Cohort Study

Neutrophil to lymphocyte ratio and in-hospital mortality among patients with SARS-CoV-2: A retrospective study

Maryam Salah Al-Mazedi, Rajesh Rajan, Mohammed Al-Jarallah, Raja Dashti, Ahmad Al Saber, Jiazhu Pan, Kobalava D. Zhanna, Hassan Abdelnaby, Wael Aboelhassan, Farah Almutairi, Naser Alotaibi, Mohammad Al Saleh, Noor AlNasrallah, Bader Al-Bader, Haya Malhas, Maryam Ramadhan, Peter A. Brady, Ibrahim Al-Zakwani, Parul Setiya, Mohammed Abdullah, Moudhi Alroomi, Gary Tse

A. Dept. of Medical Laboratory Technology, Public Authority for Applied Education and Training, Kuwait
B. Department of Cardiology, Sabah Al Ahmed Cardiac Centre, Al Amiri Hospital, Kuwait City, Kuwait
C. Department of Mathematics and Statistics, University of Strathclyde, Glasgow, G1 1XH, UK
D. Department of Internal Medicine with the Subspecialty of Cardiology and Functional Diagnostics Named After V.S. Moiseev, Institute of Medicine, Peoples’ Friendship University of Russia (RUDN University), Moscow, Russian Federation
E. Department of Infectious Diseases, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
F. Department of Medicine, Division of Gastroenterology, Al Sabah Hospital, Kuwait
G. Department of Medicine, Division of Gastroenterology, Jaber Al Ahmed Hospital, South Surra, Kuwait
H. Department of Medicine, Al Adam Hospital, Haidiya, Kuwait
I. Department of Emergency Medicine, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait
J. Department of Obstetrics and Gynecology, Maternity Hospital, Kuwait City, Kuwait
K. Department of Cardiology, Illinois Masonic Medical Center, Chicago, IL, USA
L. Department of Pharmacology & Clinical Pharmacy, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman & Gulf Health Research, Muscat, Oman
M. Department of Agrometeorology, College of Agriculture, G.B.Pant University of Agriculture & Technology, Pantnagar, Uttarakhand, India
N. Department of Infectious Diseases, Infectious Diseases Hospital, Shuwaikh Medical Area, Kuwait
O. Cardiovascular Analytics Group, Hong Kong, China; Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, 300221, China

A R T I C L E   I N F O

Keywords:
- SARS-CoV-2
- Neutrophil to lymphocyte ratio (NLR)
- In-hospital mortality

A B S T R A C T

The goal of this study was to investigate in-hospital mortality in patients suffering from acute respiratory syndrome coronavirus 2 (SARS-CoV-2) relative to the neutrophil to lymphocyte ratio (NLR) and to determine if there are gender disparities in outcome. Between February 26 and September 8, 2020, patients having SARS-CoV-2 infection were enrolled in this retrospective cohort research, which was categorized by NLR levels ≥9 and <9. In total, 6893 patients were involved included of whom5951 had NLR <9, and 302 had NLR ≥9. The age of most of the patients in the NLR<9 group was 50 years, on the other hand, the age of most of the NLR ≥9 group patients was between 50 and 70 years. The majority of patients in both groups were male (61.1%). The ICU admission time and mortality rate for the patients with NLR ≥9 was significantly higher compared to patients with NLR <9. Logistic regression’s outcome indicated that NLR ≥9 (odds ratio (OR), 24.9; 95% confidence interval (CI): 15.5–40.0; p < 0.001), male sex (OR, 3.5; 95% CI: 2.0–5.9; p < 0.001) and haemoglobin (HB) (OR, 0.95; 95% CI: 0.94–0.96; p < 0.001) predicted in-hospital mortality significantly. Additionally, Cox proportional hazards analysis (B = 4.04, SE = 0.18, HR = 56.89, p < 0.001) and Kaplan–Meier survival probability plots also indicated that NLR≥9 had a significant effect on mortality. NLR ≥9 is an independent predictor of mortality (in-hospital) among SARS-CoV-2 patients.

