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Original Article

Time Course of Leukocyte Normalization Following Blunt Head Trauma: A Prospective Observational Cohort Study

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Background: This study aimed to characterise the time course of white blood cell (WBC) count normalisation in patients with isolated blunt head trauma and to examine whether this time course differs by injury severity (Glasgow Coma Scale, GCS) or computed tomography (CT) findings.

Methods: We conducted a prospective cohort study of 173 adult patients with blunt head trauma presenting to the surgical emergency department of Al-Zahra University Hospital, Isfahan, Iran, in 2020. WBC counts were measured at admission and every 8 hours for the first 48 hours, then daily until normalisation or discharge. Normalisation was defined as the first WBC value within the laboratory reference range (4,400–11,000/mm³), confirmed on the subsequent measurement. Time to normalisation was compared across GCS and CT-finding categories using the Kaplan–Meier method and log-rank test. Categorical comparisons used the chi-square or Fisher's exact test. Data were analysed using SPSS v22.

Results: At admission, 60% of patients (n = 104) had leukocytosis, 38% (n = 67) had a normal WBC count, and 1% (n = 2) had leukopenia. Mean WBC count at admission was 12,564.18/mm³ (95% CI 11,915.77–13,212.85) and was significantly higher in men than women (P = 0.011). Among the 104 patients with leukocytosis at admission, the mean time to normalisation was 2.32 days (95% CI 1.98–2.65) and did not differ significantly by CT finding (P = 0.614) or GCS category (P = 0.111).

***Conclusion*:** In patients with isolated blunt head trauma and no clinical evidence of infection, trauma-related leukocytosis generally resolved within approximately three days, regardless of GCS category or CT findings.

Keywords: White Blood Cell, Leukocyte Count, Blunt Head Trauma

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Introduction

Elevated white blood cell and neutrophil counts are usually nonspecific markers of infection, inflammation, tissue necrosis, bleeding, or physiological stress. Leukocytosis and neutrophilia are associated with tissue damage in the heart, intestine, skeletal muscle, and brain (1–5).

Numerous studies have shown that leukocytosis frequently accompanies acute traumatic brain injury. The underlying mechanism remains debated and may reflect structural damage to brain tissue or increased sympathetic and adrenal cortical activity. Traumatic brain injury is associated with increased circulating catecholamines due

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to stimulation of the adrenal medulla (1, 6, 7). Increased cortisol levels have also been reported in critically ill patients with acute head injury (8, 9).

Elevated cortisol and catecholamine levels are associated with the severity of head trauma and may be markers of neurological outcomes (6, 10). Catecholamines mobilise neutrophil stores, while corticosteroids reduce neutrophil egress. Inflammatory reactions following head trauma, mediated by lymphocytes and activated microglia, are of particular importance; this response is sometimes mistaken for early post-traumatic infection, prompting infectious-disease consultation and antibiotic therapy (6, 11, 12).

Head trauma patients exhibit many features of the acute-phase response, including increased cytokine levels. Intracranial cytokine production is thought to contribute to cerebral oedema; increased blood–brain barrier permeability and leukocyte activation after brain injury increase leukocyte adhesion (7, 13).

Several studies report that concussion and severe brain trauma are associated with leukocytosis at emergency department arrival, and that a higher degree of leukocytosis has been linked with worse clinical prognosis and more complications (1, 3, 14).

Because leukocytosis is common after head trauma and WBC count is frequently used to help identify infection, understanding the expected time course of WBC normalisation in patients without infection is clinically important. It may help avoid unnecessary antibiotic use and its associated risks, including antimicrobial resistance and prolonged hospitalisation (1, 6). Therefore, the present study investigated the time course of WBC normalisation following isolated blunt head trauma and its association with injury severity (GCS) and CT findings in adult patients without clinical evidence of infection.

