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Original Article

Clinical and Hematological Predictors for Return of Spontaneous Circulation in Patients With Out-of-Hospital Cardiac Arrest

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Background: To investigate the association of clinical and hematological parameters with return of spontaneous circulation (ROSC) in out-of-hospital cardiac arrest (OHCA).
Methods: Clinical data of successive non-traumatic adult OHCA patients with available laboratory data of complete blood count and peripheral blood smear at emergency department (ED) arrival were requested. Hematological parameters were collected and calculated, and logistic regression and survival analysis were performed for association of ROSC with the parameters.
Results: From December 2015 to December 2016, a total of 188 OHCA patients transported to our ED were enrolled. In ROSC group, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were significantly higher and smudge cell count was significantly lower when compared with non-ROSC group. In the univariate regression, NLR more than 2.0 (odds ratio [OR]: 2.40, 95% confidence interval [CI]: 1.31–4.41; $p = 0.004$) and smudge cell count less than 0.45×10^9/L (OR: 0.33, 95% CI: 0.15–0.71; $p = 0.004$) were significantly associated with ROSC in OHCA. In logistic regression, bystander witnessed (OR: 3.15, 95% CI: 1.59–6.27; $p = 0.001$) and prehospital epinephrine use (OR: 2.15, 95% CI: 1.10–4.23; $p = 0.026$) were significantly associated with ROSC in OHCA. NLR and smudge cell count were also seemingly related to ROSC in OHCA, but without statistical significance. In survival analysis, neither NLR nor smudge cell count was associated with patient survival to discharge in OHCA.
Conclusions: NLR and smudge cell count at ED arrival could be potential indicators of ROSC in OHCA.

Key words: *out-of-hospital cardiac arrest, return of spontaneous circulation, smudge cell, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio*

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Introduction

Out-of-hospital cardiac arrest (OHCA) still remains one of the major health issues globally, though lots of efforts have been made over these decades. It was estimated that incidence of adult OHCA was about 55 per 100,000 person-years in the world, accompanied with a poor survival to discharge rate from 0.3% to 20.4%.[1-5] To date, a large amount of factors related to clinical outcome of OHCA have been identified. Among these prognostic factors, witnessed cardiac arrest, bystander cardiopulmonary resuscitation (CPR), presence of initially shockable rhythm and prehospital achievement of return of spontaneous circulation (ROSC) were considered important in enhancement of overall survival till hospital discharge in OHCA.[3,4] However, limited studies indicated the timely laboratory evaluation on the prognosis of OHCA. Recently, it was demonstrated that neutrophil-to-lymphocyte ratio (NLR) of more than 6.0 as well as the presence of flagged abnormalities in differential count of blood cells was associated with increased mortality in OHCA, on the basis of automated blood cell analysis at admission.[6] Known as a marker reflecting the balance between systemic inflammation and the immune status, NLR was proved to be a predictor on clinical outcome of cancer patients.[7,8] Nevertheless, the influence of NLR and abnormal differential on patient outcomes of OHCA remains relatively controversial and additional research efforts were warranted, in perspective of laboratory medicine and clinical practice.

In this study, we aimed to survey potential predictors on the basis of the blood parameters at emergency department (ED) arrival for the prognosis in the OHCA group. We also investigated the morphological characteristics in peripheral blood smear at ED arrival as the potential indicators of ROSC and survival interval in the patients experiencing OHCA.

Methods

Study Design and Data Collection

The investigation was conducted in Far Eastern Memorial Hospital (FEMH) during the study interval of December 1, 2015 to December 31, 2016, based on a retrospective study design. Patients with OHCA who were sent to ED of FEMH for further management were enrolled. Among these, non-adult (patient age less than 20 years old), traumatic (including committed suicide) OHCAs, patients with the do-not-resuscitate (DNR) request, patients without laboratory examinations in hematology and patients without complete data as mentioned below were excluded. The prehospital data was obtained via reviewing the emergency medical service (EMS) sheet and clinical data were collected via electronic medical chart review, including patient age, gender, location of OHCA, bystander witnessed, bystander CPR, EMS support, response time, scene time, transport time, initial rhythm and prehospital drug treatment including epinephrine. Furthermore, the information regarding the consent of DNR order from the family of OHCA patients after arrival at ED was requested. The ROSC status was defined as sustained ROSC, in which signs of circulation persisted without chest compression for 20 consecutive minutes. Length of intensive care unit (ICU) and length of general ward stay were also recorded in the OHCA group. The research approval was acquired from the research ethics committee of FEMH (107020-E) and the investigation was conducted in accordance with the Declaration of Helsinki in 1964.

