NLR (N = 38). No significant association between having a secondary infection and NLR group $p = 0.61$. NLR neutrophil-to-lymphocyte ratio.

Table 3
Prevalence of Secondary Infections among RSV Patients in the First Seven Days from Admission. [a]Others including swabs taken from wounds, stool cultures, and biopsy cultures *RSV*- Respiratory Syncytial Virus.

	Gram Positive	Gram Negative	Fungi	Total
Blood Culture Number (%)	12 (2.56)	15 (3.2)	1 (0.21)	28 (5.97)
Urinary Culture Number (%)	5 (1.07)	34 (7.25)	4 (0.85)	43 (9.16)
Sputum Culture Number (%)	10 (2.13)	14 (2.99)	2 (0.43)	26 (5.54)
Other Site[a] Number (%)	5 (1.07)	4 (0.85)	3 (0.64)	12 (2.55)
Total Number (%)	32 (6.82)	67 (14.28)	10 (2.13)	109 (23.24)

neutrophil-based inflammation. Neutrophil recruitment in inflammation in general and in lung injury specifically consists of two phases. The initial stage is the influx of circulating neutrophils to the lung tissue (rapid phase), and it is followed by a late persistent phase, which includes recruitment of the large mass of neutrophils produced in the bone marrow. This process may be driven by SDF-1 signalling [40]. The flip side of neutrophilia with a high NLR is lymphopenia, which also follows a temporal pattern. In influenza pneumonia, for example, the CD-8 lymphocyte response is biphasic, with rapid expansion of lymphocyte population only after 6 days from the start of infection. This late phase correlates with viral clearing from the lungs [41]. In RSV, different cytokine patterns result in different inflammatory responses. A Th-1 response characterized by IFN-γ and IL-2 production can lead to viral clearance, while proinflammatory cytokines, such as interleukin (IL) IL-4, IL-6, IL-10 and IL-13 lead to an inflammatory response associated with lung damage [42]. Moreover, acute RSV infection in infants is associated with lymphopenia, possibly induced by lymphocyte apoptosis and a loss of CD-8 T cells [43]. Thus, the NLR trend may represent the temporal evolvement of an aberrant response to the pathogen and persistent inflammation [44], with a time-dependent elevation in neutrophils and a time-dependent depletion of lymphocytes. The use of longitudinal blood counts for prognostic input has been reported for other respiratory viruses and bacterial infections, and has been proposed as a tool to guide therapy [45]. In our model, a positive NLR trend was associated with a twofold risk for death and the need of mechanical ventilation.

There are several inherent limitations to our study. First, its observational retrospective design limited control for unmeasured confounders. Second, our study was carried out in a single medical center. Third, our study population was limited to patients with severe respiratory illness which required hospitalization, thereby excluding RSV patients with mild illness and warranting further study in order to determine the implication of NLR in that group as well. Finally, due to the COVID-19 pandemic, new infection protective measures had been employed and there was heightened awareness to respiratory symptoms and infections in the public. One can postulate that the epidemiology of patients with respiratory symptoms seeking medical attention may change from the one represented in our cohort.

To conclude, based upon on a large cohort of RSV patients, we developed a practical prognostic tool for clinicians in the management of adults with RSV infections. To the best of our knowledge, this is the first large-scale report of a prognostic model based upon NLR levels for RSV. A patient whose NLR levels within the first 48 h of admission do not decrease compared to those measured at admission has a twofold risk for an adverse outcome. In an era of respiratory pandemics, such a prognostic tool can help guide the therapeutic management and placement of RSV patients.

Ethical approval

The study was reviewed and approved by the Tel Aviv Sourasky Medical Center's institutional review board.

Author contribution statement

Eden Shusterman: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Lior Prozan: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Guy Choshen: Analyzed and interpreted the data.

Ahuva Weiss-Meilik and Amos Adler: Contributed reagents, materials, analysis tools or data.

Jacob Nadav Ablin: Analyzed and interpreted the data; Wrote the paper.

Orly Kehat: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Data availability statement

