JOURNAL OF SURGICAL RESEARCH • NOVEMBER 2021 (267) 755–761

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Late Mortality Prediction of Neutrophil-to-Lymphocyte and Platelet Ratio in Patients With Trauma Who Underwent Emergency Surgery: A Retrospective Study

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A R T I C L E I N F O

Article history:
Received 3 August 2020
Received in revised form
28 September 2020
Accepted 1 November 2020
Available online 11 February 2021

Keywords:
Injury severity score
Mortality
Neutrophil
Platelet
Trauma

A B S T R A C T

Background: We aimed to evaluate the usefulness of neutrophil-to-lymphocyte (N/L) and neutrophil-to-lymphocyte platelet (N/LP) ratios in predicting late mortality of patients with trauma who underwent emergency surgery.

Materials and methods: We retrospectively evaluated patients with trauma older than 19 y who underwent emergency surgery at our level I trauma center. Blood count–based ratios (N/L and N/LP at days 1, 3, and 7 of hospitalization) and trauma scores were analyzed. Statistical analysis was performed using univariable logistic regression and receiver operating curves.

Results: A total of 209 patients were evaluated. N/LP at day 7, N/L at day 7, Trauma Injury Severity Score, Revised Trauma Score, and Injury Severity Score were significantly associated with late mortality. Area under the receiver operating characteristic curves for predicting mortality was highest for N/LP at day 7 (0.867 [95% confidence interval 0.798-0.936], $P < 0.001$). The group with N/LP greater than the cutoff value (9.3, sensitivity 77.3%, specificity 83.1%) at day 7 showed higher mortality than the group with N/LP less than the cutoff value (35.4% *versus* 3.2%, $P < 0.001$, respectively) at day 7.

Conclusions: N/LP at day 7 may be a superior predictor of late mortality compared with preexisting trauma scores in patients with major trauma undergoing emergency surgery, by better reflecting the systemic inflammation status.

Ethical approval: This retrospective study was approved by the Ajou Institutional Review Board, and the requirement of written informed consent was waived by the committee (AJIRB-MED-MDB-18-322). It was also registered with the Clinical Research Information Service (http://cris.nih.go.kr, KCT0004131).

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https://doi.org/10.1016/j.jss.2020.11.088

Introduction

Deaths after trauma are distributed into three distinct phases. The first peak is immediate death, usually caused by massive head injury or bleeding. The second peak called early death usually occurs in the first 24 h and is caused by hypoxia, hypovolemia, or severe head trauma. Both first and second peaks are mainly associated with the injury itself. Conversely, the third peak, called late death, occurs days or weeks after the injury and is mainly associated with the multiorgan dysfunction syndrome (MODS). MODS is associated with immunological dysfunction, which occurs in patients who survive the first and second peaks.[1-3] In severely injured patients, trauma activates nearly all components of the immune system, including proinflammatory and anti-inflammatory components. The imbalance of these two components can result in systemic inflammatory response syndrome (SIRS), or sepsis, which can further lead to MODS that has a high risk of death.[1,4] Therefore, the detection of the imbalance between proinflammatory and anti-inflammatory responses can be helpful to predict development of MODS and late death.

Neutrophil-to-lymphocyte ratio (N/L) has been reported as a simple and reproducible tool for detecting the imbalance between proinflammatory and anti-inflammatory response. In stress and systemic inflammation, the neutrophil counts increase and lymphocyte counts decrease,[5,6] reflecting the magnitude of the stress and inflammation.[7] In addition, N/L was reported to be associated with mortality in critically ill patients with trauma[7] and patients with severe hemorrhage and massive transfusion.[8] In addition to this, the N/L combined with the platelet count (neutrophil-to-lymphocyte platelet ratio; N/LP) was recently introduced as a superior predictor of mortality after cardiovascular surgery.[6] Moreover, platelet count alone, which is associated with inflammatory injury to the major organs, is associated with long-term mortality in coronary artery bypass graft surgery[9] and severely injured patients with trauma.[10] Therefore, the combination of N/L and platelet count may increase the predictive power for mortality. However, the predictive power of N/LP has not previously been evaluated in patients with trauma. Furthermore, it is unknown whether the N/LP at a particular time point has a higher predictive power.

