



## Cohort Study

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

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## ABSTRACT

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  $\geq 9$  and  $< 9$ . In total, 6893 patients were involved included of whom 6591 had NLR  $< 9$ , and 302 had NLR  $\geq 9$ . 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  $\geq 9$  group patients was between 50 and 70 years. The majority of patients in both groups were male 2211 (66.1%). The ICU admission time and mortality rate for the patients with NLR  $\geq 9$  was significantly higher compared to patients with NLR  $< 9$ . Logistic regression's outcome indicated that NLR  $\geq 9$  (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  $\geq 9$  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.

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## 1. Introduction

The NLR can be employed as an indicator to examine SARS-CoV-2 disease's severity [1], with higher NLR intensities consistent SARS-CoV-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 bacteraemia 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 [10–13].

A positive RT-R swab from the nasopharynx confirmed SARS-CoV-2 infection. The Ministry of Health in Kuwait standardized the care of all patients according to protocol. The standing committee for health co-ordination and medical research at the Ministry of Health in Kuwait approved the procedure and waived the need for informed consent (Institutional review board number 2020/1422).

Patients were categorized by NLR levels  $\geq 9$  and  $< 9$ . The primary outcome was death due to COVID-19, as specified by ICD 10 code U07.1. The following laboratory and clinical information were collected: sociodemographic factors, co-morbidity, clinical presentation, laboratory results, and length of ICU and hospital stay for data entry, an electronic case-record format (CRF) was employed. The neutrophil-lymphocyte ratio (NLR) was computed by dividing the absolute count of neutrophils by the absolute number of lymphocytes. Patients were divided into two groups: those with an NLR  $> 9$  and those with an NLR  $< 9$ .

## 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  $\chi^2$  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  $\geq 9$ . The findings revealed that, in the NLR  $< 9$  cohort, the maximum number of patients was  $< 50$  years ( $n = 2002$ , 64%), and in the NLR  $\geq 9$  cohort, the maximum number of patients was 50–70 years ( $n = 132$ , 58%). In the NLR  $< 9$  cohort, 35% of the participants were females and 65% were males, whereas in the NLR  $\geq 9$  cohort, 20% of the participants were females, and 80% were males. The median duration of ICU admission was longer in the NLR  $\geq 9$  (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  $\geq 9$  ( $n = 132$ , 44%) was also high compared to that of patients with NLR  $< 9$  ( $n = 40$ , 1%) [Table 1].

Haemoglobin (g/L) ( $133 \pm 19.8$ ), lymphocytes ( $10^9/L$ ) ( $2.33 \pm 1.24$ ) and platelet count ( $10^9/L$ ) ( $288 \pm 102$ ) for patients with NLR  $< 9$  were significantly elevated when compared to patients whose NLR is  $\geq$

9, whereas the white blood cell count ( $10^9/L$ ) ( $17.1 \pm 9.24$ ), neutrophils ( $15.2 \pm 8.61$ ), prothrombin time (sec) ( $17.7 \pm 7.12$ ), international normalized ratio ( $1.34 \pm 0.59$ ) and activated partial thromboplastin time (sec) ( $47.8 \pm 24.4$ ) 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  $\geq 9$  (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  $\geq 9$ '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  $\geq 9$  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).

	All n = 6893	NLR <9 n = 6591	NLR $\geq 9$ n = 302	p value	n
Age, years, n (%)				<0.001	3343
$\geq 70$	215 (6.43%)	173 (5.55%)	42 (18.4%)		
50–70	1072 (32.1%)	940 (30.2%)	132 (57.9%)		
<50	2056 (61.5%)	2002 (64.3%)	54 (23.7%)		
Gender, n (%)				<0.001	3343
Female	1132 (33.9%)	1087 (34.9%)	45 (19.7%)		
Male	2211 (66.1%)	2028 (65.1%)	183 (80.3%)		
ICU admission, median (IQR)	0 (0–4)	0 (0–3)	2 (0–10)	<0.001	3343
LOS, admission to discharge, median (IQR), days	13 (2–31)	13 (2–31)	13 (2–35)	0.358	2886
ICU LOS, median (IQR), days	9 (0–38)	10 (0–39)	8 (0–30)	0.141	408
Mortality, n (%)	172 (2.50%)	40 (0.61%)	132 (43.7%)	<0.001	6893

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

**Table 2**

Laboratory characteristics of the patients stratified by neutrophil to lymphocyte ratio (NLR).

Characteristic, mean ± SD	All N = 6893	NLR <9 N = 6591	NLR ≥9 N = 302	p value	n
Hemoglobin, (g/L)	132 (21.2)	133 (19.8)	100 (25.5)	<0.001	6893
WBC, (10 <sup>9</sup> /L)	7.66 (3.94)	7.23 (2.84)	17.1 (9.24)	<0.001	6893
LYM, (10 <sup>9</sup> /L)	2.27 (1.25)	2.33 (1.24)	0.88 (0.53)	<0.001	6893
NEU, (10 <sup>9</sup> /L)	4.56 (3.64)	4.07 (2.23)	15.2 (8.61)	<0.001	6893
PLT, (10 <sup>9</sup> /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].

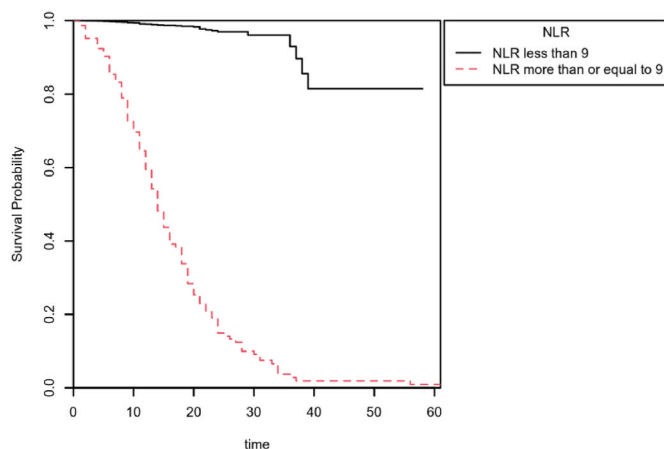
Our study does have some limitations: First, because the study was retrospective, causal inference was limited, and confounding factors that were unmeasured such as clinical comorbidities and drugs could have influenced the results. Furthermore, because our analysis covered all COVID-19 positive individuals 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				Wald Statistic	p value	95% Confidence interval(odds ratio scale)	
	Estimate	Standard error	Odds ratio	z			Lower bound	Upper bound
(Intercept)	0.842	0.633	2.320	1.329	1.768	0.184	0.671	8.023
Hemoglobin	-0.051	0.005	0.950	-9.874	97.498	<0.001	0.940	0.960
NLR ≥9	3.215	0.242	24.901	13.285	176.500	<0.001	15.497	40.013
Male gender	1.240	0.274	3.457	4.532	20.542	<0.001	2.022	5.912
Age (50–70)	0.360	0.250	1.433	1.440	2.073	0.150	0.878	2.339
Age (≥70)	-0.196	0.385	0.822	-0.510	0.261	0.610	0.387	1.746

Note. Mortality level Dead coded as class 1.



**Fig. 1.** Kaplan-Meier survival plot of Mortality grouped by neutrophil to lymphocyte ratio (NLR).

**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.

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**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.

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## 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.

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