Characteristics of the Course of Anemia as a Consequence of Combat Injuries in Military Servicemen Participating in High-Intensity Combat Actions

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ABSTRACT

Introduction:

During the full-scale war in Ukraine, the number of military personnel suffering from combat injuries with the development of anemia significantly increased. The work aimed to generalize and study the clinical and hematological characteristics of anemia in service members who received gunshot and blast injuries during combat operations.

Materials and Methods:

We examined 264 servicemen within 6 months (main group). They took part in hostilities and received gunshot and shrapnel wounds accompanied by blood loss. The control group consisted of 87 practically healthy service members. Complete blood test was performed on an automatic hematology analyser ABX Micros ES 60 of the company Horiba ABX. We determined the level of ferritin using the enzyme immunoassay method ELISA, the concentration of serum iron using the photometric method, and C-reactive protein (CRP) using the immunoturbidimetric latex method (quantitatively). The studies' results were processed using variational statistics. For each group of patients, the arithmetic mean (M), the standard deviation (б), and the error of the arithmetic mean (m) were calculated. We used the statistical processing package STATISTICA 10 (Statsoft Inc.).

Results:

Isolated injuries accounted for 50.89%, injuries to two or more anatomical areas—49.11%, injuries to limbs and large joints—30.6%, chest—14.66%, abdominal cavity—21.9%, and polytrauma—32.84%. All patients had blood loss, but its degree was not countable. The number of erythrocyte mass transfusions ranged from 2 to 7 (3.5 ± 0.7 on average). A total of 39.42% of victims were delivered in a severe condition, and 60.58% in a moderate condition. We divided the patients into the groups: 1st group ($n = 60$) where the blood was tested after in 1 month after injury, 2nd ($n = 42$)—2 months, 3rd ($n = 37$), 4th ($n = 31$), 5th ($n = 26$), and 6th ($n = 24$) in 3, 4, 5, and 6 months. We observed an initial increase in the number of leukocytes and platelets, and a decrease in the levels of erythrocytes, hemoglobin, MCV, and MCH, an increase in the absolute number of granulocytes and monocytes, and a decrease in the number of lymphocytes. In all, 7.9% of patients were diagnosed with severe anemia, 44.7% with moderate, and 40.4% with mild. The ferritin level exceeded the control group's results almost three times, while the iron content in the blood serum was significantly reduced. The hemoglobin level did not normalize within six months in most service members with anemia (because of severity or complications of the injuries and multiple surgeries). The CRP was elevated for 6 months after injury. Correlation analysis confirmed a positive relationship between the level of hemoglobin, the number of leukocytes, and the level of CRP.

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Preliminary results were not presented.

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Conclusions:
We view combat anemia as more than a hematology issue. It needs prompt, coordinated care from various fields. Interventions may include blood transfusions, surgery, and correcting iron levels. We can decrease the concentration of pro-inflammatory cytokines through anti-inflammatory therapy. Additionally, possible adrenergic modulation can promote erythropoiesis.

INTRODUCTION

Ukrainian militaries are the most vulnerable population for combat injuries. They are active in the conflict caused by Russia's aggression against Ukraine. The prevalence of anemia among them has increased as a result of combat injuries. These injuries involve severe damage to soft tissues and bones, and massive contamination. Delaying the evacuation to Role/Echelon III and IV hospitals worsens injuries and their prognosis.[1] During World War II, gunshots caused 99.98% of all injuries.[2] But, local wars have caused a rise in mine-blast injuries.[3,4] They account for 70% of all injuries in conflicts since World War II.[4] Mine-blast trauma has many causes. These are a blast wave (barotrauma), fragment damage, a fall or collision, and exposure to flames, smoke, and dust.[5] Combat-combined wounds are usually more severe than many traumas in peacetime. Gunshot trauma primarily results in penetrating wounds. These can lead to severe blood loss and shock. They need urgent surgery to stop the bleeding.[6]

Studies have proven that patients with severe injuries develop persistent anemia. It is because of impaired erythropoiesis.[7] This anemia and the need for RBC transfusions raise mortality. This is true regardless of shock severity.[8–10] This persistent anemia after an injury does not depend on blood plasma EPO levels. After an injury, EPO in plasma is two to eight times higher than in healthy controls.[11] Researchers link it to systemic inflammation.[12] Also, it causes hematopoietic progenitor cells to move to damaged tissues.[11,13,14] It reduces bone marrow cellularity and suppresses erythroid progenitor cell growth.[11,14] Finally, it alters iron metabolism[15,16] because of long-term stress. It causes adrenergic modulation.[17]

Often, the causes of anemia in injuries, such as trauma or the rupture of large vessels, are clear. However, identifying the source of anemia requires a diagnostic study in other instances.