The aim of this study was to evaluate the usefulness of blood count–based ratios (N/L and N/LP at hospital day 1, 3, and 7) in predicting late mortality of patients with trauma after emergency surgery. In addition, we also evaluate the predicting power of the blood count–based ratios compared with preexisting trauma scores, Injury Severity Score (ISS), Revised Trauma Score (RTS), and Trauma Injury Severity Score (TRISS).

Materials and Methods

This study was performed at a single center: a level 1 trauma center. This retrospective study was approved by the institutional review board, and the requirement of written informed consent was waived by the committee. It was also registered with the Clinical Research Information Service. This study included patients with trauma older than 19 y who underwent emergency surgery between January 2015 and December 2017 at the level 1 trauma center. Deaths occurring after 2 d were defined as late deaths.[3] We excluded the patients who expired within 48 h which implied early death.[11]

The following data of the patients were collected from the electronic medical records and trauma registry: patient characteristics and treatment outcomes, including, age, sex, ISS, RTS, TRISS, Glasgow Coma Scale (GCS), shock index, and laboratory results (lactate, base deficit, and fibrinogen) at trauma-bay arrival, and treatment outcomes, including length of hospital stay, intensive care unit (ICU) stay, mortality, and interval between admission and death. The blood count–based ratios N/L and N/LP at days 1, 3, and 7 of hospitalization were calculated using differentiated leukocyte counts. The specific formulae were as follows: N/L was calculated via division of absolute neutrophil count by absolute lymphocyte count. N/LP was calculated via multiplication of N/L by 100 followed by division by platelet count.[6]

$$\text{Neutrophil/lymphocyte ratio} = \frac{\text{Absolute neutrophil count } (10^9/\text{ L})}{\text{Absolute lymphocyte count } (10^9/\text{ L})}$$

$$\text{Neutrophil/lymphocyte platelet ratio} = \frac{\text{Absolute neutrophil count } (10^9/\text{ L}) \times 100}{\text{Absolute lymphocyte count } (10^9/\text{ L}) \times \text{ Platelet count } (10^9/\text{ L})}$$

The blood cell count value at day 1 was the most initial laboratory result after the patient arrived at the trauma center. If multiple differential blood cell counts were reported on day 3, or day 7, the results that were conducted at a time similar to that of the first laboratory tests were used. Data of patients who died between day 3 and day 7 (four patients) were treated as missing data while analyzing N/L and N/LP ratios at day 7.

Statistical analysis

We compared a total of nine prediction tools, including blood count–based ratios (N/L and N/LP at hospital days 1, 3, and 7) and the preexisting trauma scores (ISS, RTS, and TRISS). Univariable logistic regression was used to determine the relationship between each prediction tool and late mortality.

Receiver operating characteristic (ROC) curve analysis was used to assess the predictive capacity of blood count–based ratios (N/L and N/LP at days 1, 3, and 7) and the preexisting trauma scores (ISS, RTS, and TRISS) on late mortality. These analyses were reported as area under the curve and 95% confidence intervals (CIs). Pairwise comparisons of ROC curves were used to compare the predictability of mortality for ISS, RTS, TRISS, N/L ratios, and N/LP ratios to determine the superior tool. The optimal cutoff values of each tool were established using the maximum Youden index on the ROC curve. Kaplan–Meier survival analysis and log-rank test were used to compare the survival between the groups based on the cutoff value.