The authors do not have permission to share data.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A.R. Falsey, E.E. Walsh, Respiratory syncytial virus infection in adults, Clin. Microbiol. Rev. 13 (3) (2000) 371–384.
[2] A.R. Falsey, et al., Respiratory syncytial virus infection in elderly and high-risk adults, N. Engl. J. Med. 352 (17) (2005) 1749–1759.
[3] C.B. Duncan, et al., Risk factors for respiratory failure associated with respiratory syncytial virus infection in adults, J. Infect. Dis. 200 (8) (2009) 1242–1246.
[4] B. Chuaychoo, et al., Clinical manifestations and outcomes of respiratory syncytial virus infection in adult hospitalized patients, J. Clin. Virol. 117 (2019) 103–108.
[5] D.P. Shah, et al., Immunodeficiency scoring index to predict poor outcomes in hematopoietic cell transplant recipients with RSV infections, Blood J. Am. Soc. Hematol. 123 (21) (2014) 3263–3268.
[6] A.R. Falsey, et al., Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness, J. Infect. Dis. 209 (12) (2014) 1873–1881.
[7] R. Nuriev, C. Johansson, Chemokine regulation of inflammation during respiratory syncytial virus infection [version 1; Peer Review: 3 Approved], F1000Res. 8 (1837) (2019).
[8] M.S. Habibi, et al., Neutrophilic inflammation in the respiratory mucosa predisposes to RSV infection, Science 370 (6513) (2020) eaba9301.
[9] C.D. Russell, et al., The human immune response to respiratory syncytial virus infection, Clin. Microbiol. Rev. 30 (2) (2017) 481–502.
[10] P. Forget, et al., What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res. Notes 10 (1) (2017) 12.
[11] M. Tomita, et al., Preoperative neutrophil to lymphocyte ratio as a prognostic predictor after curative resection for non-small cell lung cancer, Anticancer Res. 31 (9) (2011) 2995–2998.
[12] H.S. Kim, et al., Neutrophil to lymphocyte ratio for preoperative diagnosis of uterine sarcomas: a case-matched comparison, Eur. J. Surg. Oncol. 36 (7) (2010) 691–698.
[13] B. Azab, et al., Usefulness of the neutrophil-to-lymphocyte ratio in predicting short-and long-term mortality in breast cancer patients, Ann. Surg Oncol. 19 (1) (2012) 217–224.
[14] M.J. Proctor, et al., A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study, Eur. J. Cancer 47 (17) (2011) 2633–2641.
[15] Y. Koza, Neutrophil–Lympocyte Ratio and Cardiovascular Diseases: An Update, SAGE Publications Sage CA, Los Angeles, CA, 2016.
[16] X. Hao, et al., The relationship between hematological indices and autoimmune rheumatic diseases (ARDs), a meta-analysis, Sci. Rep. 7 (1) (2017) 1–9.
[17] C.P. de Jager, et al., The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia, PLoS One 7 (10) (2012).
[18] R. Terradas, et al., Eosinophil count and neutrophil-lymphocyte count ratio as prognostic markers in patients with bacteremia: a retrospective cohort study, PLoS One 7 (8) (2012).
[19] M. Bozbay, et al., Neutrophil-to-lymphocyte ratio as a prognostic marker in infective endocarditis: in-hospital and long-term clinical results, J. Heart Valve Dis. 23 (5) (2014) 617–623.
[20] Y. Zhang, et al., Neutrophil–lymphocyte ratio as an early new marker in AIV-H7N9-infected patients: a retrospective study, Therapeut. Clin. Risk Manag. 15 (2019) 911.
[21] A. Indavarapu, A. Akinapelli, Neutrophils to lymphocyte ratio as a screening tool for swine influenza, Indian J. Med. Res. 134 (3) (2011) 389.
[22] J. Liu, et al., Neutrophil-to-lymphocyte ratio predicts severe illness patients with 2019 novel coronavirus in the early stage, J Tansl Med 18 (2020) 206.
[23] Y. Xiaohong, et al., Application of neutrophil-lymphocyte ratio in the diagnosis of influenza in preschool children, Am. J. Health Res. 7 (6) (2019) 100–103.
[24] A.S. Chan, A. Rout, Use of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in COVID-19, J. Clin. Med. Res. 12 (7) (2020) 448.
[25] Y. Liu, et al., Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19, J. Infection. 8 (1) (2020) e6–e12.
[26] X. Feng, et al., Immune-inflammatory parameters in COVID-19 cases: a systematic review and meta-analysis, Front. Med. 7 (2020) 301.
[27] D. Tatum, et al., Neutrophil-to-lymphocyte ratio and outcomes in Louisiana COVID-19 patients, Shock (Augusta, Ga.) 54 (2020) 652–658.
[28] F.A. Lagunas-Rangel, Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis, J. Med. Virol. 92 (2020) 1733–1734.
[29] D.M. Simadibrata, et al., Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 Patients: a meta-analysis, Am J Emerg Med 42 (2021) 60–69.
[30] C. Troeger, et al., Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet Infect. Dis. 18 (11) (2018) 1191–1210.
[31] E. Von Elm, et al., The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies, Bull. World Health Organ. 85 (2007) 867–872.

[32] M.E. Charlson, et al., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chron. Dis. 40 (5) (1987) 373–383.
[33] A.R. Falsey, et al., Respiratory syncytial virus infection in elderly and high-risk adults, N. Engl. J. Med. 352 (17) (2005) 1749–1759.
[34] A.D. Colosia, et al., The epidemiology of medically attended respiratory syncytial virus in older adults in the United States: a systematic review, PLoS One 12 (8) (2017), e0182321.
[35] S. Jain, et al., Community-acquired pneumonia requiring hospitalization among US children, N. Engl. J. Med. 372 (9) (2015) 835–845.
[36] L. Prozan, et al., Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 compared with Influenza and respiratory syncytial virus infection, Sci. Rep. 11 (1) (2021), 21519.
[37] A.B. Petrone, et al., Temporal dynamics of peripheral neutrophil and lymphocytes following acute ischemic stroke, Neurol. Sci. 40 (9) (2019) 1877–1885.
[38] G.P. Machado, et al., Temporal pattern of neutrophil-to-lymphocyte ratio in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, Coron. Artery Dis. 30 (8) (2019) 631–633.
[39] F. Riché, et al., Reversal of neutrophil-to-lymphocyte count ratio in early versus late death from septic shock, Crit. Care 19 (2015) 439.
[40] J.M. Petty, et al., Pulmonary stromal-derived factor-1 expression and effect on neutrophil recruitment during acute lung injury, J. Immunol. 178 (12) (2007) 8148–8157.
[41] M.A. Myers, et al., Dynamically linking influenza virus infection kinetics, lung injury, inflammation, and disease severity, Elife 10 (2021), e68864.
[42] C.D. Russell, et al., The human immune response to respiratory syncytial virus infection, Clin. Microbiol. Rev. 30 (2) (2017) 481–502.
[43] M.F.E. Roe, et al., Lymphocyte apoptosis in acute respiratory syncytial virus bronchiolitis, Clin. Exp. Immunol. 137 (1) (2004) 139–145.
[44] C. Nathan, A. Ding, Nonresolving inflammation, Cell 140 (6) (2010) 871–882.
[45] C.D. Russell, et al., The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis, J. Infect. 78 (5) (2019) 339–348.