MATERIALS AND METHODS

We did an observational study. It was a retrospective analysis of the medical records of patients treated at the National Military Medical Clinical Center "Main Military Clinical Hospital" of the Armed Forces of Ukraine (NMMCC "MMCH") from 2022 to 2024. We chose 264 injured service members from a random sample within 6 months (main group). They fought and got gunshot and shrapnel wounds, causing blood loss. They were hospitalized at the NMMCC "MMCH" at different times after the injury. The control group consisted of 87 almost healthy service members. The study utilized a longitudinal sampling approach. Every patient in the 6th cohort was also in the earlier ones. That means they were in the 1st cohort and the ones after it. It allowed us to track blood and chemical levels over time in the same group of patients. We followed and sampled patients over time. Each patient in the later cohorts (e.g., the 6th cohort) was also part of the earlier cohorts. This reflects the progression of their condition and treatment over time.

The study included only 1 complete blood test (CBT) for each patient in the group. For the patients in the 1st group, it was the first CBT at the initial admission to the NMMCC "MMCH." The team conducted the first CBT on day 30 after the injury for the 2nd group, on day 60 for the 3rd group, on day 90 for the 4th group, on day 120 for the 5th group, and on day 150 for the 6th group.

At NMMCC "MMCH" during treatment, these patients' CBT indicators were in the 1st group and partly in the 2nd and 3rd groups. After 1 to 3 months of treatment, the staff evacuated most patients to other facilities. Some of these patients were later re-admitted to NMMCC "MMCH" because of severe wounds or for surgery. We included these patients in the 2nd, 3rd, 4th, 5th, and 6th groups. Thus, we checked CBT in 264 wounded in the 1st group, 63 in the 2nd, 37 in the 3rd, 31 in the 4th, 26 in the 5th, and 19 in the 6th.

We used an automatic hematology analyser, ABX Micros ES 60, from Horiba ABX, for a CBT. We measured ferritin using the ELISA enzyme immunoassay method. We measured serum iron using the photometric method. We measured C-reactive protein (CRP) using a quantitative immunoturbidimetric latex method. We processed the results of the studies using variational statistics. For each group of patients, we calculated the mean (M), the standard deviation (σ), and the error of the mean (m). We used the statistical processing package STATISTICA 10 (Statsoft Inc.).

NMMCC's "MMCH," a Role 4 health care institution, admitted most of the wounded. It provides specialized and expert medical care after stabilizing at previous stages of care.

Patients mainly complained of pain in the wound area. They also experienced dizziness when standing, unconsciousness, headaches, and tinnitus. They felt a "pulsation" in their heads or bodies. Other symptoms included chest pain, shortness of breath, and palpitations during physical exertion.

RESULTS

When service members were admitted to the National Military Medical Clinical Center "Main Military Clinical Hospital" after receiving injuries and being stabilized (usually 3-7 days after the injury), a significant difference ($P < .05$) was found in comparison with similar data in the control group ($6.5 \pm 1.56 \times 10^9$/L and $247.63 \pm 6.34 \times 10^9$/L). There was an

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increase in the number of leukocytes ($9.07 \pm 1.37 \times 10^9$/L) and platelets ($404.62 \pm 3.01 \times 10^9$/L). In almost all examined patients, a decrease in the average levels of erythrocytes ($3.79 \pm 0.6 \times 10^{12}$/L), hemoglobin ($108.86 \pm 6.81$ g/L), and erythrocyte parameters such as MCV (83.07 ± 0.94 fl) and MCH (28.85 ± 1.03 pg) was observed in comparison with similar data in the control group ($4.99 \pm 0.46 \times 10^{12}$/L, 158.46 ± 1.18 g/L, 90.53 ± 0.58 fl, 31.61 ± 0.20 pg, respectively). The leukocyte formula in wounded service members showed a significant ($P < .001$) increase in the absolute number of granulocytes ($6.4 \pm 1.91 \times 10^9$/L) and monocytes ($0.59 \pm 0.16 \times 10^9$/L), alongside a decrease in the absolute number
of blood lymphocytes ($1.99 \pm 0.60 \times 10^9$/L) compared to the control group ($3.95 \pm 1.32 \times 10^9$/L, $0.31 \pm 0.11 \times 10^9$/L, and $2.3 \pm 0.61 \times 10^9$/L, respectively).

The severity of anemia revealed that 7.9% of patients were diagnosed with severe anemia, 44.7% had moderate anemia, and 40.4% had mild anemia. The majority of these cases were of the normocytic and normochromic type. According to our results, anemia in wounded service members was normocytic in 86.76% of cases and normochromic in 86.76% of cases.