After determining the superior tool, we used the Mann–Whitney *U*-test for the continuous data and the chi-square or Fisher exact test for categorical data during comparison of groups based on the cutoff value. The results were reported as medians and interquartile ranges (IQRs) for continuous variables and frequencies and percentages for categorical variables. All statistical analyses were performed using SPSS, version 25.0 for Windows (IBM Corp., Armonk, NY, USA) and SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA). We considered $P < 0.05$ as statistically significant.

Results

Patient characteristics

A total of 256 patients with trauma underwent emergency surgery from January 2015 to December 2017 at the level 1 trauma center. We excluded the 47 patients who died within 48 h to clarify late mortality. Thus, 209 patients with trauma were evaluated in this study. The median age of patients was 49 [IQR 37.5-61.0] years, and males (80.4%) outnumbered females. The median values of injury severity were as follows: ISS 23 [IQR 16-34], RTS 7.11 [IQR 5.44-7.84], and TRISS 91.0 [IQR 70.2-97.8], and the initial GCS was 15 [IQR 7-15]. The overall mortality rate was 11.5% (24 of 209), whereas the mortality attributed to multiorgan dysfunction was 9.1% (19 of 209), which accounted for 79.2% of total mortality. The median interval between hospital admission and death was 21 [IQR 11-51] days (Table 1).

Table 1 – Baseline characteristics of patients.

Parameter	Patients ($n = 209$)
Age, y	49 [37.5 to 61.0]
Male sex	168 (80.4)
Injury severity	
ISS	23 [16 to 34]
RTS	7.11 [5.44 to 7.84]
TRISS, %	91.0 [70.2 to 97.8],
Initial state	
GCS	15 [7 to 15]
Shock index	0.9 [0.7 to 1.2]
Lactate, mmol/L	4.57 [3.24 to 6.91]
Base deficit, mmol/L	−8.4 [−11.15 to −6.10]
Fibrinogen, mg/dL	147 [113.0 to 174.5]
Outcome	
Length of stay, d	42 [21 to 66]
ICU stay, d	15 [7 to 37]
Mortality	24 (11.5)
Mortality d/t MODS	19 (9.1)
Interval between admission and death, d	21 [11 to 51]

Values are presented as median [interquartile range] or number of patients (%).

Predictors of mortality

Univariable logistic regression analysis showed that N/L at day 7 and N/LP at day 7 were significantly related to overall late mortality (N/L at day 7, $P = 0.001$; N/LP at day 7, $P < 0.001$). All trauma scores, including ISS, RTS, and TRISS, were also related to overall late mortality (ISS, $P = 0.015$; RTS, $P = 0.010$; TRISS, $P = 0.001$) (Table 2). Because blood count–based ratios at day 1 and day 3 were not significantly related to late mortality in univariable analysis, they were excluded from further analysis.

In accordance with the ROC curve analysis, the area under the curve for predicting overall late mortality was highest for N/LP at day 7 (0.867 [95% CI 0.798-0.936], $P < 0.001$), followed by TRISS (0.735 [95% CI 0.639-0832], $P < 0.001$), and N/L at day 7 (0.719 [95% CI 0.599-0.839, $P < 0.001$]) (Table 3). Moreover, during pairwise comparisons, N/LP at day 7 showed significant superiority in prediction of mortality than other prediction tools (Table 4).

N/LP as indicator of prognosis

We established the cutoff value of N/LP at day 7 as 9.3 (sensitivity 77.3%, specificity 83.1%). Overall survival between

Table 2 – Univariable logistic regression analysis for the mortality.

Prediction tool	OR	95% CI	*P*-value
ISS	1.04	1.01 to 1.07	0.015
RTS	0.74	0.60 to 0.93	0.010
TRISS	0.98	0.97 to 0.99	0.001
N/L at day 1	0.93	0.85 to 1.02	0.138
N/LP at day 1	0.98	0.92 to 1.04	0.440
N/L at day 3	1.00	1.00 to 1.01	0.459
N/LP at day 3	1.00	1.00 to 1.01	0.179
N/L at day 7	1.05	1.02 to 1.08	0.001
N/LP at day 7	1.03	1.01 to 1.05	<0.001

OR = odds ratio.

