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ORIGINAL RESEARCH

Association Between Neutrophil Density and Survival in Trauma Patients Admitted to the Intensive Care Unit; a Retrospective Cohort Study

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Abstract: **Introduction:** Altered immune responses, in particular neutrophil changes, are perceived to play a key role in immune responses to trauma. This study aimed to evaluate the association of neutrophil changes with patients' survival in severe trauma cases. **Methods:** The current retrospective cohort study was conducted using data from patients admitted in the intensive care unit (ICU) of a trauma center in Shiraz, Iran, between 2016 and 2021. Patients were divided into three groups (i.e., normal, neutropenia, and neutrophilia) based on neutrophil count at the time of ICU admission, and the association of neutrophil count with in-hospital mortality was analyzed. **Results:** 2176 patients with the mean age of 37.90 ± 18.57 years were evaluated (84.04% male). The median trauma severity based on injury severity score (ISS) in this series was 9 (4 -17). Patients were divided in to three groups of neutrophilia (n = 1805), normal (n = 357), and neutropenia (n = 14). There were not any significant differences between groups regarding age distribution (p = 0.634), gender (p = 0.544), and trauma severity (p = 0.197). The median survival times for the normal, neutropenia, and neutrophilia groups were 49 (IQR: 33 -47) days, 51 (IQR: 8- 51) days, and 38 (IQR: 26 - 52) days, respectively (p = 0.346). The log-rank test showed a statistically significant difference between the three groups adjustment for ISS ($p \leq 0.001$). For each unit increase in ISS, the hazard ratio increased by 2%. In ISS 9-17, the hazard ratio increased by 11% compared to ISS<4. Also, in ISS>17, the hazard ratio increased by 76% compared to ISS<4 in ICU-hospitalized patients. **Conclusion:** In general, the findings of the present study showed that the survival rate of patients in the normal group after ISS adjustment was higher than the other two groups. Also, the Cox model showed that the mortality risk ratio in the neutropenia group was 15 times higher than the normal group.

Keywords: Neutrophils; Survival; Neutropenia; Wounds and Injuries; Multiple trauma; Trauma Severity Indices

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1. Introduction

Recently, WHO has estimated that trauma accounts for 5.8 million mortalities, annually (1, 2). In recent years, trauma-caused mortalities have substantially declined owing to advances in treatment approaches, particularly in patients under blood clot and blood loss treatments. However, secondary complications such as sepsis, multiple organ failure (MOF), and nosocomial infections may harm trauma pa-

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tients or even cause death (3).

Neutrophils constitute 60-70% of circulatory leukocytes in the body, playing a key role in innate immunity and host defense against invading pathogens, as well as eliciting inflammation-induced tissue damage (4). In healthy individuals, circulatory neutrophils are primarily naïve cells, which are subsequently activated by recognizing damage-associated molecular patterns (DAMPs) through their pathogen-associated molecular patterns (PAMPs), thereby maintaining the immune system homeostasis (5). Upon inflammation, neutrophils properly respond to microenvironmental signals and obtain distinct functional phenotypes, commonly referred to as neutrophil heterogeneity (6, 7). Besides, trauma can affect neutrophils (8). Indeed, neutrophils are the first line of defense against microbial pathogens and trauma and commence inflammatory responses. Trauma-induced modulations in neutrophils, ultimately lead to post-traumatic complications e.g., multiple organ failure and acute respiratory distress syndrome (8). At a wide range of time points after traumatic injury, ex vivo studies have reported significant changes in many neutrophil functions (9-14) that probably contribute to the development of secondary complications.

Experimental studies indicate a direct relationship between trauma severity and the consequent tissue impairment and/or neutrophil dysfunction (15). In addition, depending on the stage of injury, neutrophils can contribute to repair mechanisms or exacerbate the pathophysiology of trauma (16).

A retrospective study (17) explored neutrophils' involvement in severe trauma to uncover the link between trauma severity and neutrophils' phenotype/function. However, given that we only obtained the basic blood test information on neutrophils' percentage from patients at the time of admission, we were encouraged to investigate the impact of neutrophil density on trauma patients' survival. For this purpose, we attempted to evaluate neutrophil counts in patients with adjusted injury severity to determine neutrophils' overall effects.

As mentioned, there is an important balance between pro-inflammatory and anti-inflammatory systems in the immune response to trauma. The imbalance between these systems plays an important role in the post-injury outcomes of critically ill patients (18, 19). Understanding the link between neutrophil dysfunction (neutropenia, or neutrophilia) and patients' survival may yield appropriate early biomarkers for clinical applications and treatment of trauma patients. Therefore, this study aimed to evaluate the association of neutrophil changes with patients' survival in severe trauma cases admitted to intensive care unit (ICU).