Materials and Methods

Study Design and Setting

This was a prospective observational cohort study conducted in 2020. The study population included all patients referred to the surgical emergency department of Al-Zahra University Hospital, Isfahan, Iran, with isolated blunt head trauma.

Participants

Inclusion criteria

patients aged 18–70 years with mild, moderate, or severe non-penetrating (blunt) head trauma presenting to the Al-Zahra emergency department within six hours of injury.

Exclusion criteria

age <18 or >70 years; clinical criteria for brain death at presentation; any clinical evidence of infection or inflammation (defined below); use of medications known to affect WBC count; menstruation or pregnancy; malignancy; immunodeficiency; prior radiation therapy; vascular, haematologic, renal, adrenal, or hepatic disease; history of allergic reactions or recent vaccination; recent myocardial infarction or burns; hospitalisation or surgery shortly before the index trauma; need for neurosurgical intervention; head trauma attributed to seizure or substance/alcohol intoxication; and associated abdominal or thoracic trauma, long-bone fractures, extensive soft-tissue injury, or lacerations requiring surgical repair.

Non-Infected Status

Non-infected status at enrolment and throughout hospitalisation was determined by the treating surgical team based on the absence of fever (temperature >38.3°C), the absence of a clinically identified source of infection (e.g., pneumonia, urinary tract infection, wound infection), and the absence of radiographic findings suggestive of infection. Infection status was reassessed daily for the duration of the study period.

Data Collection

At emergency department presentation, an initial blood sample was drawn for WBC and platelet counts. Demographic characteristics, injury history, and laboratory results were recorded in a structured case-report form. WBC counts were repeated every 8 hours for the first 48 hours after admission, then daily until either

normalisation was confirmed or the patient was discharged.

Primary Outcome

The primary outcome was time to WBC normalisation, defined as the interval from hospital admission (time origin) to the first WBC measurement within the laboratory reference range (4,400–11,000/mm³), with normalisation confirmed by a subsequent in-range measurement. Patients who were discharged before WBC normalisation was documented were censored at the time of discharge for time-to-event analyses.

Statistical Analysis

Data were analysed using SPSS software, version 22. Continuous variables are presented as mean and 95% confidence interval; categorical variables are presented as frequencies and percentages.

The normality of continuous variables was assessed using the Shapiro–Wilk test, supplemented by visual inspection of histograms and Q–Q plots. Between-group comparisons of continuous variables were performed using the Mann–Whitney U test.

Categorical variables were compared using the chi-square test; Fisher's exact test was used instead where expected cell frequencies were small (<5), including for the location-of-trauma and CT-finding comparisons.

Time to WBC normalisation was estimated using the Kaplan–Meier method, with between-group comparisons by the log-rank test, and results are presented as mean time to normalisation alongside the 95% confidence interval.

Results

Of 173 eligible patients, the mean age was 38.67 years (95% CI 36.18–41.16); 86% (n = 149) were male. There was no significant difference in mean age between men and women (P=0.126).

Mean length of hospitalisation was 6.58 ± 3 days, with no significant difference by sex (P= 0.920). Mean admission temperature was 37.24°C (95% CI 37.18–37.30), with no significant relationship to sex (P= 0.082); no patient was hypothermic at admission.

Mean WBC count at admission was 12,564.18/mm³ (95% CI 11,915.77–13,212.85): 38% of patients (n = 67) had a normal WBC count, 60% (n = 104) had leukocytosis, and 1% (n = 2, both female) had leukopenia. Mean platelet count on the first hospital day was 200,570.55/mm³ (95% CI 192,225.18–208,915.92); 81.5% of patients (n = 141) had a normal platelet count.

Admission WBC count differed significantly by sex (P= 0.011; Table 1): 64% of men (n= 95) had leukocytosis, versus 54% of women (n = 13) with a normal count (P = 0.0018).

Two female patients (8%, n= 2/24) had leukopenia; no male patients had leukopenia. Platelet counts did not differ significantly by sex (81% of men (n = 121) and 83% of women [n = 20] had normal platelet counts, P = 0.803).