Table 3 – Descriptive statistics of the receiver operating characteristic (ROC) curve.

Prediction tool	Cutoff*	Sensitivity (%)	Specificity (%)	AUC	95% CI	P-value
ISS	37.0	41.7	84.9	0.637	0.517 to 0.756	0.015
RTS	6.5	66.7	63.8	0.657	0.540 to 0.774	0.004
TRISS	71.5	62.5	78.9	0.735	0.639 to 0.832	<0.001
N/L at day 7	13.2	59.1	82.5	0.719	0.599 to 0.839	<0.001
N/LP at day 7	9.3	77.3	83.1	0.867	0.798 to 0.936	<0.001

AUC = area under the curve.
*Cutoff values were defined by the Youden index that maximizes the sum of the sensitivity and specificity.

the patient groups based on values above and below (including equal) the cutoff value was compared using Kaplan–Meier curves. The log-rank test revealed a significant difference in survival between the high-N/LP-at-day-7 group and low-N/LP-at-day-7 group ($P < 0.001$). The high-N/LP-at-day-7 group showed a relatively poor survival (Figure).

In addition, while contrasting the baseline characteristics, the high-N/LP-at-day-7 group showed a higher score of ISS and lower scores of RTS and TRISS, which implied more severe injuries compared with the low-N/LP-at-day-7 group. Moreover, other initial state characteristics, including GCS, lactate level, base deficit, and fibrinogen level, were also poor in the high-N/LP-at-day-7 group, except shock index, which was not significantly different between the two groups. Relatively more blood was transfused in the high-N/LP-at-day-7 group ($P < 0.001$) (Table 5). The high-N/LP-at-day-7 group had a longer hospital stay (40 [IQR 21-60] days *versus* 54 [IQR 26-92] days, respectively, $P = 0.048$), longer ICU stay (13 [IQR 6-31] days *versus* 25 [IQR 14-59] days, $P < 0.001$), and higher mortality (3.2% *versus* 35.4%, $P < 0.001$) (Table 6) than the low-N/LP-at-day-7 group.

Discussion

To the best of our knowledge, this is the first study to evaluate the association between late mortality and N/LP——a ratio that includes leukocyte and platelet counts in patients with trauma after emergency surgery. This retrospective study showed that among blood count–based ratios at various time points, N/LP at day 7 and N/L at day 7 predicted late mortality in patients with trauma who underwent emergency surgery. Furthermore, the predictability of N/LP at day 7 was higher than that of the preexisting trauma scores, ISS, RTS, and TRISS. Moreover, patients with N/LP above the cutoff value of 9.3 at day 7 showed 11 times higher late mortality than that of patients below the cutoff value.

The present study showed that blood count–based ratios at relatively late stages (N/L at day 7 and N/LP at day 7) could effectively predict late mortality. However, relatively earlier (days 1 and 3 of hospitalization) N/L and N/LP were not significantly related to late mortality. Duchesne *et al.*[8] also showed that N/L at day 10 was an independent prognostic factor of mortality, whereas N/L at day 3 was not in patients with severe hemorrhage. Similarly, Dilektasli *et al.*[7] showed that N/L at day 5 was a better predictor than N/L at day 2 in patients with trauma. As such, previous studies suggested that late N/L was better related to mortality than early N/L, which is consistent with our results. In accordance with the two-hit theory in patients with trauma, the first hit, that is, injury severity, results in the priming of the inflammatory system, while the second hit, that is, infection, stress from surgery, transfusion, and so forth, results in exaggerated release of oxygen free radicals, causing an inappropriate inflammatory response, and further tissue injury.[12] The increase in N/L or N/LP over time may be related to the exaggerated inflammatory process of the second hit. Polymorphonuclear leukocytes, such as neutrophils, eosinophils, and basophils, are usually programmed to undergo apoptosis within 24 h after leaving the bone marrow, to minimize autoimmune tissue injury. Ogura *et al.*, however, reported that apoptosis of polymorphonuclear leukocytes after trauma may be inhibited for up to 3 wk.[12] Furthermore, certain clinical situations, such as SIRS and sepsis can also delay apoptosis of neutrophils.[13,14] Therefore, the numerator in N/L and N/LP, that is, the level of neutrophils, tends to increase in patients with severe trauma. Conversely, the apoptosis of lymphocytes, the denominator in N/L and N/LP, usually peaks at day 3 after initial trauma, thereby decreasing the level of lymphocyte. An inverse relationship between lymphocyte count and