2. Methods

2.1. Study design and setting

The current retrospective cohort study was carried out using data from trauma patients admitted to ICU of Shahid Rajaee Hospital (Imtiaz), Shiraz, Iran, between 2016 and 2021. Patients were divided into three groups (i.e., normal, neutropenia, and neutrophilia) based on neutrophil count at the time of ICU admission and the association of neutrophil count with in-hospital mortality were analyzed. The Ethics Committee approved this study at Shiraz University of Medical Sciences (IR.SUMS.SCHEANUT.REC.1400.006). This information was collected for the purpose of research by the Trauma Research Center of Shahid Rajaei Hospital using the patients' files; therefore, due to the nature of the research, informed consent was obtained from the patients themselves or their legal guardians upon the arrival of the patients. In addition, the private medical information of the patients remained confidential, and the researchers were not provided with the name, surname, and national code for the confidentiality of the patients' information

2.2. Participants

All trauma patients over 18 years old, who presented to the ICU of the mentioned hospital were enrolled. Patients who were transferred to another hospital or whose final outcomes regarding in-hospital mortality or survival was not available were exclude. Additionally, all women regardless of pregnancy status were included in the study, but those who died in the emergency department and patients who died within 6 hours of hospital admission were excluded from the study. Also, patients were followed for the duration of their hospital stay or at subsequent hospital visits, but were not specifically followed for post-discharge trauma deaths.

2.3. Data gathering

The variables included the demographic information (age and gender), hospitalization information (date and time of ICU admission and discharge), patients' outcome at the time of discharge from ICU (in-hospital mortality), injury mechanism (accidents or others), patients' consciousness status at the time of ICU admission (Glasgow coma scale (GCS), Pupil 1 and 2), the injury severity score)ISS), patients' vital signs (heart rate [HR], respiratory rate [RR], systolic blood pressure [SBP], and diastolic blood pressure [DBP]), and arterial blood gas analysis (blood acidity [PH], arterial blood carbon dioxide [PCO2], arterial blood oxygen [PAO2] levels and using artificial respiration device, FiO2), as well as laboratory information (blood sugar [BS], blood urea nitrogen [BUN], creatinine [Cr], sodium [Na], potassium [K], prothrombin time PT], partial thromboplastin time [PTT], international normalized ratio [INR], hemoglobin, lymphocyte, fibrinogen, white blood

Table 1: Patients' baseline characteristics

Characteristic	Neutropenia N = 14	Normal N = 357	Neutrophilia N =1805	P[a]
Age (year)				
Mean ± SD	33.50 ± 15.35	38.21 ± 18.43	38.26 ± 18.68	0.634
Gender				
Female	1 (0.29)	61 (17.63)	284 (82.08)	0.544
Male	13 (0.71)	296 (16.17)	1521 (83.11)	
Cause of injury				
Accidentsd	10 (0.61)	261 (16.00)	1360 (83.38)	0.610
Othere	4 (0.74)	96 (17.71)	442 (81.55)	
Length of stay, Median (IQR)				
ICU	3 (0.75 - 8.25)	3 (1 - 9)	6 (2 - 12)	0.0001
Hospital	2.5 (1.75 - 6.25)	7 (2 - 17)	10 (4 - 38)	0.0001
Vital signs on arrival, Median (IQR)				
O2 saturation (%)	93 (90.75 - 96.25)	93 (89 - 96)	93 (90 - 96)	0.917
SBP (mmHg)	116.5 (103 - 137.75)	123 (107 - 138.75)	127 (110 - 139)	0.037
DBP (mmHg)	75 (59.5 - 87.5)	78 (65.5 - 87)	80 (70 - 88)	0.063
GCS	13 (7 - 15)	13 (7 - 15)	12 (7 - 15)	0.318
RR (/minute)	19.5 (17.75 - 21.25)	20 (17 - 22)	20 (17 - 22)	0.974
PR (/minute)	104.14 (21.73)	104.04 (23.64)	101.45 (24.42)	0.174
Pupils (first hour)				
Responsive	13 (0.71)	314 (17.05)	1515 (82.25)	0.314
Unresponsive	0 (0.00)	24 (14.04)	147 (85.96)	
ISS				
Median (IQR)	9 (8 - 16.5)	9 (4 - 17.25)	12 (5 - 18)	0.197
Intubated				
Yes	4 (0.54)	113 (15.13)	630 (84.34)	0.863
No	8 (0.71)	175 (15.57)	941 (83.72)	