Trauma location was unrecorded/unknown for 53% of patients (n= 92). Among the 81 patients with a documented laterality, injury was most often right-sided in men (24.83%, n = 37) and left-sided in women (33%, n = 8), with no significant sex difference (P = 0.220). The most common CT findings were subarachnoid haemorrhage (26%, n = 45 overall) and contusion (25%, n = 43 overall), with no significant difference by sex (P = 0.252). Basic characteristics by sex are shown in **Table 1.**

CT findings were not significantly associated with GCS category overall (P = 0.082; **Table 2),** although contusion (26%, n = 11) and subarachnoid haemorrhage (23%, n = 10) were the most frequent findings among patients with poor consciousness (GCS ≤ 8).

Among the 104 patients with leukocytosis included in the time-to-event analysis, 78 achieved confirmed WBC normalisation during hospitalisation, while 26 were censored at discharge before confirmed normalisation. The mean time to WBC normalisation was 2.32 days (95% CI 1.98–2.65), with no significant difference by CT finding (P=0.614) or GCS category (P=0.111) **(Table 3).**

Table 1. Basic characteristics of patients with blunt head trauma by sex

Variables	Male (n=149)	Female (n=24)	P-value
Age (Year); Mean (95%CI)	37.81 (35.20-40.42)	44 (36.03-51.96)	0.126
Number of Days of Hospitalization; Mean (95%CI)	6.6 (6.09-7.11)	6.46 (5.46-7.27)	0.920
Body Temperature; Mean (95%CI)	37.22 (37.16-37.29)	37.34 (37.19-37.49)	0.082
Location of Trauma; n (%)			
Right	37 (24.83)	4 (17)	P= 0.220*
Left	31 (20.80)	8 (33)	
Both Sides	1 (0.67)	-	
Unknown	80 (53.80)	12 (50)	
CT Scan; n (%)			
Normal	3 (2)	2 (8)	P= 0.252**
Epidural Hematoma (EDH)	15 (10)	2 (8)	
Subdural Hematoma (SDH)	20 (13)	1 (4)	
Subarachnoid Hemorrhage (SAH)	36 (24)	9 (38)	
SAH with SDH or Intracerebral hemorrhage (IVH)	10 (7)	-	
Contusion	36 (24)	7 (29)	
Contusion Along with other Types of Hematomas	29 (20)	3 (13)	
Blood counts at the time of admission; Mean (95%CI) (/mm^3)			
White Blood Cell	12,922.60 (12,225.42-13,619.79)	10,383.75 (8,778.26-11,989.24)	0.011
Platelets	199,488.88 (191,132.53-207,765.43)	206,125 (178,005.77-234,244.23)	0.890
Grouping of Blood Parameters at the Time of Admission; n (%) (/mm3)			
White Blood Cell			
Normal (4,400-11,000/mm^3)	54 (36)	13 (54)	P= 0.0018***
Leukocytosis (>11,000/mm^3)	95 (64)	9 (38)	
Leukopenia (<4,400/mm^3)	-	2 (8)	
Platelets			
Normal (150,000-450,000/mm^3)	121 (81)	20 (83)	0.803
Thrombocytopenia (<150,000/mm^3)	28 (19)	4 (17)	

* Patients with bilateral and unspecified injury were excluded from the analysis

** Comparison with three groups was performed as SAH, contusion, and other types of hematomas. Patients with normal CT scan were excluded from the analysis