Table 4 – Pairwise comparison of receiver operating characteristic (ROC) curves of risk factors for the mortality.

Prediction tool	ISS	RTS	TRISS	N/L ratio at day 7	N/LP ratio at day 7
ISS	1.000	0.003	<0.001	0.260	<0.001
RTS		1.000	0.027	<0.001	<0.001
TRISS			1.000	<0.001	<0.001
N/L at day 7				1.000	<0.001
N/LP at day 7					1.000

Data are *P*-values, which are significant when $<1.4 \times 10^{-3}$ ($1.4 \times 10^{-3} \fallingdotseq 0.05/36$), that is, Bonferroni correction for multiple comparisons.

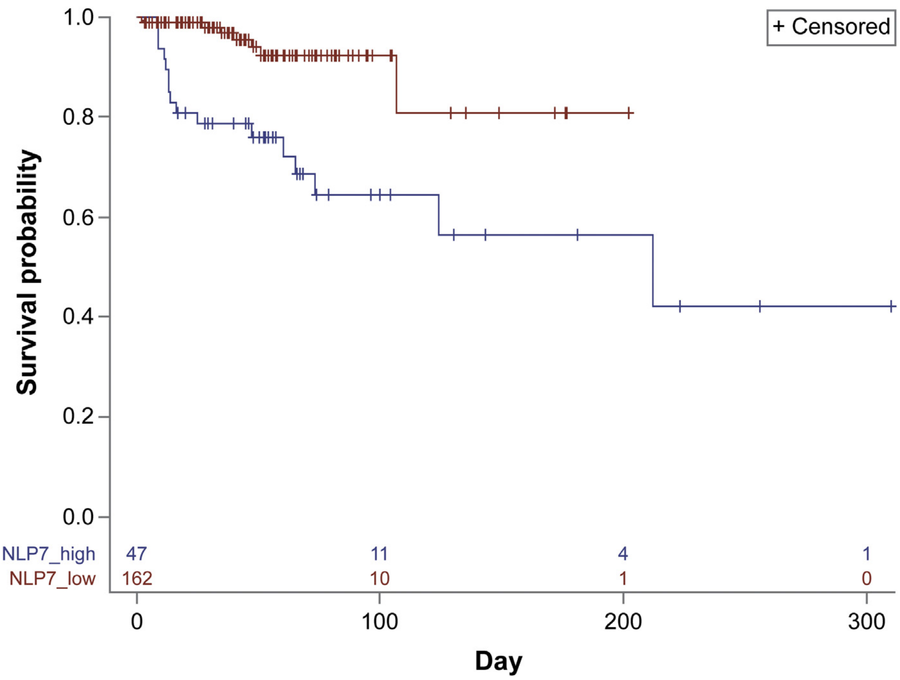

Fig – Kaplan–Meier survival analysis of neutrophil-to-lymphocyte platelet ratio (N/LP) at day 7. The red line is the low-N/LP-at-day-7 group (below or equal to cutoff value), and the blue line is the high-N/LP-at-day-7 group (above cutoff value). The cutoff value of N/LP at day 7 is 9.3 (sensitivity 77.3%, specificity 83.1%). Log-rank test results in $P < 0.001$.

