



# Types and outcomes of cytopenia in critically ill patients

Zahra Bagheri<sup>1</sup>, Zohreh Labbani-Motlagh<sup>1</sup> , Mahtabalsadat Mirjalili<sup>2</sup>, Iman Karimzadeh<sup>2</sup>  & Hossein Khalili<sup>\*1</sup> 

<sup>1</sup>Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Clinical Pharmacy, Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

\*Author for correspondence: Tel.: +98 216 695 4709; Fax: +98 216 695 4709; [Khalilih@sina.tums.ac.ir](mailto:Khalilih@sina.tums.ac.ir)

Cytopenia is common complication in critically ill patients. **Aim:** Incidence and pattern of different types of cytopenia as well as its impact on mortality and length of stay in critically ill patients were evaluated. **Methods:** Critically ill patients with any kind of cytopenia for more than 2 days were evaluated. **Results:** Anemia was the most common type of cytopenia in the patients (99.14%), followed by lymphocytopenia (32.17%), thrombocytopenia (27.82%), and leukopenia (19.13%). Mortality rate was significantly higher in patients with anemia ( $p < 0.0001$ ), thrombocytopenia ( $p < 0.0001$ ), leukopenia ( $p < 0.0001$ ), neutropenia ( $p = 0.004$ ), lymphopenia ( $p = 0.002$ ) and pancytopenia ( $p < 0.0001$ ). Higher duration of anemia, lymphopenia and thrombocytopenia were associated with longer intensive care unit stay ( $p < 0.0001$ ,  $p < 0.0001$  and  $p < 0.001$ , respectively). **Conclusion:** Among all assessed variables, incidence of thrombocytopenia could independently predict the mortality.

First draft submitted: 13 March 2020; Accepted for publication: 4 May 2020; Published online: 4 June 2020

**Keywords:** critically ill • cytopenia • intensive care unit • mortality

Cytopenia is defined as blood cell counts below the lower limit of normal. Several types of cytopenia exist, depending on which blood cell line is decreased, including anemia, thrombocytopenia, lymphopenia, leukopenia and neutropenia [1]. According to the WHO, anemia is defined as hemoglobin (Hgb) concentration below 12 g/dl for females and 13 g/dl for males.

About 60–70% of critically ill patients have mean Hgb concentration below 12 g/dl at admission and 40–50% experience anemia during their ICU stay [2]. Critically ill patients who did not receive transfusions had a mean reduction of 0.52 g/dl/day in their Hgb level [3]. Even after intensive care unit (ICU) discharge, about half of the patients suffer from anemia for 6 months [4].

Various conditions in critically ill patients such as blood loss, inflammation and decreased erythropoietin production can lead to anemia [5]. Medicines can induce anemia via bone marrow suppression, interacting with nutrients [6], reducing erythropoietin synthesis and bleeding induction [5]. The relation between anemia with mortality and morbidity has been well established. In critically ill patients, anemia results in an increase in mortality rate, myocardial infarction, mechanical ventilation duration [5] and hospitalization period [7].

Thrombocytopenia is defined as a platelet count below 150,000 cells/ $\mu$ l. The incidence of thrombocytopenia in critically ill patients is about 20–25% in different populations [8]. It has been demonstrated that early thrombocytopenia (on day 4 after ICU admission) is more prevalent than late thrombocytopenia (on day 14 after ICU admission) but late thrombocytopenia is more predictive of death than earlier in the ICU course [9]. Sepsis (52%), disseminated intravascular coagulation (25%), drug-induced thrombocytopenia (10%), massive blood loss (8%), immune thrombocytopenia (3%), thrombotic microangiopathy (1%) and heparin-induced thrombocytopenia (1%) are the most common causes of thrombocytopenia [8]. Some conditions, such as bilirubin rise, cardiac arrest, having a central catheter, heparin use and respiratory failure are risk factors for thrombocytopenia [10]. Even in critically ill patients without documented thrombocytopenia, a 30% decrease in platelet counts within normal

range leads to higher mortality rates [11]. Critically ill patients being thrombocytopenic for more than 4 days have 4–6 folds higher mortality rates in comparison to normocytic one [8].