The analysis of biochemical parameters in wounded service members with anemia showed that the level of ferritin, 367.56 ± 14.8 ng/L, exceeded the control group's result (135.9 ± 13.5 ng/L) by almost three times. In contrast, the iron content in blood serum (9.64 ± 0.9 μmol/L) was significantly ($P < .001$) reduced compared to the control group (14.5 ± 0.8 μmol/L). Additionally, the concentration of CRP (106.43 ± 5.6 g/L) in the injured service members was considerably higher than in the control group (5.48 ± 0.54 g/L).

Dynamic monitoring of patients established that in 1 month after the injury, the number of leukocytes in the patients was significantly ($P1 < .001$) higher than the results obtained in the control group (**Table 1**).

The level of leukocytes in injured service members was significantly higher than in the control group ($P1 < .001$) and remained higher in service members from other groups throughout the entire observation period ($P2 < .001$) (**Table 1**). We also observed a significant increase in the concentration of platelets in injured patients compared to the control group. This elevated level of blood platelets was maintained throughout the 6-month observation period.

The number of erythrocytes in the patients' blood 1 month after the injury was significantly ($P1 < .001$) reduced compared to the data of the control group patients. Two months after the injury, the number of erythrocytes in the patients was still significantly ($P1 < .001$) lower than in the control group, but was significantly higher ($P2 < .001$) than in the wounded at the end of the first month of treatment (**Table 1**). By the end of the 3rd month after the injury, the number of erythrocytes was significantly higher than that of patients in the control group and in the 1st and 2nd groups of wounded. However, the number of peripheral blood erythrocytes did not reach the values of the control group until the end of the 6th month of observation (**Table 1**).

Similar dynamics were observed regarding changes in hemoglobin and hematocrit levels. Positive changes were noted in these indicators starting from the second month of observation. However, normalization was not observed during the 6 months of treatment (**Table 1**).

The average volume of erythrocytes (MCV) in the wounded was significantly reduced 1 month after the injury compared to the control group and continued to decrease until the fourth month. From the fourth month, MCV values tended to increase, but no significant difference was found between the control group and patients in the 1st, 2nd, 3rd, 4th, and 6th groups.

The average content of hemoglobin in erythrocytes (MCH) in service members was significantly reduced 1 month after the injury compared to the control group's data. The MCH value gradually decreased until the fourth month of observation, and a tendency to increase was noted from the fourth month. However, the MCH index did not reach typical values within 6 months.

The average concentration of hemoglobin in erythrocytes (MCHC) remained below average values until the end of the sixth month of treatment. It showed a slight increase in the first month, continued to decrease until the fifth month, and then increased slightly from the fifth month onward, but it did not reach average values.

The erythrocyte distribution width (RDW) did not differ from standard values initially but gradually increased, reaching maximum values between 4 and 6 months. This indicates the presence of two populations of erythrocytes: older erythrocytes and those formed after the injury.

Within 1 month after the injury, an increase in the absolute number of blood granulocytes to $8.96 \pm 0.14 \times 10^9$/L and a decrease in the absolute number of lymphocytes to $1.82 \pm 0.008 \times 10^9$/L were observed compared to the data of the control group ($3.96 \pm 0.14 \times 10^9$/L and $2.3 \pm 0.07 \times 10^9$/L, respectively) ($P < .001$) (Figure 1, Figure 2).

A characteristic feature of the blood of the wounded 1 month after the injury was a significant ($P < .001$) increase in the number of monocytes ($0.59 \pm 0.02 \times 10^9$/L) compared to the control group ($0.31 \pm 0.03 \times 10^9$/L) (Figure 3). This increased level of blood monocytes ($P < .001$) was maintained during the 2nd ($0.48 \pm 0.01 \times 10^9$/L), 3rd ($0.47 \pm 0.03 \times 10^9$/L), and 4th ($0.41 \pm 0.03 \times 10^9$/L) months of obse rvation. Only after 5 and 6 months, the absolute levels of blood monocytes ($0.36 \pm 0.03 \times 10^9$/l and $0.37 \pm 0.03 \times 10^9$/l, respectively) practically did not differ ($P > .05$) from the control group (Figure 3).

The wounded with anemia had a higher CRP level (106.43 ± 5.6 g/L) than the control group (5.48 ± 0.54 g/L) during the entire observation period ($P1 < .001$). At the end of the 2nd month of observation, the CRP level (43.95 ± 10.09 g/L) decreased to almost half of the values

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Table 1. The Results of the Study of Peripheral Blood in the Wounded During 6 Months of Observation (M± 2 m)