Laboratory Values

The first-recorded laboratory data of leukocyte count, hemoglobin concentration, platelet count and differential count of leukocytes were collected at ED arrival. The complete blood count and peripheral blood smear were performed by an automated hematology analyzer (XE-2100, Sysmex Corp. Kobe, Japan).[9] The differential count of leukocytes on morphological examination was reviewed. The count of banded and segmented neutrophils, eosinophils, basophils, monocytes, lymphocytes, atypical lymphocytes and immature granulocytes (including blasts, promyelocytes, myelocytes and metamyelocytes) as well as percentage of smudge cells in total lymphocytes were estimated by morphological examination. To avoid artificial production of smudge cells, at least two slides were made in each case of OHCA, either by the automated hematology analyzer or the medical technologist. The slide with the least smudge cells was selected for morphological evaluation. Laboratory indicators, including NLR, lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), immature-to-total granulocyte ratio (ITGR) and smudge cell count, were thus calculated according to the differential count of leukocytes on morphological examination for further analysis.

Statistical Analysis

The demographic data, data with resuscitation features, laboratory data and clinical data regarding patient outcomes were presented as median (interquartile range, IQR) or number (%). Mann–Whitney U test was used to evaluate the significant difference of continuous variables and the chi-square test was used to compare the categorical variables between groups of ROSC and non-ROSC. The cut-off level in each laboratory indicator was decided at a relatively high Youden index after analysis of receiver operating characteristic (ROC) curve. The chi-square test was also used to evaluate the association of these laboratory indicators with ROSC status. Age, gender as well as the resuscitation features which were found to be statistically significant between ROSC and non-ROSC groups would be further adjusted in the multivariate binary logistic regression models. Kaplan–Meier analysis was also used to evaluate the association between laboratory indicators and survival interval in OHCA. A p value of 0.05 and less was considered statistically significant. The statistical analysis was performed using IBM SPSS statistical software (version 19.0; IBM Corp., Armonk, NY, USA).

Results

During the study interval, a total of 714 patients with OHCA events were sent to our ED and 215 were enrolled due to complete laboratory data and morphological examination on blood smear. Among these, 3 pediatric patients with OHCA, 9 adult patients with traumatic OHCA, and 15 patients with OHCA who had the DNR order before arrival at ED were excluded from the analysis. Eventually, a total of 188 OHCA patients were registered and divided into ROSC (n = 94) and non-ROSC groups (n = 94). The demographic data, including data with resuscitation features, laboratory data and outcomes in both groups were shown in Table 1. The percentage of bystander witnessed of the OHCA patients was significantly higher in ROSC group in comparison with that in non-ROSC group (48.9% vs. 25.5%, $p < 0.001$). There was no remarkable difference in distribution of the OHCA locations, EMS support and prehospital time intervals in both groups. The percentage of bystander CPR ranged from 31.9% to 37.2% in the OHCA patients, without difference between these groups ($p = 0.540$). Notably, the percentage of initially shockable rhythm in the OHCA patients was significantly lower in ROSC group than in non-ROSC group (9.5% vs. 22.3%, $p = 0.027$). Besides, the percentage of prehospital epinephrine use in the OHCA cases was higher in ROSC group than in non-ROSC group (47.9% vs. 34.0%, $p = 0.054$).

In laboratory examination (Table 1), the total leukocyte count of the OHCA patients with ROSC was seemingly higher than that in non-ROSC group (13.59 with IQR of 9.74–18.50 $\times 10^9$/L vs. 12.66 with IQR of 10.62–15.86 $\times 10^9$/L, $p = 0.095$). The hemoglobin level was significantly lower in ROSC group than in non-ROSC group (11.0 with IQR of 8.4–12.6 g/dL vs. 12.0 with IQR of 9.0–14.4 g/dL, $p = 0.026$), and there was no statistical difference of platelet level between ROSC and non-ROSC group (200 with IQR of 126–275 $\times 10^9$/L vs. 174 with IQR of 119–254 $\times 10^9$/L, $p = 0.242$). Besides, the neutrophil count of the OHCA patients was significantly higher in ROSC group than in non-ROSC group (7.56 with IQR of 4.83–11.84 $\times 10^9$/L vs. 5.69 with IQR of 3.48–9.27 $\times 10^9$/L, $p = 0.011$), and the lymphocyte count was seemingly lower in ROSC group than in non-ROSC group (4.09 with IQR of 2.21–5.94 $\times 10^9$/L vs. 4.88 with IQR of 3.01–7.12 $\times 10^9$/L, $p = 0.059$). Furthermore, the NLR of the OHCA patients was significantly higher in ROSC group than in non-ROSC group (1.80 with IQR of 0.85–4.11 vs. 1.24 with IQR of 0.70–2.21, $p = 0.006$). In addition to NLR, the PLR was also significantly higher in ROSC group than in non-ROSC group (48.9 with IQR of 26.9–76.2 vs. 37.3 with IQR of 21.2–58.4, $p = 0.021$). There was no apparent difference of LMR, ITGR and percentage of smudge cells in peripheral blood smear between ROSC and non-ROSC groups. Notably, the smudge cell count of the OHCA patients in peripheral blood smear was significantly lower in ROSC group than in non-ROSC group (1.01 with IQR of 0.41–1.55 $\times 10^9$/L vs. 1.13 with IQR of 0.78–1.94 $\times 10^9$/L, $p = 0.030$). In the clinical outcome, the DNR order was requested in 25 OHCA patients with ROSC (26.6%). Sixty-five patients (69.1%) were admitted to ICU for further management in ROSC of the OHCA group, with a median length of ICU and general ward stay of two days and IQR of 0–14 days. Among these, 17 (18.1%) were discharged with hemodynamically stable status.