Leukopenia in adults is defined as white blood cells count below 4000 cells/ $\mu\text{l}$  [12]. Severe leukopenia is caused by hematologic malignancies, aplastic anemia and hairy cell leukemia [13]. Sepsis or other serious illnesses can cause lymphopenia via inducing lymphocyte apoptosis [14]. Bacterial or fungal sepsis (24%), postoperative state (22%), malignancy (17%), glucocorticoid administration (15%) chemotherapy and/or radiotherapy (9%) and hemorrhage or trauma (8%) are responsible for lymphopenia [15]. One study showed that ICU patients with low baseline lymphocyte count and persistent lymphopenia on the third day after ICU admission were more prone to ICU acquired infection [16]. Critically ill patients with persistent lymphocytopenia after ICU admission are more prone to ICU acquired infections and have higher mortality rates than normal individuals [16,17].

Neutropenia is a neutrophil count below 1500 cells/ $\mu\text{l}$  and severe neutropenia describes the situation where the count of neutrophils is less than 500 cells/ $\mu\text{l}$  [13]. The prevalence of neutropenia in the US population varies from 0.38 to 4.5%, according to race (black, white and Mexican–American) [18]. Major causes of neutropenia are metastatic carcinoma, lymphoma and chemotherapeutic agents [19].

The prevalence of each type of cytopenia varies, according to cytopenic cell line, race, age, sex and clinical condition of patients [2,8]. Cytopenia is associated with longer hospitalization and ICU stay, higher risk of myocardial infraction, increased need for mechanical ventilation, higher rates of ICU acquired infection and mortality [10,16,20,21]. Thus, clarifying the causes of cytopenia and its pattern helps the clinicians to choose the best treatment plan and reduce the cost imposed on patients and the healthcare system. The aim of this study is to evaluate the pattern of cytopenia as well as its plausible impact on mortality and ICU length of stay (LOS) in critically ill patients.

## Methods

This cross-sectional study was conducted in the ICU of Imam Khomeini Teaching Hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran from 22 July 2016 to 15 May 2017. The study was approved by the Hospital Medical Ethics Committee and Institutional Review Board, and written informed consents were obtained from the patients or their family members. A sample size of 117 patients was calculated considering power of 80%, alpha error of 5% and the dropout rate of 10%.

ICU patients more than 18 years old presenting with any kind of cytopenia for more than 2 days were randomly selected and followed-up until being discharged from the ICU or being expired. The patients' demographic and clinical data including, sex, age, the reason for admission, underlying diseases, medication history, drugs administered during the ICU stay and duration of ICU stay were all recorded. Prescribed drugs were categorized into 14 groups based on The Anatomical Therapeutic Chemical classification system [22]. The severity and the causes of each type of cytopenia were classified based on previous related studies [12,13,23–25].

The definitive diagnosis of cytopenia was made if at least two consecutive peripheral blood smears or complete blood counts showed blood cell counts below the lower limit of normal. The complete data regarding the patients' cytopenia, including the onset (whether the patients had cytopenia on admission or they developed during the stay in ICU), the cause, the outcome (reversible or irreversible), the duration of cytopenia and the average value of hematological blood cells during the ICU stay were all collected. The outcome was considered as reversible if blood cell counts reached normal range or had an ascending pattern toward mild cytopenia during the ICU stay. White blood cell counts over 10,000 cells/ $\mu\text{l}$  for at least 2 consecutive days were reported as leukocytosis. Any abnormal findings in urine, cerebrospinal fluid, and blood, as well as trachea culture were noted during ICU admission. The mean value of serum creatinine, plasma magnesium level, plasma phosphorus level, C reactive protein, erythrocyte sedimentation rate, plasma iron level, plasma ferritin level and transferrin saturations were also documented. Any axillary body temperature above 38.3°C was considered as fever [26]. For patients with direct liver injury, including liver metastatic cancer, viral hepatitis, nonalcoholic fatty liver disease and autoimmune hepatitis, the Child–Pugh score was calculated based on the first reported value of albumin, total bilirubin, prothrombin ratio and international normalized ratio. Radiotherapy and drug-induced cytopenia were considered as causes of cytopenia when there were no confirmed reasons for blood cell counts below the lower limit of normal [13,27]. Disease-related causes of lymphopenia included Cushing syndrome and metastatic cancer [15]. The probability of causality assessment for cytopenia was recorded as probable, likely and definite. The case was considered as definite if it was supported by clinical condition and there were no other reasons for cytopenia, while if the cytopenia was