	Groups of patients						
Parameter	**Control** $n = 87$	**1st** $n = 264$	**2nd** $n = 63$	**3rd** $n = 37$	**4th** $n = 31$	**5th** $n = 26$	**6th** $n = 19$
WBC, $\times 10^9$/L	6.64 ± 0.19	11.73 ± 0.3 $P1 < .001$	7.76 ± 0.41 $P1 < .01$ $P2 < .001$	7.11 ± 0.35 $P1 > .05$ $P2 < .001$	7.32 ± 0.44 $P1 > .05$ $P2 < .001$	7.38 ± 0.45 $P1 > .05$ $P2 < .001$	6.94 ± 0.4 $P1 > .05$ $P2 < .001$
RBC, $\times 10^{12}$/L	5.05 ± 0.05	3.35 ± 0.03 $P1 < .001$	3.69 ± 0.08 $P1 < .001$ $P2 < .001$	4.31 ± 0.1 $P1 < .001$ $P2 < .001$	4.08 ± 0.14 $P1 < .001$ $P2 < .001$	3.94 ± 0.17 $P1 < .001$ $P2 < .001$	3.93 ± 0.14 $P1 < .001$ $P2 < .001$
Hemoglobin, g/L	158.46 ± 1.18	99.69 ± 0.93 $P1 < .001$	106.40 ± 2.12 $P1 < .001$ $P2 < .01$	118.11 ± 2.66 $P1 < .001$ $P2 < .001$	110.77 ± 3.54 $P1 < .001$ $P2 < .001$	109.85 ± 4.78 $P1 < .001$	114.42 ± 3.15 $P1 < .001$ $P2 < .001$
HCT, %	45.72 ± 0.47	28.48 ± 0.28 $P1 < .001$	30.86 ± 0.67 $P1 < .001$ $P2 < .001$	35.25 ± 0.85 $P1 < .001$ $P2 < .001$	33.05 ± 1.00 $P1 < .001$ $P2 < .001$	32.88 ± 1.35 $P1 < .001$ $P2 < .001$	33.53 ± 1.15 $P1 < .001$ $P2 < .001$
MCV, fl	90.53 ± 0.58	85.23 ± 0.24 $P1 < .001$	83.52 ± 0.65 $P1 < .001$ $P2 < .01$	82.14 ± 0.87 $P1 < .001$ $P2 < .001$	81.87 ± 1.32 $P1 < .001$ $P2 < .001$	83.85 ± 1.46 $P1 < .001$ $P2 > .05$	85.12 ± 1.75 $P1 < .001$ $P2 > .05$
MCH, pg	31.61 ± 0.20	29.87 ± 0.09 $P1 < .001$	28.86 ± 0.14 $P1 < .001$ $P2 < .001$	27.67 ± 0.36 $P1 < .001$ $P2 < .001$	27.47 ± 0.62 $P1 < .001$ $P2 < .001$	28.00 ± 0.61 $P1 < .001$ $P2 < .001$	29.46 ± 0.63 $P1 < .001$ $P2 > .05$
MCHC, g/dL	346.09 ± 2.26	351.03 ± 1.12 $P1 < .05$	346.49 ± 2.58 $P1 > .05$ $P2 > .05$	336.71 ± 2.13 $P1 < .05$ $P2 < .001$	335.90 ± 5.44 $P1 < .05$ $P2 < .001$	334.19 ± 5.20 $P1 < .05$ $P2 < .001$	346.18 ± 3.91 $P1 > .05$ $P2 > .05$
RDW, %	14.04 ± 0.09	14.95 ± 0.08 $P1 < .001$	15.28 ± 0.16 $P1 < .001$ $P2 > .05$	15.51 ± 0.24 $P1 < .001$ $P2 < .05$	16.04 ± 0.35 $P1 < .001$ $P2 < .001$	16.00 ± 0.32 $P1 < .001$ $P2 < .001$	15.93 ± 0.26 $P1 < .001$ $P2 < .01$
PLT, $\times 10^9$/L	247.63 ± 6.34	394.41 ± 12.55 $P1 < .001$ $P2 > .05$	343.97 ± 14.17 $P1 < .001$ $P2 > .05$	358.77 ± 15.14 $P1 < .001$ $P2 > .05$	417.42 ± 23.67 $P1 < .001$ $P2 > .05$	408.50 ± 24.05 $P1 < .001$ $P2 > .05$	387.74 ± 17.0 $P1 < .001$ $P2 > .05$
C-reactive protein, mg/L	5.48 ± 0.54	106.43 ± 5.61 $P1 < .001$	43.95 ± 10.09 $P1 < .001$ $P2 < .001$	31.42 ± 7.77 $P1 < .001$ $P2 < .001$	21.74 ± 7.12 $P1 < .001$ $P2 < .001$	26.13 ± 7.63 $P1 < .001$ $P2 < .001$	34.60 ± 11.25 $P1 < .001$ $P2 < .001$

*P*1—significance of the differences of average values in patients of this group in comparison with average values in patients of the control group.
*P*2—significance of the differences of average values in patients of this group in comparison with average values in patients of the 1st group.

at the end of the 1st month after the injury ($P2 < .001$). In the 3rd (31.42 ± 3.77 g/L), 4th (21.74 ± 7.12 g/L), 5th (26.13 ± 7.63 g/L), and 6th (34.6 ± 11.25 g/L) months, the CRP level was significantly higher ($P1 < .001$) than in the control group and the 1st group ($P2 < .001$). The concentration of ferritin was elevated in almost all of the wounded.