a: comparison of the three groups (One-way ANOVA or Kruskal–Wallis) or Chi square
d: Traffic accidents and accidents include: pedestrian accident, motorcyclist accident, and car accident.
e: Others include: falling from a height, being hit by a sharp object, being hit by a bullet, assault, falling to the ground, continuing treatment, suicide, and self-mutilation.
IQR: interquartile range; ISS: Injury severity score; SBP: systolic blood pressure, DBP: diastolic blood pressure; GCS: Glasgow coma scale; RR: Respiratory rate; PR: pulse rate; ICU: intensive care unit; SD: standard deviation. For neutrophils, 45-75% of white blood cell count was considered normal, while less than 4% and more than 75% were considered neutropenia and neutrophilia, respectively.

Table 2: Multiple Cox regression of survival in trauma patient

Variable	Hazard ratio	95% CI	P value
Injury severity score	1.02	(1.00,1.05)	0.042
pH	0.42	(0.21,0.82)	0.011
O2 saturation	0.990	(0.982,0.999)	0.044
Groups			
Normal (Ref)	-	-	-
Neutropenia	15.06	(1.809,125.40)	0.012
Neutrophilia	0.92	(0.42, 2.00)	0.843

CI: confidence interval. Test of proportional hazards assumption based on Schoenfeld residuals (phtest) = 0.726.

count [WBC], and neutrophils count) based on patients' profile. Patients were divided into three groups based on their circulatory neutrophil count. For neutrophils, 45-75% of WBC was considered normal, while less than 45% and more than 75% were considered neutropenia and neutrophilia, respectively. To determine the final status of the patients as our preferred outcome, the patients were followed up until the last day of hospitalization and if the patients were discharged from the hospital alive, we considered them "alive" and if the doctor diagnosed and issued a death certificate, we considered them "dead". In addition, we excluded the patients who were transferred to another treatment center due to the inability to follow up their condition. MV, in collaboration with Trauma Research Center, was responsible for data gathering.

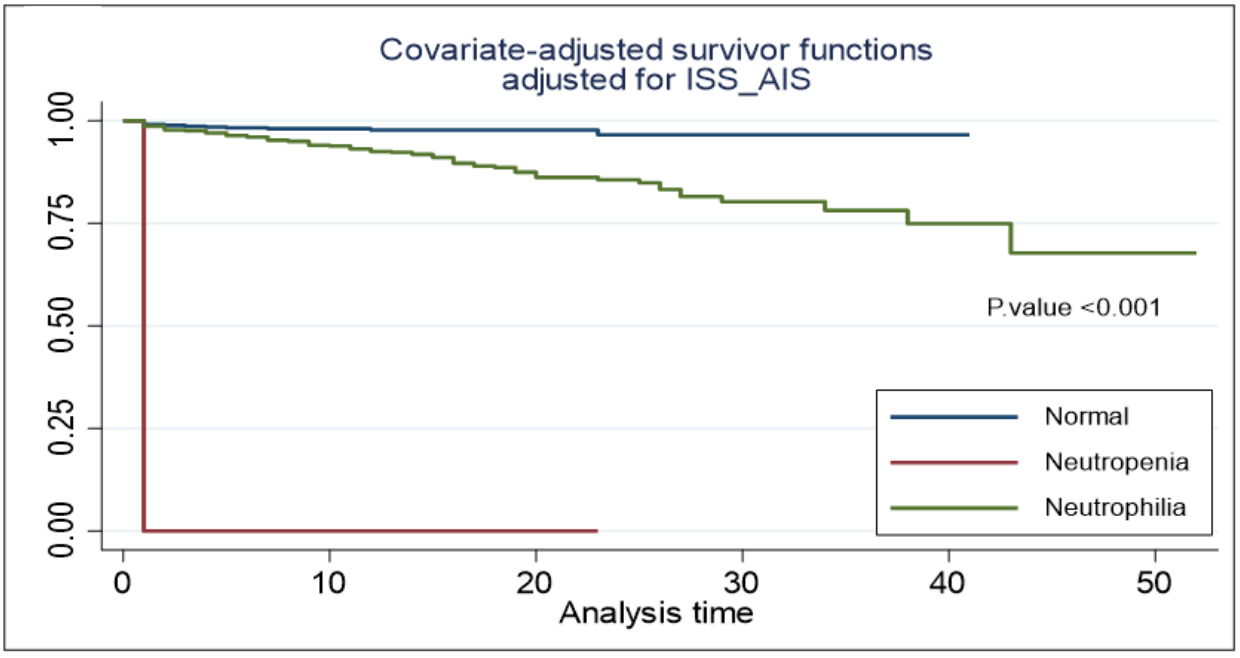

Figure 1: Kaplan-Meier diagram in trauma patients adjusted for injury severity score (ISS) in three groups of neutropenia, normal and neutrophilia. AIS: Abbreviated Injury Scale.