ISS exists, with pronounced lymphopenia occurring in patients with higher ISS.[15,16] As a result, changes in the levels of neutrophils and lymphocytes lead to an increase of N/L and N/LP, which, in turn, is believed to result from accumulation of such response.

Compared with N/L, N/LP correlated better with late mortality in our results. Platelets, one of denominators in N/LP, not only are important during hemostasis, but are also key mediators in the innate immune system. Platelets can recognize and kill pathogens, recruit leukocytes, release proinflammatory and anti-inflammatory cytokines, and participate in wound healing.[17-19] Cato *et al.*[17] reported that the lower peak value of platelet count in patients with burn wound was associated with a higher mortality and sepsis. The decrease in

Table 5 – The relation between baseline characteristics and neutrophil-to-lymphocyte platelet ratio (N/LP) at day 7.

Parameter	N/LP 7 ≤ 9.3 ($n = 157$)	N/LP 7 > 9.3 ($n = 48$)	P-value
Age, y	49 [35.0 to 59.0]	50 [39.3 to 66.0]	0.430
Male sex	128 (81.5)	36 (76.6)	0.455
Injury severity			
ISS	22 [13 to 29]	29 [18 to 43]	<0.001
RTS	7.55 [5.75 to 7.84]	6.38 [4.62 to 7.84]	0.016
TRISS, %	92.4 [77.6 to 98.1]	81.6 [31.3 to 94.3]	<0.001
Initial state			
GCS	15 [7 to 15]	11 [6 to 15]	0.047
Shock index	0.9 [0.7 to 1.2]	1.0 [0.7 to 1.3]	0.179
Lactate, mmol/L	4.24 [3.08 to 5.85]	7.05 [3.40 to 10.38]	<0.001
Base deficit, mmol/L	−7.8 [−10.50 to −5.35]	−10.3 [−13.68 to −8.00]	<0.001
Fibrinogen, mg/dL	153 [117.0 to 180.5]	126 [96.3 to 162.3]	0.005
Transfusion			
RBC, unit	7 [4 to 13]	19 [9 to 34]	<0.001
FFP, unit	8 [3 to 12]	19 [10 to 32]	<0.001
Platelet, unit	8 [0 to 12]	16 [8 to 26]	<0.001

Values are presented as median [interquartile range] or number of patients (%).
RBC = red blood cell; FFP = fresh frozen plasma.

Table 6 – The relation between outcome variables and neutrophil-to-lymphocyte platelet ratio (N/LP) at day 7.

Parameter	N/LP 7 ≤ 9.3 (n = 157)	N/LP 7 > 9.3 (n = 48)	P-value
Outcome			
LOS, d	40 [21 to 60]	54 [26 to 92]	0.048
ICU stay, d	13 [6 to 31]	25 [14 to 59]	<0.001
Mortality	5 (3.2)	17 (35.4)	<0.001

Values are presented as median [interquartile range] or number of patients (%).
LOS = length of stay.

platelet count in patients with sepsis was also a predictive factor for mortality and MODS.[20] Previous studies performed on ICU patients showed that patients with thrombocytopenia had higher incidence of acute kidney injury, frequent episodes of major bleeding, received more transfusions, required prolonged vasopressor support, and consequently showed higher mortality rates.[20-22] Conversely, thrombocytosis is sometimes observed during the recovery period in patients with trauma, which may increase the risk of thromboembolism and yet, result in lower mortality rates compared with patients without thrombocytosis.[23] In summary, platelet counts in patients with trauma are related to overall outcomes, with lower counts associated with poorer results. Therefore, in this study, considering platelet count as one of the factors for denominator seems to have contributed to further increase the predictive power of the N/LP compared with N/L.