The cut-off levels of NLR, PLR and smudge cell count were determined as 2.0, 40 and 0.45 $\times 10^9$/L, respectively; with a relatively high Youden index after ROC curve analysis. Univariate analysis was then performed and the results showed that the val-

Table 1. The demographic data, resuscitation features, laboratory data and clinical outcome in the ROSC and non-ROSC groups of the OHCA patients[a]

Demographic data	ROSC (n = 94)	Non-ROSC (n = 94)	*p*-value
Age (years)	68 (56–79)	64 (50–79)	0.119
Gender (Male/female)	55/39	63/31	0.291
Resuscitation features			
Bystander witnessed (%)	46 (48.9)	24 (25.5)	< 0.001
Location			
Public (%)	7 (7.4)	10 (10.6)	0.446
Private (%)	56 (59.6)	59 (62.8)	0.655
Others (%)	31 (33.0)	25 (26.6)	0.337
EMS support (%)	80 (85.1)	86 (91.5)	0.256
Prehospital time intervals (min)			
Response time	5 (4–7)	5 (4-–7)	0.928
Scene time	16 (11–20)	14 (10–18)	0.222
Transport time	5 (4–8)	5 (4–7)	0.960
Bystander CPR (%)	30 (31.9)	35 (37.2)	0.540
Initially shockable rhythm (%)	9 (9.5)	21 (22.3)	0.027
Prehospital epinephrine use (%)	45 (47.9)	32 (34.0)	0.054
Laboratory data			
Leukocyte count (10^9/L)	13.59 (9.74–18.50)	12.66 (10.62–15.86)	0.095
Hemoglobin (g/dL)	11.0 (8.4–12.6)	12.0 (9.0–14.4)	0.026
Platelet (10^9/L)	200 (126–275)	174 (119–254)	0.242
Neutrophil count (10^9/L)	7.56 (4.83–11.84)	5.69 (3.48–9.27)	0.011
Lymphocyte count (10^9/L)	4.09 (2.21–5.94)	4.88 (3.01–7.12)	0.059
Neutrophil-to-lymphocyte ratio	1.80 (0.85–4.11)	1.24 (0.70–2.21)	0.006
Lymphocyte-to-monocyte ratio	8.00 (3.17–13.50)	7.50 (4.60–13.00)	0.787
Platelet-to-lymphocyte ratio	48.9 (26.9–76.2)	37.3 (21.2–58.4)	0.021
Immature-to-total granulocyte ratio	0.04 (0.00–0.08)	0.04 (0.00–0.09)	0.549
Percentage of smudge cells	25.0 (16.0–34.5)	26.0 (16.0–40.0)	0.484
Smudge cell count (10^9/L)	1.01 (0.41–1.55)	1.13 (0.78–1.94)	0.030
Clinical outcome			
DNR order (%)	25 (26.6)	—	N/A
Survival to ICU admission (%)	65 (69.1)	—	N/A
Survival to ICU and general ward discharge (%)	17 (18.1)	—	N/A
Length of ICU and general ward stay (day)	2 (0–14)	—	N/A

[a]Data were expressed as number (%) or median (interquartile range).
CPR: cardiopulmonary resuscitation; DNR: do not resuscitate; EMS: emergency medical service; ICU: intensive care unit; N/A: not applicable; OHCA: out-of-hospital cardiac arrest; ROSC: return of spontaneous circulation.

ues of NLR more than 2.0 (odds ratio [OR]: 2.40, 95% confidence interval [CI]: 1.31–4.41, $p = 0.004$), PLR more than 40 (OR: 1.83, 95% CI: 1.02–3.26, $p = 0.041$) and smudge cell count less than 0.45×10^9/L (OR: 0.33, 95% CI: 0.15–0.71, $p = 0.004$) were significantly associated with the ROSC status in the OHCA group.