*** Patients with leukopenia were excluded from the analysis

Table 2. Frequency distribution of CT scan findings by GCS, by sex

CT Scan Findings	Male; n (%)				Female; n (%)				Total; n (%)				P-value
	Mild Injury	Moderate Damage	Severe Injury	Total	Mild Injury	Moderate Damage	Severe Injury	Total	Mild Injury	Moderate Damage	Severe Injury	Total	
Normal	2 (67)	1 (33)	-	3 (100)	1 (50)	-	1 (50)	2 (100)	3 (60)	1 (20)	1 (20)	5 (100)	
Epidural hematoma (EDH)	14 (93)	-	1 (7)	15 (100)	2 (100)	-	-	2 (100)	16 (94)	-	1 (6)	17 (100)	
Subdural hematoma (SDH)	14 (70)	3 (15)	3 (15)	20 (100)	1 (100)	-	-	1 (100)	15 (72)	3 (14)	3 (14)	21 (100)	
Subarachnoid hemorrhage (SAH)	26 (72)	1 (3)	9 (25)	36 (100)	7 (78)	1 (11)	1 (11)	9 (100)	33 (73)	2 (4)	10 (23)	45 (100)	0.082 **
SAH with SDH or Intracerebral hemorrhage (IVH)	8 (80)	2 (20)	-	10 (100)	-	-	-	-	8 (80)	2 (20)	-	10 (100)	
Contusion	23 (64)	5 (14)	8 (22)	36 (100)	4 (57)	-	3 (43)	7 (100)	27 (63)	5 (12)	11 (26)	43 (100)	
Contusion Along with other Types of Hematomas	18 (62)	7 (24)	4 (14)	29 (100)	3 (100)	-	-	3 (100)	21 (66)	7 (22)	4 (12)	32 (100)	
Total	105 (70)	19 (13)	25 (17)	149 (100)	18 (75)	1 (4)	5 (21)	24 (100)	123 (71)	20 (12)	30 (17)	173 (100)	

* GCS = 13-15: Mild Injury, GCS = 9-12: Moderate Injury and GSC ≤ 8: Severe Injury

** Comparison was made with three groups of SAH, Contusion and other types of hematomas. Patients with normal CT scans were excluded from the analysis.

Table 3. Time to WBC normalization by CT finding and GCS[1]

Variables	Number of Patients With leukocytosis at the Time of Admission	Number of Patients With Normal White Blood Cells After Admission	Mean Time to Normalization of White Blood Cells After Admission; Mean (95% CI)	P-Value
CT Scan Findings				
Normal	2	1	2 (2-2)	0.614
Epidural hematoma (EDH)	10	8	2 (1.47-2.52)	
Subdural hematoma (SDH)	10	5	3.6 (1-6.79)	
Subarachnoid hemorrhage (SAH)	24	19	2.15 (1.51-2.79)	
SAH with SDH or Intracerebral hemorrhage (IVH)	8	6	1.66 (1.01-2.32)	
Contusion	28	22	2.36 (1.95-2.80)	
Contusion Along with other Types of Hematomas	22	17	2.47 (1.66-3.27)	
Total	104	78	2.32 (1.98-2.65)	
GCS				
Mild Injury	69	49	2.06 (1.73-2.38)	0.111
Moderate Damage	14	13	2.61 (1.33-3.90)	
Severe Injury	21	16	2.87 (2.09-3.65)	
Total	104	78	2.32 (1.98-2.65)	

* The comparison was made using Kaplan-Meier method and Log Rank test. 1: two patients with leukopenia were not included in the time-to-normalization analysis

Discussion

This study describes the expected time course of WBC normalisation in patients with isolated blunt head trauma who had no clinical evidence of infection at presentation. Trauma to the head is associated with an acute-phase response, including catecholamine and cortisol release and leukocytosis, and this physiological leukocytosis has previously been proposed as a marker of injury severity (6, 15). However, our primary interest here is the practical clinical question that leukocytosis raises at the bedside.

In our cohort, 38% of patients (n = 67) had a normal WBC count, 60% (n = 104) had leukocytosis, and 1% (n = 2) had leukopenia at admission; 81.5% had a normal platelet count. This distribution is broadly consistent with prior reports of leukocytosis frequency after head trauma (1, 3, 6). Admission WBC count was significantly higher in men than women in our cohort, which contrasts with the finding of Chang et al., who reported no significant sex difference in WBC count after head trauma (16). This discrepancy may reflect differences in injury mechanism, sample size, or population between studies rather than a

true biological difference, and warrants further investigation.