2.4. Statistical analysis

We analyzed the data normality using the Kolmogorov-Smirnov test and related graphs. For quantitative variables with normal distribution, mean and standard deviation (SD) were employed, and for non-normal data, the median and percentiles were reported. Besides, for qualitative variables, frequency and percentage were utilized. Analysis of variance (ANOVA) or Kruskal–Wallis test was also exploited to compare quantitative variables between the normal, neutropenia, and neutrophilia groups. Furthermore, Sidak post hoc or Mann–Whitney U test was used for subsequent comparison between the groups. In addition, the Chi-square test was utilized to compare qualitative variables between the groups. To draw graphs. In addition, for survival analysis, Kaplan-Meier adjusted for the ISS and log-rank were employed to compare the groups. Finally, both simple and multiple Cox regression analyses were utilized to explore factors associated with the survival of ICU-hospitalized trauma patients. Then, the proportional hazards assumption test based on the Schoenfeld residuals (phtest) was utilized to determine the proportional hazards assumption. All analyses were performed using STATA 12 software with a significance level of $P \leq 0.05$.

3. Results

3.1. Baseline characteristics of studied cases

Data was collected from 3782 trauma patients hospitalized in the intensive care unit. After the exclusion of patients under 18 years of age, patients transferred to another hospital, patients whose final status (death or aliveness) was not known, and patients with missing data, 2176 patients were finally evaluated. Table 1 depicts the participants' characteristics. Patients' average age was 37.90±18.57 (range 18-100) years (84.04% male). The Median trauma severity based on ISS in this series was 9 (4 -17) and the main cause of hospitalization in more than 70% of the patients was traffic accidents (pedestrian, motorcyclist, and car accidents).

Patients were divided in to three groups of neutrophilia (n = 1805), normal (n = 357), and neutropenia (n = 14) based on total neutrophil count at the time of admission to ICU. There were not any significant differences between groups regarding age distribution ($p = 0.634$). gender ($p = 0.544$), and trauma severity ($p = 0.197$).

In laboratory data, a statistically significant difference was observed between the groups only regarding the amount of K ($p = 0.002$), PTT ($p = 0.0022$), WBC ($p \leq 0.001$), Hb ($p = 0.0026$), and lymphocytes ($p \leq 0.001$).

3.2. Survival analysis

The median overall survival time was 40 (IQR: 22-51) days. Also, the median survival time for the normal, neutrope-

nia, and neutrophilia groups was 49 (IQR: 33 -47) days, 51 (IQR: 8- 51) days, and 38 (IQR: 26 - 52) days, respectively (p = 0.346). Figure 1 shows the Kaplan-Meier diagram for the groups adjusted for the ISS. Also, the log-rank test did not exhibit a statistically significant difference between the normal and neutropenia groups (p = 0.581). Likewise, no statistically significant difference was shown between the normal and neutrophilia groups (p = 0.437). However, the log-rank test showed a statistically significant difference between the three groups despite adjustment for ISS ($p \leq 0.001$). Multiple Cox analysis results are shown in Table 2. As the table depicts, for each unit increase in ISS, the hazard ratio increased by 2%. In ISS 9-17, the hazard ratio increased by 11% compared to ISS<4. Also, in ISS>17, the hazard ratio increased by 76% compared to ISS<4 in ICU-hospitalized patients. In addition, for each unit increase in blood pH, the hazard ratio decreased by 58%. In this sense, neutropenia had 15.06 times higher hazard ratio than the normal group.

4. Discussion

This retrospective study evaluated trauma patients' survival rate based on their neutrophil count (i.e., normal, neutropenia, and neutrophilia). Our findings denoted that after adjustment for ISS, the normal group's survival rate is greater than the neutropenia and neutrophilia groups. Furthermore, the Cox model revealed that each unit increase in the ISS increases the hazard ratio. Consistently, this model revealed that neutropenia increases the hazard ratio up to 15 times.