Abbreviations: NLR, Neutrophil to lymphocyte ratio; RT-PCR, Reverse Transcription Polymerase Chain Reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; AOR, adjusted Odds Ratio; ICU, Intensive Care Unit; CRF, Case Record Form; CI, Confidence Interval.

* Corresponding author.

E-mail address: cardiology08@gmail.com (R. Rajan).

https://doi.org/10.1016/j.amsu.2022.104748
Received 30 July 2022; Received in revised form 18 September 2022; Accepted 18 September 2022
Available online 1 October 2022
1. Introduction

The NLR can be employed as an indicative marker to examine SARS-CoV-2 disease’s severity [1], with higher NLR intensities consistent SARSCoV-2’s inflammatory reaction [2]. SARS-CoV-2 patients who had a cytokine storm also had elevated NLR values, and [3] NLR levels in SARS-CoV-2 have been reported as an autonomous predictor of mortality in many studies [4,5]. These outcomes predicted by NLR are thought to be dependent on age, BMI, sex, and smoking [6,7]. A meta-analysis showed that higher NLR predicts worse outcome in SARS-CoV-2 patients, and [8] the NLR predicts bacteremia better than all other existing markers [9].

2. Methods

This retrospective cohort study included 6893 SARS-CoV-2-positive patients above the age of 18, both non-Kuwaitis and Kuwaitis, enrolled between February 26 and September 8, 2020. All data were extracted from the electronic medical records from two Kuwait tertiary care hospitals, Al Adan General Hospital and Jaber Al-Ahmed Hospital [10–12].

3. Statistical analysis

Continuous variables were summarized as the standard deviations and means or interquartile ranges and medians, while categorical variables were stated as the percentages and frequencies. Student’s or Wilcoxon-Mann–Whitney t-tests were used for continuous variables, whereas the Pearson χ² test was used for categorical variables. To examine the influence of NLR on in-hospital mortality adjusting for haemoglobin, age, and sex, a Logistic regression analysis was employed. The Cox proportional hazards model was employed to see if haemoglobin had a significant effect on the mortality hazard. p<0.05 was the set level of significance. Statistical analysis was carried out using R software [14] and SPSS version 27 (SPSS, IL, USA).

4. Results

Of the 6893 patients, 6591 had NLR <9, and 302 had NLR ≥9. The findings revealed that, in the NLR <9 cohort, the maximum number of patients was <50 years (n = 2002, 64%), and in the NLR ≥9 cohort, the maximum number of patients was 50–70 years (n = 132, 58%). In the NLR <9 cohort, 60% of the patients were females and 45% were males, whereas in the NLR ≥9 cohort, 70% of the participants were females, and 80% were males. The median length of ICU admission was longer in the NLR ≥9 (2.00 [0.00; 10.3]) cohort than in the NLR <9 (0.00 [0.00; 3.00]) cohort. The mortality rate of patients with NLR ≥9 (n = 132, 44%) was also high compared to that of patients with NLR <9 (n = 40, 1%) [Table 1].

Haemoglobin (g/L) (133 ± 19.8), lymphocytes (10^9/L) (2.33 ± 1.24) and platelet count (10^9/L) (288 ± 102) for patients with NLR <9 were significantly elevated when compared to patients whose NLR is ≥9, whereas the white blood cell count (10^9/L) (17.1 ± 9.24), neutrophils (15.2 ± 8.61), prothrombin time (sec) (17.7 ± 7.12), international normalized ratio (1.34 ± 0.59) and activated partial thromboplastin time (sec) (47.8 ± 24.4) were significantly higher for patients whose NLR is >9 than for patients with NLR <9 [Table 2].