Correlation and regression analysis (Supplementary Figure 1) found a link between leukocyte levels and CRP content ($r = 0.36$, $P < .05$). It also found a link between leukocyte and ferritin levels ($r = 0.46$, $P < .05$) (Supplementary Figure 2). The data show that shrapnel and gunshot wounds cause blood loss. This leads to posthemorrhagic anemia in the wounded. After 3 to 7 days of stabilizing the injuries, leukocytosis, thrombocytosis, and anemia appear. The anemia is usually normochromic and normocytic. Wounded service members' peripheral blood shows some changes. There is an increase in granulocytes and monocytes and a decrease in lymphocytes. Anemia in injured service members occurs with a rise in CRP and ferritin.

DISCUSSION

We studied the clinical and blood-related features of anemia in service members with combat wounds in high-intensity, long-term war zones. Combat trauma, in conditions of increased fire density from small arms and the widespread use of explosive ammunition, leads to a higher incidence of wound polytrauma. This results in increased blood loss at the prehospital stage and severe shock, necessitating rapid surgical intervention to stop the bleeding. Researchers have found that gunshot injuries often cause multiple combined lesions, with their frequency ranging from 25% to 60%. These types of wounds were observed in 14% of military personnel even during World War II.[1–5,18,19]

Acute uncontrolled massive blood loss is the main complication. It is a leading cause of death in injured service members, especially those with gunshot and shrapnel wounds.[20] Military doctors found that 50% of patients with severe bleeding do not get timely care. They die before reaching the hospital. Also, doctors find that 30% of patients die within 2

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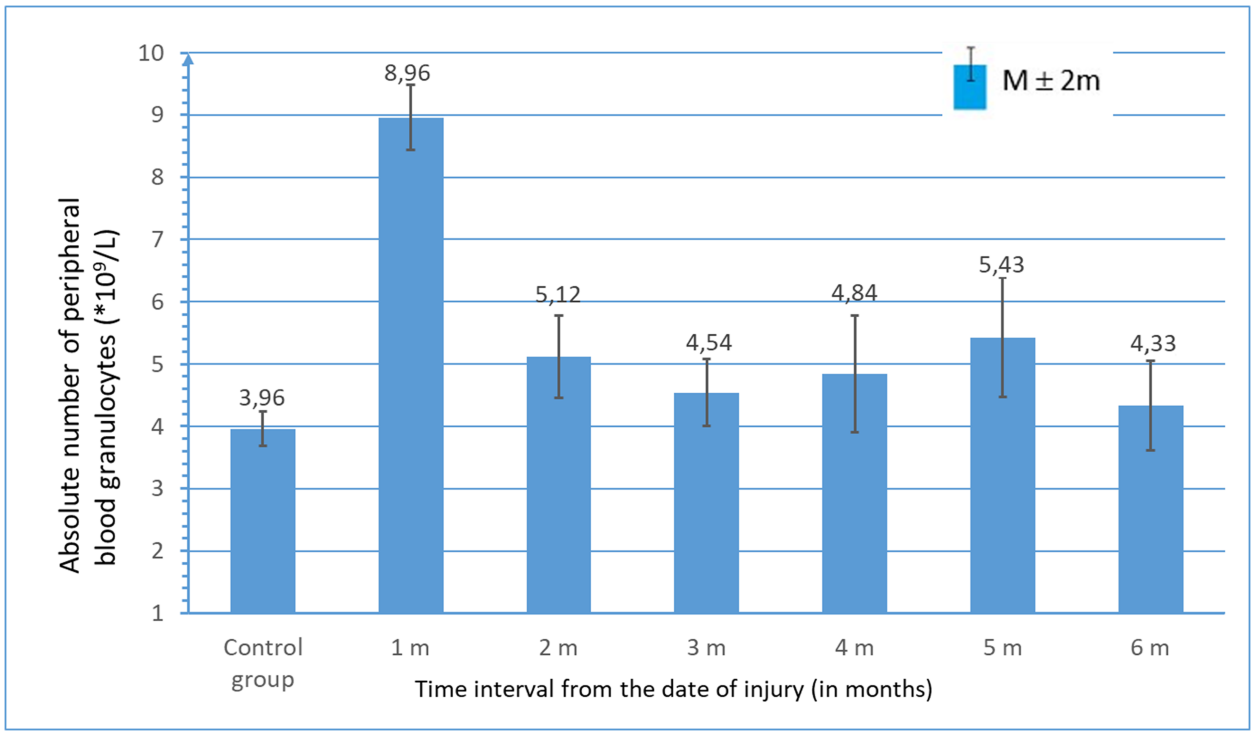


Figure 1. The absolute number of blood granulocytes at different time intervals from the injury.