The N/LP ratio was first introduced in a study performed by Koo *et al.*,[6] where they found that high N/LP was associated with postoperative acute kidney injury and 5-year mortality in patients who underwent cardiovascular surgery. This study used a cutoff value of 3.0, and N/LP above 3.0 was associated with a poor outcome. The cutoff value used in our study was 9.32, which is higher than that in previous study, but showed similar trends associated with poor outcomes at higher values. The difference between our cutoff value and previously published values could be a result of the time of data acquisition, as our study used data only after the trauma event, whereas Koo *et al.*'s work used preinjury data before surgery. The primary endpoints were also different, with late mortality in our study and acute kidney injury and 5-year mortality in Koo *et al.*'s study, and this may also have affected the difference of cutoff values. To the best of our knowledge, no other prior studies have reported about N/LP ratio and its predictive power in any other fields including trauma.

Severe degree of injury at the time of trauma can cause intense proinflammatory and anti-inflammatory response, which places the patient at risk of SIRS, sepsis, and finally late mortality.[1,24] Therefore, theoretically, the preexisting trauma scores, reflecting injury severity, could predict late mortality in patients with trauma. In the present study, trauma scores, including ISS, RTS, and TRISS, all predicted late mortality. The predictability of all three scores, however, was lower than that of N/LP, and the predictability of ISS and RTS was even lower than that of N/L. Previous studies also suggested a limited predictability of trauma scores for late mortality in patients with trauma. Wang *et al.*[25] showed that only ISS, not RTS, predicted late mortality in patients with pelvic fractures. Garber *et al.*[26] showed that the predictive power of TRISS was lower in late death than in early death. The reason that the preexisting trauma scores have limits in predicting late mortality is that those scores do not consider the risk factors for late mortality. The known risk factors for late mortality were sepsis, MODS, surgical complications, age, and preexisting diseases, whereas the risk factors for early mortality were hemorrhage, injury severity, and brain injury.[7,25,27,28] For a more accurate prediction, the need for separation of prediction tools based on early and late death has emerged. Furthermore, the calculation of trauma scores is cumbersome and difficult to determine in certain situations. For example, some scores which include respiratory rate and GCS are difficult to determine in intubated patients. In contrast, N/LP at day 7 showed superior prediction of late mortality compared with the preexisting trauma scores, including TRISS, and was easy to determine. Therefore, N/LP at day 7 could be a useful tool for prediction of late mortality in patients with trauma.

Limitations

The present study has some limitations. First, the retrospective design has inherent selection bias. Second, this study did not include the other widely used scores, such as Acute Physiology and Chronic Heath Disease Classification System or Sequential Organ Failure Assessment Score for comparison, because of unrecorded information during the target period in our facility. Third, this study was performed at a single center, and the sample size was small. In addition, the population included in this study was limited to patients with trauma who underwent emergency surgery. For generalization of conclusion to other populations, such as other trauma centers, patients of different age distributions, or patients who did not have emergency surgery, large multicenter studies are required to further prove the usefulness of N/LP in late mortality prediction.

Conclusion

In conclusion, in this retrospective study, both N/L and N/LP at day 7 of hospitalization as well as the preexisting trauma scores predicted late mortality in patients with trauma who underwent emergency surgery. However, N/LP at day 7 of hospitalization could be a superior tool for predicting late mortality than the preexisting trauma scores. Multicenter prospective studies with larger samples are needed to confirm these findings.

Acknowledgment

We would like to thank Editage (www.editage.co.kr) for English language editing.

Authors' contribution

Y.J.C. contributed to literature searches, study design, data analysis, writing, and critical revision. J.L. contributed to literature searches, study design, data analysis, writing, and critical revision. J.H.P. contributed to methodology and data analysis. D-G.H. contributed to data acquisition. E.H. contributed to data acquisition. I.K.Y. contributed to study design, writing, critical revision, and supervision.

Source of funding: This work was supported by the intramural research fund of Ajou University Medical Center, South Korea.

Disclosure

The authors have no conflict of interest.

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