To further evaluate the association of hematological indicators at ED arrival in ROSC in the OHCA patients, the models of multivariate binary logistic regression was designed and performed (Table 2). The following confounding factors, including age, gender, bystander witnessed, prehospital epinephrine use and initially shockable rhythm were adjusted. The analysis of multivariate binary logistic regression model revealed that bystander witnessed (OR: 3.15, 95% CI: 1.59–6.27, $p = 0.001$) and prehospital epinephrine use (OR: 2.15, 95% CI: 1.10–4.23, $p = 0.026$) were significantly associated with ROSC in OHCA. Besides, NLR of more than 2.0 (OR: 2.13, 95% CI: 0.99–4.58, $p = 0.052$) and smudge cell count of less than 0.45×10^9/L (OR: 0.44, 95% CI: 0.18–1.05, $p = 0.064$) were seemingly associated with ROSC of the OHCA patients, but there was no statistical significance. PLR of more than 40 was not associated with ROSC of the OHCA patients (OR: 1.08, 95% CI: 0.52–2.26, $p = 0.829$). In Kaplan–Meier survival analysis, it revealed that NLR of more than 2.0 and smudge cell count of less than 0.45×10^9/L were prone to patient survival in the early course of admission, but there was no significantly association of survival interval in the OHCA patients ($p = 0.375$ and 0.753, respectively; Fig. 1).

Discussion

Our main finding indicated that several laboratory indicators, including NLR and smudge cell count in peripheral blood smear at ED arrival, were associated with ROSC of the OHCA patients. We also explored the prognostic role of NLR and smudge cell count in relationship with ROSC status and survival interval in OHCA. To the best of our knowledge, this is the first study to illustrate the association of NLR, PLR and smudge cell count in peripheral blood smear via both automated hematology analysis and morphological assessment with ROSC of OHCA in the Taiwanese population. The laboratory indicators, NLR and smudge cell count, appeared to be predictive of ROSC in the OHCA population, thus facilitating the process of patient care and information provided to clinicians and the relatives.

As one of the simple and cost-effective parameters, NLR was often used for the assessment of systemic inflammatory status and response. Accumulating evidence revealed that an elevated NLR was greatly associated with poor prognosis in cardiovascular diseases,[10-12] septic shock[13] and a variety of solid cancers.[7,8,14-17] Further study also indicated that a positive change of NLR (higher than initial NLR) was significantly related to decreased survival rate when compared with the negative change (lower than initial NLR) in gastric and pancreatic cancers, and even had a better performance in predicting the prognosis than the initial NLR.[18,19] Although the detailed mechanisms by which the NLR was predictive of clinical outcomes has not been totally understood yet, it was

Table 2. The multivariate binary logistic regression analysis in the ROSC and non-ROSC groups of OHCA patients[a]

Binary logistic regression	OR	95% CI	*p*-value
Age	1.01	0.99–1.03	0.275
Gender (female)	0.70	0.36–1.36	0.290
Bystander witnessed	3.15	1.59–6.27	0.001
Initially shockable rhythm	0.40	0.16–1.01	0.051
Prehospital epinephrine use	2.15	1.10–4.23	0.026
NLR > 2.0	2.13	0.99–4.58	0.052
PLR > 40	1.08	0.52–2.26	0.829
Smudge cell count > 0.45×10^9/L	0.44	0.18–1.05	0.064

[a]The model was adjusted by age, female, bystander witnessed, prehospital epinephrine use and initially shockable rhythm.
CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; OHCA: out-of-hospital cardiac arrest; OR: odds ratio; PLR: platelet-to-lymphocyte ratio; ROSC: return of spontaneous circulation.