Logistic regression analysis was conducted to examine the effect of NLR on all causes of in-hospital mortality while adjusting for haemoglobin, sex, and age. The analysis revealed a significant effect of NLR on mortality. Male patients had a higher mortality rate (odds ratio (OR), 3.46; 95% confidence interval (CI): 2.02–5.91; p < 0.001) compared with patients who had NLR ≥9 (OR, 24.9; 95% CI: 15.5–40.0; p < 0.001). Furthermore, the study also showed that higher haemoglobin (OR, 0.950; 95% CI: 0.94–0.96; p < 0.001) levels were less probably associated with all causes of in-hospital mortality. Table 3 summarizes the results of the logistic regression analysis [Table 3].

To determine whether the NLR had any impact on all cause in-hospital mortality, a Cox proportional hazards model was used. NLR ratio predicted risk of all cause of in-hospital mortality. The NLR ≥9’s coefficient was significant (B = -4.04, SE = 0.18, HR = 56.89, p < 0.001), indicating that at any precise time, an observation in the NLR ≥9 will have a hazard that is 56.89 times as large as those that had NLR <9. The Kaplan–Meier survival probability plot over time for NLR is illustrated in Fig. 1.

5. Discussion

The main finding of this study is that NLR is an autonomous predictor of in-hospital mortality in patients with SARS-CoV-2. Specifically, fatality in SARS-CoV-2 patients with NLR ≥9 was 25 times higher than that in patients with NLR <9. Moreover, in patients with NLR >9, the average length of ICU stay was higher. Mortality rate in males was high compared to females with NLR >9. A lower haemoglobin concentration was also associated with higher mortality. These findings are most likely related to the gravity of infection and the intensity of the immunological response, both of which may be linked to an increase in fatalities.

Many studies have shown that the NLR can be used as an indicator to detect SARS-CoV-2 infection, especially pneumonia [15]. A higher NLR was associated with a 2-fold probability of SARS-CoV-2 infection [16]. As the assessment of NLR is faster than RT-PCR, emergency room physicians can use NLR as a diagnostic tool to identify critically ill

Table 1
Demographic and clinical characteristics of the patients stratified by neutrophil to lymphocyte ratio (NLR).

| Age, years, n (%) | All n = 6893 | NLR <9 n = 6591 | NLR ≥9 n = 302 | p value | n |
|------------------|-------------|----------------|---------------|---------|---|
| 0–19 | 215 (6.4%) | 173 (5.5%) | 42 (10.9%) | <0.001 | 3343 |
| 20–39 | 1072 (32.1%) | 940 (28.4%) | 132 (31.6%) | | |
| 40–59 | 2056 (61.5%) | 1962 (59.6%) | 94 (21.2%) | | |
| 60–70 | 1132 (33.9%) | 1087 (32.1%) | 45 (11.5%) | <0.001 | 3343 |
| Gender, n (%) | | | | | |
| Male | 2211 (66.1%) | 2028 (60.9%) | 183 (46.9%) | <0.001 | 3343 |
| Female | 1132 (33.9%) | 1087 (34.1%) | 45 (11.5%) | | |
| ICU admission, median (IQR) | | | | | |
| LOS, admission to discharge, median (IQR) | 13 (2–31) | 13 (2–31) | 13 (2–35) | 0.358 | 2886 |
| ICU LOS, median (IQR) | 9 (0–38) | 10 (0–39) | 8 (0–30) | 0.141 | 408 |
| Mortality, n (%) | 172 (2.50%) | 40 (6.1%) | 132 (43.7%) | <0.001 | 6893 |

ICU, intensive care unit; IQR, interquartile range; LOS, length of hospital stay.

Table 2

| Statistic | Description | Reference 1 | Reference 2 | Reference 3 | Reference 4 |
|-----------|-------------|-------------|-------------|-------------|-------------|
| NLR | Normalized ratio | 1.34 ± 0.59 | 0.001 | | |
| AUC | Area under the curve | 0.5689 | | | |
| p value | Probability value | <0.001 | | | |