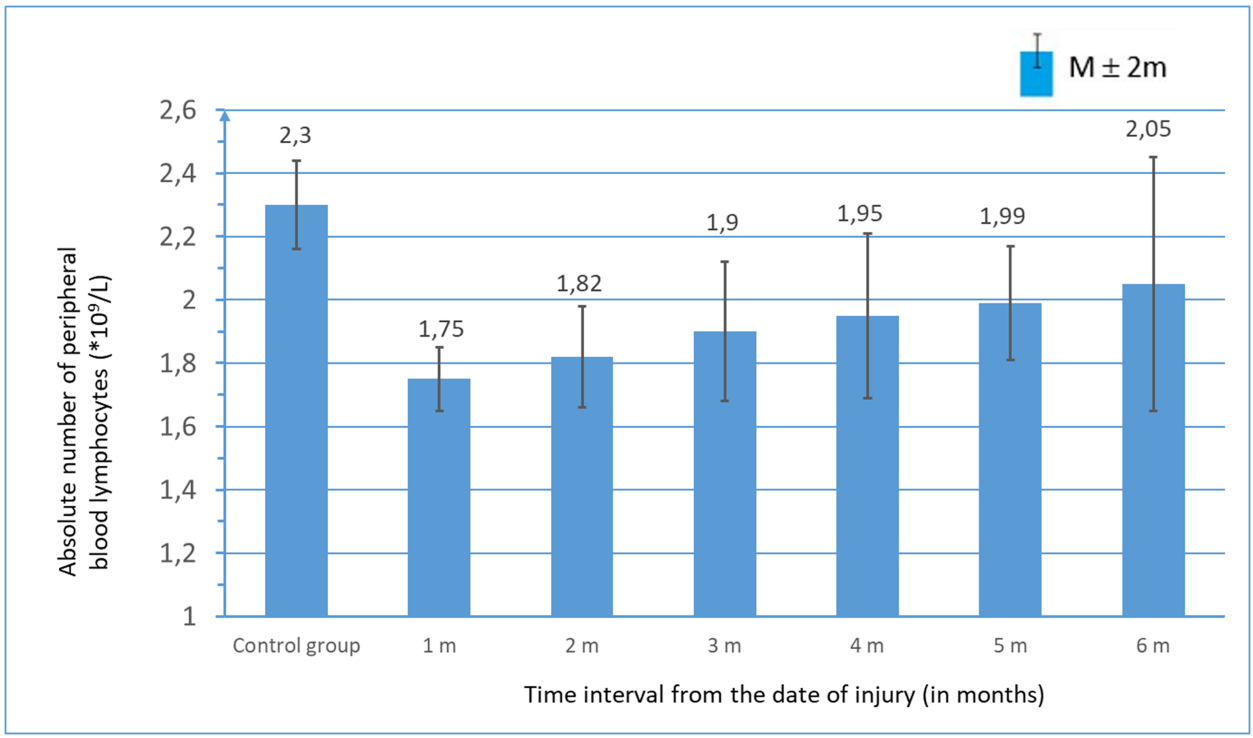


Figure 2. The absolute number of blood lymphocytes at different time intervals from the injury.

h of being moved to the ICU.[21,22] So, the "golden hour" concept is crucial for these patients. The first hour after an injury is key to survival.[23]

A shorter time from care to hospitalization, along with modern tests and treatments, lowers the mortality rate of such patients.[24] Damage control resuscitation is a new way to treat