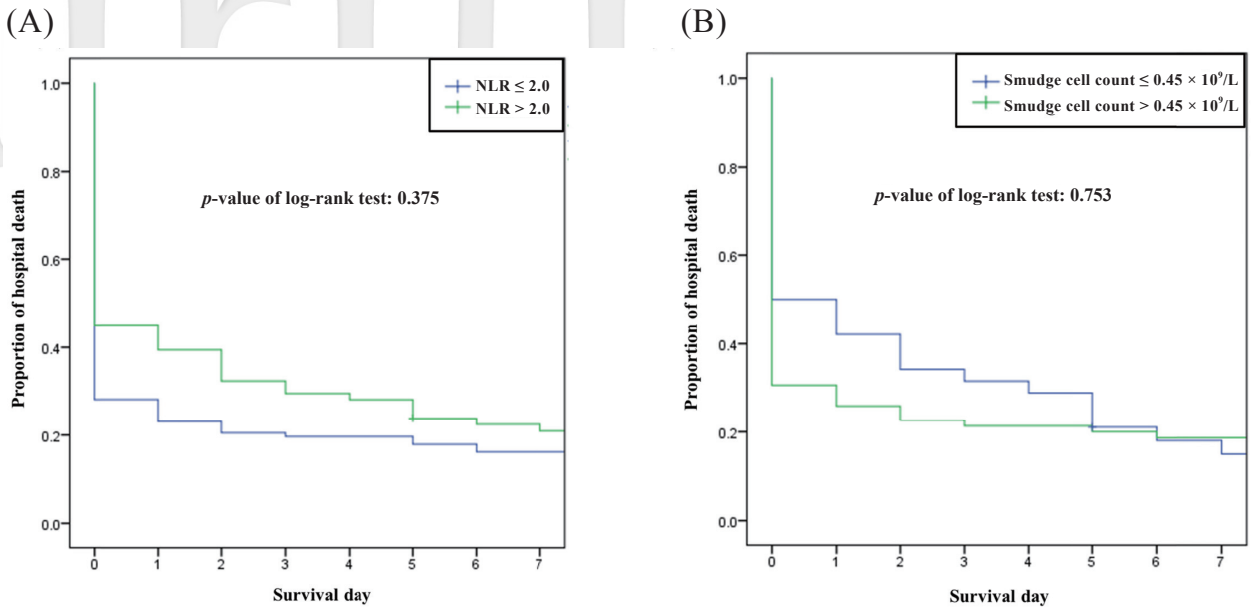

Fig. 1. The Kaplan–Meier analysis to investigate the relationship of neutrophil-to-lymphocyte ratio (NLR) and smudge cell count in survival interval of the out-of-hospital cardiac arrest (OHCA) patients. (A) The effect of NLR on survival interval in OHCA. (B) The effect of smudge cell count on survival interval in the OHCA patients.

believed that combined effects of relative neutrophilia and lymphocytopenia might mediate proinflammatory cytokine release, subsequently lead to tissue inflammation and injury due to severe and uncontrolled innate immune system activation.[13,19,20] Recently, the predictive role of NLR in OHCA was investigated, and it was shown that NLR of 6 and more or abnormal differential count based on automated hematology analyzer was independently associated with poor survival in comparison with NLR less than 6 in the OHCA group by Weiser et al.,[6] which was inconsistent with our results. It was also observed that expression of interleukin (IL)-8 and IL-10 was significantly higher in the non-survivor group than in the survivors of OHCA at ROSC,[21] which may partially and indirectly elucidate the pathophysiology and role of NLR in OHCA. As is well known, IL-8 plays a pivotal role in the neutrophil chemotaxis, and IL-10 belongs as an anti-inflammatory cytokine that suppresses type 1 T helper cell-mediated cytokine release and induces B cell activation and antigen production. Interestingly, another study conducted by Başer et al. revealed that NLR at initial was seemingly higher in the survivors than in the decedents of the post-cardiac arrest (PCA; 6.0 with IQR of 10.3 vs. 3.3 with IQR of 6.7, p = 0.07).[22] The above results appeared to be partially consistent with our data, indicating that higher value of initial NLR could be predictive of ROSC after PCA management. Başer et al. further investigated the therapeutic efficacy of targeted temperature management (TTM) on the PCA patients and found that NLR of survivors was remarkably lower than that of decedents during TTM.[22] Besides, there was no obvious difference of body temperature at admission among the group with NLR less than 6, NLR of 6 and more as well as abnormal differential count (35.7 with IQR of 35.2–36.3°C vs. 35.5 with IQR of 34.8–36.2°C vs. 35.6 with IQR of 34.8–36.2°C, p = 0.099); and the percentage of TTM was significantly higher in the group of NLR of 6 and more than of NLR less than 6 (76% vs. 61%, p < 0.001), as shown by Weiser et al.[6] These results implied that body temperature could affect the value of NLR at admission in the OHCA population. One previous study has shown that hypothermia could reduce neutrophil circulation and release from bone marrow,[23] thus possibly leading to a decrease of NLR. It was also reported that OHCA patients with low body temperature of 34.0°C and less had poor survival rates at admission in comparison with those who had higher body temperature than 34.0°C.[24] This phenomenon could partially explain why the value of NLR was higher in survivors than in decedents of PCA in both the data described by Başer et al.[22] and in our study. However, the NLR in the survivors of PCA shown by Başer et al.[22] exceeded the referenced normal range, whereas the NLR in

the ROSC group of OHCA was within the referenced range in our results.[25] It was not surprising that our data partially differed from those reported in the previous studies, since the deviation could be presented due to the investigation in different study populations and regions, and the etiologies varied case by case in the PCA and OHCA populations. Eventually, the predictive role of NLR should be carefully interpreted in the prognosis of OHCA, and further prospective investigation on the prognostic performance of NLR remains to be disclosed.