Table 3

| Statistic | Description | Reference 1 | Reference 2 | Reference 3 | Reference 4 |
|-----------|-------------|-------------|-------------|-------------|-------------|
| NLR | Normalized ratio | 1.34 ± 0.59 | 0.001 | | |
| AUC | Area under the curve | 0.5689 | | | |
| p value | Probability value | <0.001 | | | |
Table 2

| Characteristic                                      | All       | NLR < 9    | NLR ≥ 9    | p value | n  |
|----------------------------------------------------|-----------|------------|------------|---------|----|
| Hemoglobin, (g/L)                                  | 132 (21.2)| 133 (19.8) | 100 (25.5) | <0.001  | 6893|
| WBC, (10⁹/L)                                        | 7.66 (3.94)| 7.23 (2.84) | 17.1 (9.24) | <0.001  | 6893|
| LYM, (10⁹/L)                                        | 2.27 (1.25)| 2.33 (1.24) | 0.88 (0.53) | <0.001  | 6893|
| NEU, (10⁹/L)                                        | 4.56 (3.64)| 4.07 (2.23) | 15.2 (8.61) | <0.001  | 6893|
| PLT, (10⁹/L)                                        | 287 (105) | 288 (102)  | 247 (141)  | <0.001  | 6892|
| PT, seconds                                        | 14.3 (4.52)| 13.9 (3.94)| 17.7 (7.12) | <0.001  | 2353|
| INR                                                | 1.06 (0.37)| 1.03 (0.32) | 1.34 (0.59) | <0.001  | 2353|
| APTT, seconds                                       | 33.3 (10.9)| 31.7 (6.46) | 47.8 (24.4) | <0.001  | 2277|

WBC, white blood cell; LYM, lymphocytes; NEU, neutrophils; PLT, platelet; PT, prothrombin; INT, international normalized ratio; APTT, activated partial thromboplastin time.

SARS-CoV-2 patients and triage them with proper care [17]. The predictive value of the NLR is beyond that of SARS-CoV-2, as it could be used as a diagnostic tool for cardiovascular diseases and chronic obstructive pulmonary diseases (COPD) [18–21]. NLR >4 is an autonomous predictor of in-hospital mortality, especially in patients with acute COPD exacerbation [22]. Several studies have shown the mortality prediction capability of the NLR in SARS-CoV-2 [23–27].

The NLR value in patients who have acute COPD exacerbation is 8.13, and the incidence of death was reported to be higher [28]. NLR is inversely associated with desaturation and a good predictor of exacerbations [29]. In another study, it was stated that an NLR >7 predicts fatalities in patients with bacteraemia [30]. In community acquired pneumonia (CAP), the NLR is considered an independent predictor of the severity of disease [31,32]. Several studies have recommended the NLR as a prognostic indicator to assess the severity of SARS-CoV-2 disease [33]. The NLR can be used for posttreatment confirmation regarding the absence of SARS-CoV-2 [34–36]. The predictive usefulness of NLR has been proven in pneumonia and in tumours [37,38]. NLR can predict mortality in various other conditions apart from infectious diseases, such as polymyositis, intracerebral haemorrhage (ICH), dermatomyositis and acute coronary syndrome (ACS) [39–41].

Our study does have some limitations. First, because the study was retrospective, causal inference was limited, and confounding factors that were unmeasured such as clinical comorbidities and drugs could have influenced the results. Furthermore, because our analysis covered all COVID-19 positive individuals in Kuwait, it is likely that it contained mostly milder forms of the condition.

Table 3

Impact of neutrophil to lymphocyte ratio (NLR) on mortality using multivariate logistic regression.

| Wald Test                  | Estimate | Standard error | Odds ratio | z     | Wald Statistic | p value | 95% Confidence interval (odds ratio scale) |
|----------------------------|----------|----------------|------------|-------|----------------|---------|------------------------------------------|
| (Intercept)                | 0.842    | 0.633          | 2.320      | 1.329 | 1.768          | 0.184   | 0.871 to 8.023                           |
| Hemoglobin                 | –0.051   | 0.005          | 0.950      | –9.874| 97.498         | <0.001  | 0.940 to 0.960                           |
| NLR ≥ 9                    | 3.215    | 0.242          | 24.901     | 13.285| 176.500        | <0.001  | 15.497 to 40.013                         |
| Male gender                | 1.240    | 0.274          | 3.457      | 4.532 | 20.542         | 0.001   | 2.022 to 5.912                           |
| Age (50–70)                | 0.360    | 0.250          | 1.433      | 1.440 | 2.073          | 0.150   | 0.878 to 2.339                           |
| Age (≥70)                  | –0.196   | 0.385          | 0.822      | –0.510| 0.261          | 0.610   | 0.387 to 1.746                           |

Note. Mortality level Dead coded as class 1.