The central finding of this study is that time to WBC normalisation did not differ significantly by CT finding or GCS category: the mean time to normalisation was approximately 2.3 days regardless of injury severity as assessed by these measures. This finding argues against using the rate of WBC normalisation itself as a severity marker and instead supports its use as a general reference window: because normalisation is expected within roughly three days irrespective of injury severity, leukocytosis persisting substantially beyond this window may justify further clinical assessment for secondary infection, although this hypothesis requires validation in comparative studies. We emphasise that this study did not compare infected and non-infected patients directly, so this three-day window should be interpreted as a descriptive reference derived from a non-infected cohort, not as a validated clinical decision threshold; prospective studies directly comparing time-to-normalisation trajectories in infected versus non-infected patients, alongside standard infection biomarkers, are needed to establish its diagnostic or stewardship value.

Other investigators have examined the relationship between admission WBC count and injury severity or outcome, which is a related but distinct question from the one addressed here. Gürkanlar et al. (6)

Reported a significant relationship between WBC count and GCS. Chang et al. (16) found a significant positive association between injury severity score and initial WBC count, although WBC count alone had limited value in individual-patient discrimination. Mukherjee et al. (17) reported that higher WBC and neutrophil counts, and neutrophil-to-lymphocyte ratio, were independently associated with longer hospital stay and worse outcome in paediatric traumatic brain injury. Paladino et al. (18)

Found that although trauma patients had higher WBC counts than uninjured comparators, both remained within the normal range, and concluded that WBC count added little diagnostic value in major trauma. Whalen et al. (19) and Hassan et al. (15), using different animal and mechanistic models, did not find a direct relationship between brain oedema and leukocyte accumulation. Taken together, admission WBC level and time to WBC normalisation appear to capture different clinical information; our data specifically address the latter.

Limitations

This study has several limitations. First, non-infected status was determined clinically, without a standardised biomarker protocol (CRP, procalcitonin) or routine microbiological culture; subclinical or early infection may have been misclassified as absent. Second, excluding patients with associated fractures, soft-tissue injury, or multi-system trauma produced a highly selected population of isolated blunt head trauma, which limits generalisability to the broader emergency department trauma population. Third, we did not include a comparator group of infected patients, so the observed normalisation window cannot be directly validated as a threshold for distinguishing infected from non-infected patients or as an antibiotic-stewardship decision rule; it should be regarded as hypothesis-generating rather than confirmatory. Fourth, this was a single-centre study with a relatively small number of female patients, limiting the precision of sex-stratified estimates. Fifth, the time-to-event comparisons were unadjusted, and residual confounding cannot be excluded. Finally, some categorical comparisons involved small cell counts, for which Fisher's exact test is reported as the more appropriate method.

Conclusion

In this prospective cohort of patients with isolated blunt head trauma and no clinical evidence of infection, 60% had leukocytosis at admission. WBC normalisation occurred at a similar rate regardless of GCS category or CT finding, with a mean time to normalisation of approximately 2.3 days. These findings provide a descriptive reference window: persistent leukocytosis beyond approximately three days may warrant further clinical evaluation for secondary infection. Because this

study did not directly evaluate antibiotic prescribing or compare infected with non-infected patients, these findings should be considered hypothesis-generating; prospective, comparative studies incorporating standard infection biomarkers are needed before this window is used as a formal antibiotic-stewardship threshold.

Declaration

Availability of data and materials

available from the corresponding author on reasonable request and subject to institutional approval

Conflict of Interest

The authors declare that they have no competing interests.

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Authors' contribution

All authors contributed to this project and article equally. Also all authors approved the final manuscript

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Ethics approval and consent to participate

None

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