In addition to NLR, PLR, LMR and ITGR were also known as the simple and inexpensive laboratory markers that could reflect systemic inflammatory condition and immune response. Similar to NLR, it was demonstrated that the above indicators played predictive roles in the clinical outcome of cardiovascular diseases,[26-28] sepsis[29,30] and cancers.[31-33] However, the relationship between the laboratory indicators of PLR and LMR and OHCA remains unexplained. Previously, it was reported that high ITGR was markedly associated with post-resuscitation shock in the OHCA patients.[34] Nevertheless, it seemed that ITGR was unable to predict the clinical outcome of OHCA in our study population.

Previously, the smudge cell was considered as an artifact in peripheral blood smear due to the cellular fragility during improper slide preparation, and was thus deemed to be of minimal clinical significance.[35] However, recent studies described the association of smudge cells with chronic lymphocytic leukemia (CLL).[36-39] It was revealed that the percentage of smudge cells in peripheral blood smear was independently associated with the prognosis in CLL.[36-39] Besides, CLL patients with the percentage of smudge cells of 30% and less had a significantly lower risk of death (HR: 0.47, 95% CI of 0.32–0.71, $p < 0.001$) and longer median survival interval (6.0 vs. 3.5 years) but lower survival rate (51% vs. 81%) than those with the percentage of smudge cells more than 30%.[38] Further research elucidated that decreased expression of vimentin, cluster of differentiation 38 (CD38) and 70 kD zeta-associated protein (ZAP-70) was contributed to the fragility of lymphocytes, leading to the production of smudge cells.[36-38] Furthermore, it was observed that the percentage of smudge cells could be elevated in solid and blood cancers, infections and OHCA, but was not predictive of clinical outcome because of limited case number.[40] In the present study, there was no difference of the percentage of smudge cells between ROSC and non-ROSC groups of OHCA. Interestingly, however, the smudge cell count in peripheral blood smear was seemingly higher in the non-ROSC group than the ROSC group of OHCA. The smudge cell count may provide certain information regarding clinical outcome of OHCA to clinicians in ED for further management and therapeutic strategies. However, the mechanism of increased production of smudge cell in OHCA remains to be explored.

There were some major limitations in our study. First, this investigation was a retrospective study design with limited case number and the participants in this study population were all Taiwanese. Thus, it should be certain bias leading to some discrepancies, such as that the proportion of initial shockable rhythm was significantly higher in the non-ROSC group in comparison with that in the ROSC group in our study. Second, the lack of initial body temperature data of these OHCA patients in the EMS sheet and medical record in ED led to difficulties in evaluating the effect of hypothermia on the concentration of circulating neutrophils and thus in analyzing the association of NLR at admission with the clinical outcome of OHCA. And the lack of following examination on complete blood count and morphological examination in peripheral blood smear made it failed to observe the change of NLR in the OHCA patients. Also, the neurological outcome was not recorded and not analyzed in the OHCA group with ROSC after discharge in our study. Besides, though at least two slides were made in each OHCA patient either by the automated hematology analyzer or the medical technologist and slide with the least smudge cells was selected for morphological evaluation, the possibility could not be totally excluded in which part of the presence of smudge cells in the smear was due to artifact.

Conclusions

The present study revealed that higher value of NLR and lower smudge cell count at ED arrival seemed to be associated with a higher rate of ROSC in the OHCA population. NLR and smudge cell count at ED arrival could be potential indicators of ROSC status in patients experiencing OHCA events.

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Conflicts of Interest Statement

The authors declare no conflict of interest.