6. Conclusions

NLR is an autonomous predictor of in-hospital mortality in SARS-CoV-2 patients, with NLR >9 associated with 25 times higher mortality compared to patients with NLR < 9. The ICU admission time and mortality rate of patients in the NLR >9 group were significantly higher.

Ethical approval

Ethics Committee Approval 1081422.

Sources of funding

No source of funding

Author contribution

MAJ participated in analysis and manuscript preparation. RR participated in data analysis and manuscript preparation. AAS and JP did the statistical analysis as well as manuscript review. All authors had access to data and take responsibility for the integrity of data and the accuracy of data analysis. All authors have read and approved the manuscript.

Registration of research studies

1.Name of the registry: Not a registry.
2.Unique Identifying number or registration ID: Not applicable.
3.Hyperlink to your specific registration (must be publicly accessible and will be checked): Not applicable.

Guarantor

Dr. Rajesh Rajan MD, Ph.D, FRCP(Lon), FRCP(Edin), FRCP (Glasg),


FRCP (Ire), FACC, FESC, FAHA. Department of Cardiology. Sabah Al Ahmed Cardiac Centre, Al Amiri Hospital Kuwait City, Kuwait, 15003.

Email: cardiology08@gmail.com. Tel: +965-65873326.

Consent

The standing committee for health coordination and medical research at the Ministry of Health in Kuwait approved the study protocol and accepted the request for waiver of the consent (Institutional the requirement of informed \1081422).

Patient consent statement

This retrospective observational study does not require patient permission. Permission to use content from other sources: This study does not include any material from other sources.

Data availability statement

The corresponding author can provide data to back up the conclusions of this study upon request. Due to privacy and ethical concerns, the data is not publicly available.

Declaration of competing interest

Nothing to disclose.

Acknowledgements

“Not applicable”.

References

[1] W. Shang, J. Dong, Y. Ren, et al., The value of clinical parameters in predicting the severity of COVID-19, J. Med. Virol. 92 (2020) 2188–2192.

[2] A.P. Yang, J.P. Liu, W.Q. Tao, H.M. Li, The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients, Int. Immunopharm. 84 (2020), 106504.

[3] M. Catanzaro, F. Fagiani, M. Racchi, E. Cornisi, S. Govoni, C. Lanni, Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2, Signal. Transduct. Targeted Ther. 5 (2020) 84.

[4] H. Hu, X. Yao, X. Xie, X. Wu, C. Zheng, W. Xia, S. Ma, Prognostic value of proinflammatory NLR, DNLR, PLR and CRP in surgical renal cell carcinoma patients, World J. Urol. 35 (2017) 261–270.

[5] G.J. Guthrie, K.A. Charles, C.S. Roxburgh, P.G. Horgan, D.C. McMillan, S.J. Clarke, The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer, Crit. Rev. Oncol. Hematol. 88 (2013) 218–230.

[6] R. Howard, A. Scheiner, P.A. Kanetsky, K.M. Egan, Sociodemographic and lifestyle pathways triggered by SARS-CoV-2, Signal Transduct. Targeted Ther. 5 (2020) 84.

[7] J.F. Chan, S.J. Um, Y.S. Kim, et al., Association of the neutrophil-to-lymphocyte ratio with mortality and cardiovascular disease in the Jackson heart study and modification by the Duffy antigen variant, JAMA Cardiol 3 (2018) 455–462.