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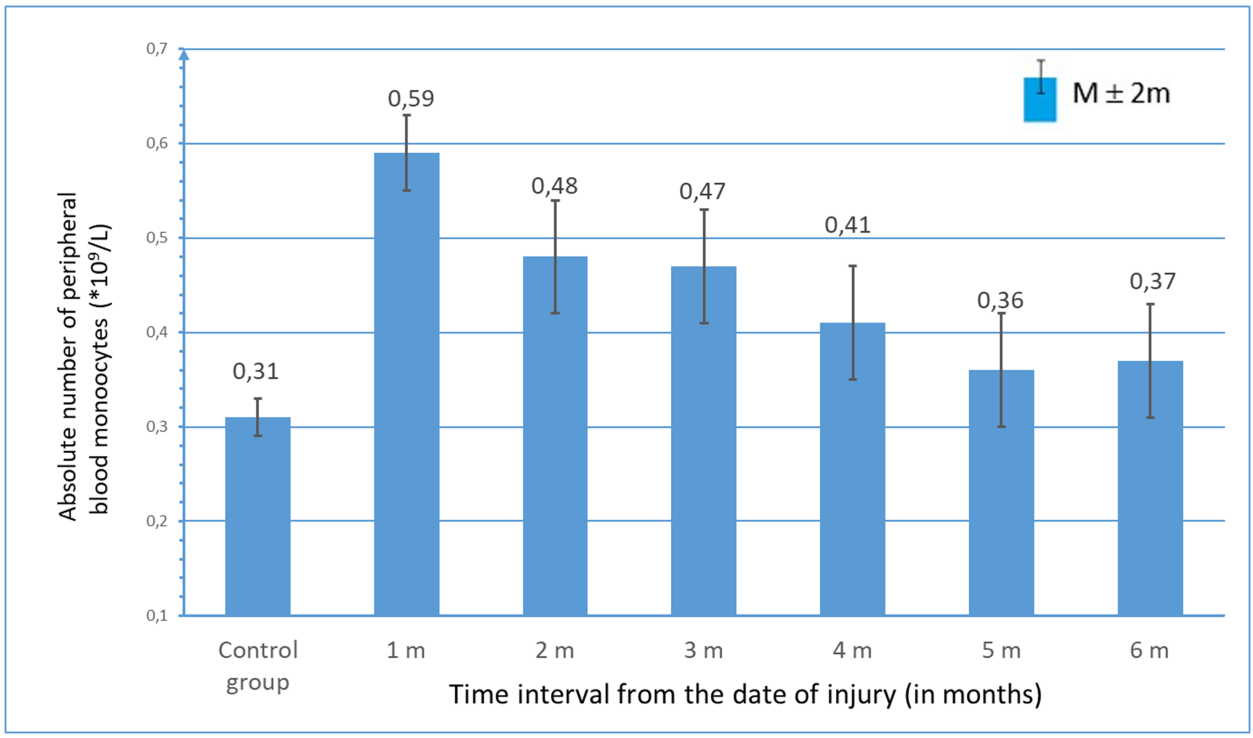


Figure 3. The absolute number of blood monocytes at different time intervals from the injury.

patients with severe bleeding from injuries. It is also known as intensive damage control therapy. It aims to restore homeostasis and reduce mortality.[25,26] Recently, a new concept, Remote Damage Control Resuscitation, has emerged. This strategy involves applying Damage control resuscitation at the prehospital stage.

Medical records show that 7.9% of service members had severe posthemorrhagic anemia. These wounded during combat operations suffered severe injuries to large vessels. This caused significant blood loss. Combat medics applied the Remote Damage Control Resuscitation strategy to them (Case 1).

In a literature review, J.A. Munley et al.[16] analyzed the pathogenetic mechanisms of anemia development in injuries. Hypercatecholaminemia has various effects. It increases pro-inflammatory cytokines after injury, such as interleukin (IL)-1α, IL-1β, IL-6, and TNF-α.[11,14,27,28] It also raises CRP[29] and nitric oxide.

After trauma, a change in these cytokines harms erythropoiesis in patients. In injuries, pro-inflammatory cytokines rise. At the same time, IL-10 levels fall. The IL-10 stimulates the growth of erythroid colonies.[30]

Pro-inflammatory cytokines harm erythropoiesis. They expand the myeloid lineage at the expense of erythroid precursors in the bone marrow (IL-1α, IL-1β).[31] They also induce the production of the iron-binding peptide hepcidin (IL-6). This leads to an inadequate decrease in blood iron levels after acute blood loss.[32] They also inhibit the growth of erythroid precursors (TNF-α).[33] Pro-inflammatory cytokines remain high for a long time after injury.[27,28,33,34] This means the wounded body is still inflamed.[28] Elevated CRP is an acute phase reactant. It indicates anemia-related inflammation.[29]

Inflammatory conditions disrupt iron homeostasis, which is necessary for adequate erythropoiesis.[35] The liver plays a crucial role in these processes. It is the leading producer of hepcidin, a peptide hormone. It regulates the release of free iron. It degrades the iron transport protein, ferroportin.[35,36] The liver is a key source of IL-6. It increases hepcidin expression and promotes iron sequestration.[35] The IL-1β is a potent inducer of hepcidin expression.[14]

Trauma patients show widespread inflammation and increased systemic hepcidin. This traps iron in the reticuloendothelial system. As a result, the body cannot produce hemoglobin during erythropoiesis. This leads to inflammatory anemia.[35,37] This condition features average or high erythrocyte indicators, such as MCV and MCH. Ferritin and CRP levels are usually elevated.

As an example, we analyzed a report from the medical history.