References

1. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. *Resuscitation* 2010;81:1479-1487. doi:10.1016/j.resuscitation.2010.08.006
2. Aschauer S, Dorffner G, Sterz F, Erdogmus A, Laggner A. A prediction tool for initial out-of-hospital cardiac arrest survivors. *Resuscitation* 2014;85:1225-1231. doi:10.1016/j.resuscitation.2014.06.007
3. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2010;3:63-81. doi:10.1161/CIRCOUTCOMES.109.889576
4. Dunne RB, Compton S, Zalenski RJ, Swor R, Welch R, Bock BF. Outcomes from out-of-hospital cardiac arrest in Detroit. *Resuscitation* 2007;72:59-65. doi:10.1016/j.resuscitation.2006.04.017
5. Grmec Š, Kupnik D. Does the Mainz Emergency Evaluation Scoring (MEES) in combination with capnometry (MEESc) help in the prognosis of outcome from cardiopulmonary resuscitation in a prehospital setting? *Resuscitation* 2003;58:89-96. doi:10.1016/S0300-9572(03)00116-3
6. Weiser C, Schwameis M, Sterz F, et al. Mortality in patients resuscitated from out-of-hospital cardiac arrest based on automated blood cell count and neutrophil lymphocyte ratio at admission. *Resuscitation* 2017;116:49-55. doi:10.1016/j.resuscitation.2017.05.006
7. Zhang XJ, Liu YG, Shi XJ, Chen XW, Zhou D, Zhu DJ. The prognostic role of neutrophils to lymphocytes ratio and platelet count in gastric cancer: a meta-analysis. *Int J Surg* 2015;21:84-91. doi:10.1016/j.ijsu.2015.07.681
8. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014;106:dju124. doi:10.1093/jnci/dju124
9. Nakul-Aquaronne D, Sudaka-Sammarcelli I, Ferrero-Vacher C, Starck B, Bayle J. Evaluation of the Sysmex Xe-2100® hematology analyzer in hospital use. *J Clin Lab Anal* 2003;17:113-123. doi:10.1002/jcla.10083
10. Bhat T, Teli S, Rijal J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. *Expert Rev Cardiovasc Ther* 2013;11:55-59. doi:10.1586/erc.12.159
11. Wang X, Zhang G, Jiang X, Zhu H, Lu Z, Xu L. Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: a meta-analysis of observational studies. *Atherosclerosis* 2014;234:206-213. doi:10.1016/j.atherosclerosis.2014.03.003
12. Hartopo AB, Puspitawati I, Setianto BY. On-admission high neutrophil to lymphocyte ratio as predictor of in-hospital adverse cardiac event in st-elevation myocardial infarction. *Acta Med Indones* 2015;47:3-10.
13. Hwang SY, Shin TG, Jo IJ, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in critically-ill septic patients. *Am J Emerg Med* 2017;35:234-239. doi:10.1016/j.ajem.2016.10.055
14. Zhou Q, Hong L, Zuo MZ, He Z. Prognostic significance of neutrophil to lymphocyte ratio in ovarian cancer: evidence from 4,910 patients. *Oncotarget* 2017;8:68938-68949. doi:10.18632/oncotarget.20196
15. Liao LJ, Hsu WL, Wang CT, et al. Prognostic impact of pre-treatment neutrophil-to-lymphocyte ratio (NLR) in nasopharyngeal carcinoma: a retrospective study of 180 Taiwanese patients. *Clin Otolaryngol* 2018;43:463-469. doi:10.1111/coa.12992
16. Wang L, Liang D, Xu X, et al. The prognostic value of neutrophil to lymphocyte and platelet to lymphocyte ratios for patients with lung cancer. *Oncol Lett* 2017;14:6449-6456. doi:10.3892/ol.2017.7047
17. Kaito S, Kanemasa Y, Sasaki Y, et al. A new prognostic score comprising lactate dehydrogenase, albumin and neutrophil to lymphocyte ratio to predict sensitivity to first-line chemotherapy in patients with peripheral T-cell lymphomas. *Int J Hematol* 2018;107:451-459. doi:10.1007/s12185-017-2362-6
18. Chen Y, Yan H, Wang YR, Shi Y, Dai GH. Significance of baseline and change in neutrophil-to-lymphocyte ratio in predicting prognosis: a retrospective analysis in advanced pancreatic ductal adenocarcinoma. *Sci Rep* 2017;7:753. doi:10.1038/s41598-017-00859-5
19. Min KW, Kwon MJ, Kim DH, et al. Persistent elevation of postoperative neutrophil-to-lymphocyte ratio: a better predictor of survival in gastric cancer than elevated preoperative neutrophil-to-lymphocyte ratio. *Sci Rep* 2017;7:13967. doi:10.1038/s41598-017-13969-x
20. de Pablo R, Monserrat J, Prieto A, Alvarez-Mon M. Role of circulating lymphocytes in patients with sepsis. *Biomed Res Int* 2014;2014:671087. doi:10.1155/2014/671087
21. Huang CH, Tsai MS, Chien KL, et al. Predicting the outcomes for out-of-hospital cardiac arrest patients using multiple biomarkers and suspension microarray assays. *Sci Rep* 2016;6:27187. doi:10.1038/srep27187
22. Başer K, Baş HD, Attaluri P, Rodrigues T, Nichols J, Nugent K. Changes in neutrophil-to-lymphocyte ratios in postcardiac arrest patients treated with targeted temperature management. *Anatol J Cardiol* 2017;18:215-222.