Neutrophils play a major role in inflammatory responses upon the occurrence or following traumatic injuries. Ensuing the trauma, neutrophils undergo significant functional changes, causing a rapid efflux of neutrophils from the bone marrow into the circulation (20). In compliance with previous studies, we showed that neutrophilia is more prevalent in the first 24 hours' post-trauma compared to neutropenia. Indeed, neutrophilia is the first post-trauma event due to the endogenous release of cortisol and catecholamine, resulting in neutrophil production and subsequent release from the bone marrow (21, 22). However, numerous studies have proposed that the increased release of neutrophils into the circulation may lead to the emergence of immature and dysfunctional neutrophil s(21-25), ultimately, resulting in peripheral tissue damage and multiple organ dysfunctions (MODS) (26-29). Hence, neutrophilia might not be correlated with the improved survival of traumatic patients as it was revealed that the normal group patients lived much longer than the neutrophilia group patients. On the other hand, neutropenia increased mortality more than 15 times in critical trauma patients. The low survival of neutropenia patients could be attributed to neutrophil dysfunction, thereby enhancing hospitalized trauma patients' sensitivity to healthcare-associated infections (30). Also, in a previous review study, by investigating the effect of trauma on neutrophil phenotype with the main purpose of using this knowledge to investigate the predictive potential of neutrophil changes on secondary complications in patients with traumatic injuries, they came to the same conclusion that changes in the markers and functions of neutrophils may be potential biomarkers that predict the outcome of trauma patients (17). In this sense, manipulating neutrophil frequency to improve patients' survival might be controversial. However, boosting neutrophils' germicidal and anti-infective capacity could be quite appealing. Of note, uncontrolled neutrophil hyperactivation may lead to significant tissue impairment, thereby contributing to development of acute respiratory distress syndrome (ARDS) and MOF. On the contrary, suppressing neutrophils' inflammatory response shortly after a traumatic insult to reduce immunity-induced tissue impairment may predispose patients to microbial infections. Therefore, developing strategies to create an equilibrium between these issues is urgently required to assist patients' recovery by modifying the immune response.

5. Limitations

The current study has several strengths such as including a large number of trauma patients. In addition, this study was conducted in the largest trauma center in southern Iran, which is a specialized center for trauma. Taking potential confounders into account (e.g., the ISS), as well as using laboratory information and ABG are other advantages of the current study. Nonetheless, the shortcomings of the current study should not also be neglected. For example, the retrospective design of study has its limitations. In this regard, we suggest the prospective investigation of neutrophils' effects on patients' survival in future studies. Also, we were not able to study neutrophil phenotypes, therefore, investigating their phenotypes is encouraged. Furthermore, our data on neutrophils was based on WBC percentages, hence, we suggest these data to be analyzed based on WBC number/L. Also, we reported neutrophils' normal range from different sources, which might have affected the results. However, we chose neutrophils' normal range based on hospital kits, which are used for correcting differential reports. Also, for neutrophil measurement, we did not have data on neutrophil counts at different time points after trauma, which should be taken into account in future studies. Finally, neutrophil changes in ICU-hospitalized patients also require further investigation.

6. Conclusion

Overall, the findings of the current study revealed that patients' survival rate in the normal group after adjustment for ISS was higher than the neutropenia and neutrophilia

groups. Also, the Cox model showed that the hazard ratio in the neutropenia group was 15 times higher than that of the normal group. Hence, fixing neutrophil disorder may plummet the hazard ratio in trauma patients. Indeed, one of the core findings of the current review is that the survival rate can be predicted using neutrophil count, which can be measured using a simple blood sample. In addition, neutrophil count could have a predictive value for the risk assessment of trauma patients. Moreover, we suggest neutrophil changes during patients' ICU hospitalization to be further investigated.

7. Declarations

7.1. Acknowledgments

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7.2. Competing Interests Statement

The authors of this study declared no competing interests.

7.3. Fundings and supports

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7.4. Authors' contribution

HG is the lead author and guarantor and contributed to interpreting the data and revising the manuscript. MV and SHP planned the study and led the drafting and revising of the manuscript. MV, MS, MH, SHP, PB and GS contributed to interpreting the data and drafting and revising the manuscript. All authors approved the submitted version of the manuscript. All authors have contributed to the preparation of the manuscript, have read, and approved the submitted manuscript. All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors and agree with the manuscript. The work is original and not under consideration by any other journal.

7.5. Data Availability

The data that support the findings of this study are available from the corresponding author, [HGH], upon reasonable request.

7.6. Ethics approval and consent to participate

The Ethics Committee approved this study at Shiraz University of Medical Sciences (IR.SUMS.SCHEANUT.REC.1400.006). Informed consent was obtained from all subjects or their legal guardians to use their data for research.

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