[8] S. Rahmirad, M.R. Ghaffary, M.H. Rahmirad, F. Rashidi, Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease, Tuberk Tobek 65 (2017) 25–31.

[9] J. Lian, C. Jin, S. Hao, et al., High neutrophil-to-lymphocyte ratio associated with progression to critical illness in older patients with COVID-19 pneumonia, J. Am. Med. Assoc. 323 (2020) 1389–1389.

[10] A. Ma, J. Cheng, J. Yang, M. Dong, X. Liao, Y. Kang, Neutrophil-to-lymphocyte ratio as a predictive biomarker for moderate-severe ARDS in severe COVID-19 patients, Crit. Care 24 (2020) 288.

[11] J.J. Zhang, Y.Y. Cao, G. Tan, et al., Clinical, radiological and laboratory characteristics and risk factors for severity and mortality of 289 hospitalized COVID-19 patients, Allergy 76 (2021) 533–550.

[12] D. Feng, F. Zhou, L. Luo, et al., Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study, Lancet Haematol 7 (2020) e671–e678.

[13] J. Fu, J. Kong, W. Wang, et al., The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: a retrospective study in Suzhou China, Thromb. Res. 192 (2020) 3–8.

[14] F. Teng, H. Ye, T. Xue, Predictive value of neutrophil to lymphocyte ratio in patients with acute exacerbation of chronic obstructive pulmonary disease, PLoS One 13 (2018), e0204377.

[15] H. Lee, S.J. Um, Y.S. Kim, et al., Association of the neutrophil-to-lymphocyte ratio with lung function and exacerbations in patients with chronic obstructive pulmonary disease, PLoS One 11 (2016), e0156511.

[16] R. Terradas, S. Grau, J. Blanch, et al., Eosinophil count and neutrophil-lymphocyte count ratio as prognostic markers in patients with bacteremia: a retrospective cohort study, PLoS One 7 (2012), e42860.

[17] N.B. Yoon, C. Son, S.J. Um, Why is the neutrophil-to-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia, Ann. Lab. Med. 33 (2013) 105–110.

[18] C.P. de Jager, P.C. Wever, E.F. Gemen, et al., The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia, PLoS One 7 (2012), e46561.

[19] M. Seyit, E. Avci, R. Nar, et al., Neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio and platelet to lymphocyte ratio to predict the severity of COVID-19, Am. J. Emerg. Med. 40 (2021) 110–114.

[20] J.F. Chan, S. Yuan, K.-H. Kok, et al., A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster, Lancet 385 (2020) 514–523.

[21] D. Wang, B. Hu, C. Hu, J. Zhu, X. Liu, J. Zhang, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhuan, China, J. Am. Med. Assoc. 323 (2020) 1061–1069.

[22] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan City, China, J. Am. Med. Assoc. 323 (2020) 1069.

[23] J. Liu, Y. Liu, P. Xiang, et al., Neutrophil-to-lymphocyte ratio predicts critical illness in COVID-19 patients with moderate COVID-19 disease in the early stage, J. Transl. Med. 18 (2020) 206.

[24] A. Giede-Jeppe, A. Boberger, L.Z. Dal Verme, et al., Neutrophil-to-lymphocyte ratio and clinical outcome in COVID-19: a report from the Italian front line, Int. J. Antimicrob. Agents 56 (2020), 106017.

[25] J.Y.-H. Ha, H. Jeur, D.J. Goo, Baseline peripheral blood neutrophil-to-lymphocyte ratio could predict survival in patients with adult polyglucosan body disease/dystrophic myotonia: a retrospective observational study, PLoS One 13 (2018), e0194111.

[26] B. Azah, M. Zahir, K.F. Wilsbe, Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-SLT-elevation myocardial infarction, Am. J. Cardiol. 106 (2010) 479–476.

[27] A. Giede-Jeppe, T. Bobinger, S.T. Gerner, Neutrophil-to-lymphocyte ratio is an independent predictor for in-hospital mortality in spontaneous intracerebral hemorrhage, Cerebrovasc. Dis. 44 (2017) 26–34.