doi:10.14744/AnatolJCardiol.2017.7716
23. Biggar WD, Bohn D, Kent G. Neutrophil circulation and release from bone marrow during hypothermia. *Infect Immun* 1983;40:708-712.
24. Hovdenes J, Røysland K, Nielsen N, et al. A low body temperature on arrival at hospital following out-of-hospital-cardiac-arrest is associated with increased mortality in the TTM-study. *Resuscitation* 2016;107:102-106. doi:10.1016/j.resuscitation.2016.08.011
25. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? *BMC Res Notes* 2017;10:12. doi:10.1186/s13104-016-2335-5
26. Silva N, Bettencourt P, Guimarães JT. The lymphocyte-to-monocyte ratio: an added value for death prediction in heart failure. *Nutr Metab Cardiovasc Dis* 2015;25:1033-1040. doi:10.1016/j.numecd.2015.07.004
27. Wang Q, Ma J, Jiang Z, Wu F, Ping J, Ming L. Association of lymphocyte-to-monocyte ratio with in-hospital and long-term major adverse cardiac and cerebrovascular events in patients with ST-elevated myocardial infarction. *Medicine (Baltimore)* 2017;96:e7897. doi:10.1097/MD.0000000000007897
28. Vakili H, Shirazi M, Charkhkar M, Khaheshi I, Memaryan M, Naderian M. Correlation of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio with thrombolysis in myocardial infarction frame count in ST-segment elevation myocardial infarction. *Eur J Clin Invest* 2017;47:322-327. doi:10.1111/eci.12736
29. Nierhaus A, Klatte S, Linssen J, et al. Revisiting the white blood cell count: immature granulocytes count as a diagnostic marker to discriminate between SIRS and sepsis-a prospective, observational study. *BMC Immunol* 2013;14:8. doi:10.1186/1471-2172-14-8
30. Liu WY, Lin SG, Wang LR, et al. Platelet-to-lymphocyte ratio: a novel prognostic factor for prediction of 90-day outcomes in critically ill patients with diabetic ketoacidosis. *Medicine (Baltimore)* 2016;95:e2596. doi:10.1097/MD.0000000000002596
31. Che YQ, Shen D, Zhang SM, Qi J. Identification of immature granulocytes in cancer chemotherapy patients by cell counting vs. microscopic examination of blood smears. *Mol Clin Oncol* 2014;2:207-211. doi:10.3892/mco.2014.243
32. Wongrakpanich S, George G, Chaiwatcharayut W, et al. The prognostic significance of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in patients with multiple myeloma. *J Clin Lab Anal* 2016;30:1208-1213. doi:10.1002/jcla.22004
33. Chan JCY, Chan DL, Diakos CI, et al. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. *Ann Surg* 2017;265:539-546. doi:10.1097/SLA.0000000000001743
34. Sauneuf B, Bouffard C, Cornet E, et al. Immature/total granulocyte ratio: a promising tool to assess the severity and the outcome of post-cardiac arrest syndrome. *Resuscitation* 2014;85:1115-1119. doi:10.1016/j.resuscitation.2014.04.017
35. Macdonald D, Richardson H, Raby A. Practice guidelines on the reporting of smudge cells in the white blood cell differential count. *Arch Pathol Lab Med* 2003;127:105.
36. Nowakowski GS, Hoyer JD, Shanafelt TD, et al. Using smudge cells on routine blood smears to predict clinical outcome in chronic lymphocytic leukemia: a universally available prognostic test. *Mayo Clin Proc* 2007;82:449-453. doi:10.4065/82.4.449
37. Nowakowski GS, Hoyer JD, Shanafelt TD, et al. Percentage of smudge cells on routine blood smear predicts survival in chronic lymphocytic leukemia. *J Clin Oncol* 2009;27:1844-1849. doi:10.1200/JCO.2008.17.0795
38. Johansson P, Eisele L, Klein-Hitpass L, et al. Percentage of smudge cells determined on routine blood smears is a novel prognostic factor in chronic lymphocytic leukemia. *Leuk Res* 2010;34:892-898. doi:10.1016/j.leukres.2010.02.038
39. Gogia A, Raina V, Gupta R, et al. Prognostic and predictive significance of smudge cell percentage on routine blood smear in chronic lymphocytic leukemia. *Clin Lymphoma Myeloma Leuk* 2014;14:514-517. doi:10.1016/j.clml.2014.02.007
40. Chang CC, Sun JT, Liou TH, et al. Clinical significance of smudge cells in peripheral blood smears in hematological malignancies and other diseases. *Asian Pac J Cancer Prev* 2016;17:1847-1850. doi:10.7314/APJCP.2016.17.4.1847