Case 1

A 54-year-old junior sergeant was wounded by enemy shelling in the combat zone on January 25, 2023. Shrapnel from the shells had penetrated his chest. Diagnosis included: "Explosive injury (25.01.23). Fire combined shrapnel thoraco-abdominal-skeletal wound: gunshot blind

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penetrating thoraco-abdominal wound on the left. It damaged the lower lobe of the left lung, diaphragm, and splenic corner of the colon. Also, there are many gunshot fractures of the 5th, 6th, 7th, and 10th ribs on the left. Left-sided hemopneumothorax. Right-sided pneumothorax. Post-traumatic pneumonitis on the left. Damage to the left dome of the diaphragm. Necrosis of the splenic corner of the colon complicates it due to entrapment. Blunt cardiac injury. Fracture of the internal epicondyle of the right thigh and right tibia. Post-traumatic bronchopleural fistula on the left, limited empyema of the pleura. Functioning transversostomy. Condition after skin flap transplantation in the left thigh area."

A CBT on admission (31.01) to the NMMCC "MMCH" after primary care in the military mobile hospital (transfusion of erythrocyte mass, fresh frozen plasma, albumins) found normochromic, normocytic anemia. He had leukocytosis, neutrophilia, absolute monocytosis, and lymphopenia (Supplementary Table 1). Anemia in patient S. persisted during 5 months of observation. After 1 month of treatment, patient's S. blood lymphocytes were $2.3 \pm 0.5 \times 10^9$/L. This was similar to the control group. In contrast, monocytes only normalized after three months. They were the same as in the control group ($0.29 \pm 0.11 \times 10^9$/L). CRP and ferritin levels were much higher than in the control group (CRP 5.48 ± 0.54 g/L and ferritin 135.9 ± 13.5 ng/L). In contrast, blood serum iron was much lower than in healthy individuals (14.5 ± 0.8 μmol/L) (Supplementary Table 2).

Anemia of inflammation develops after injuries and can persist for some time.[6–8,29–31] Its pathogenesis results from three main factors. First, adrenergic modulation of erythropoiesis.[17] Second, pro-inflammatory cytokines harm erythropoiesis.[11,33,34] Third, long-term disturbances in iron metabolism.[32] Our studies support the researchers' findings about long-lasting anemia after injuries.[9,10,38] Some service members in our study groups had anemia from combat injuries. Their hemoglobin levels did not normalise within 6 months. It is likely because of the injuries, complications, and surgeries. Correlation analysis confirmed a link between military personnel's hemoglobin, leukocyte, and CRP levels. The CRP level, an inflammation indicator, stayed high for 6 months after the injury. We found a relationship between hemoglobin levels, leukocyte counts, and CRP levels. In our study, we observed persistent anemia (within 6 months). Several factors could explain it: adrenergic modulation of erythropoiesis,[16] surgery, and inflammation. Some patients in the group had many surgeries during medical evacuations. Inflammation affects the further release of cytokines.[29] We observed an increased CRP level. Heidari B. says that elevated CRP levels show inflammation linked to anemia. They are an acute phase reactant.[29] Burn trauma raises cortisol, catecholamines, cytokines, and acute-phase proteins. It does so, like wounds or other combat injuries. This happens within 3 years after the burn.[33] Hypercatecholaminemia has various effects on the body. It increases the expression of cytokines that inhibit erythropoiesis. These include IL-1α, IL-2, IL-6, IL-10, and TGF-β.[39]

CONCLUSIONS

We view combat anemia as more than a hematology issue. It needs prompt, coordinated care from various fields. Interventions may include blood transfusions, surgery, and correcting iron levels. We can decrease the concentration of pro-inflammatory cytokines through anti-inflammatory therapy. Additionally, possible adrenergic modulation can promote erythropoiesis.

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SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. All data are freely accessible. (A sample list of data availability statements from Oxford University Press can be found here.)

INSTITUTIONAL REVIEW BOARD (HUMAN SUBJECTS)

Not applicable.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)

Not applicable.

INSTITUTIONAL CLEARANCE

Institutional clearance approved.

INDIVIDUAL AUTHOR CONTRIBUTION STATEMENT

S.A.H. assisted in concept and design of the study, data collection, data analysis and interpretation, writing an article.

G.V.O. assisted in data analysis and interpretation, writing an article, editing the article, the final approval of the article.

I.P.G. assisted in data analysis and interpretation, writing an article, editing the article, the final approval of the article.

O.Y.A. assisted in concept and design of the study, data collection, data analysis and interpretation, writing an article.

A.V.H. assisted in data analysis and interpretation, writing an article, editing the article.

V.M.O. assisted in data collection.

I.A.K. assisted in data collection, data analysis and interpretation, editing the article.

Ilona V. Malysh assisted in data collection.

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S.V.T. assisted in data collection.
A.Y.H. assisted in data collection.
V.Y.C. assisted in data collection.
All authors read and approved the final manuscript.

CLINICAL TRIAL REGISTRATION

Not applicable.

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