induced by one or two causes and four or more causes other than the main cause, the case was identified as likely and probable, respectively [28].

The data were analyzed by SPSS version 24 (IL, USA). Categorical variables were presented as absolute and relative (percentage) frequencies. Continuous variables were expressed as mean  $\pm$  standard deviation. Pearson test and Kruskal–Wallis test were used to show any possible correlation between variables. Fisher's exact test and Chi-square test were used to statistically compare qualitative and quantitative data, respectively. The influence of different factors related to cytopenia on the overall outcome (expired or discharged) was evaluated by multivariate logistic regression analysis.  $p < 0.05$  was considered as the significance level.

## Results

Totally, 117 cytopenic patients including 69 women (60%) and 48 men (40%) were assessed during the study period. The mean (SD) age of the patients was 53 (18) years and 58.97% of them were females. The demographic and clinical data of patients are shown in [Table 1](#).

Totally, 13 patients were admitted to ICU due to elective surgery, 15 patients for trauma and 89 patients for other medical conditions, including pneumonia; sepsis; Guillain–Barré syndrome; pancytopenia; venous thrombosis; and hemolysis, elevated liver enzymes and low platelet count syndrome.

The range of ICU stay was 2–79 days (with a median of 6 days). Totally, 29 patients (24.8%) died during the study period and 88 patients were discharged from ICU.

A total of 100 patients suffered from underlying diseases. The most prevalent underlying diseases were cardiovascular (48.69%), cancer (41%) and endocrine diseases (24.34%). The onset, outcome and mean value of duration of each type of cytopenia, as well as the mean value of blood cell counts are shown in [Table 2](#). Most of patients did not have cytopenia on admission and became cytopenic during ICU stay. Cytopenia was reported irreversible for the majority of the patients. The results showed that 99.14, 32.17, 27.82, 19.13, 6.83, 5.21 and 5.21% of cytopenic patients suffered from anemia, lymphocytopenia, thrombocytopenia, leukopenia, neutropenia and pancytopenia, respectively.

The causes, frequencies and probability of causality assessment for each type of cytopenia are reported in [Table 3](#). Blood loss due to surgery and trauma was the main cause of anemia in both expired and discharged groups by 61 cases (52.6% overall). One pancytopenic patient who had abortion with methotrexate due to ectopic pregnancy was the only case of drug-induced anemia. The reasons responsible for leucopenia in nearly 55% of patients were sepsis and viral infection. Six neutropenic patients distributed equally (33.3%) between three subclassifications (sepsis and viral infection, hematologic malignancy and drug induced and radiotherapy). Blood loss was the most common cause of lymphopenia (22 cases [59.5%]). Eight cases of thrombocytopenia were due to coagulopathy (overall 25%). Pancytopenia occurred in six patients, mainly due to the administration of chemotherapy drugs. All of these patients died.

The association between the overall outcome and demographic data including age, sex, cause of ICU admission, presence of underlying disease and the history of taking medications before ICU admission are presented in [Table 4](#). The mean of age was significantly higher ( $p = 0.02$ ) in expired patients in comparison to discharged ones ( $60.93 \pm 17.4$  vs  $50.96 \pm 18.6$  years). However, no significant difference was observed between overall outcome and other mentioned factors.

Further analysis was conducted to show the impact of each type of cytopenia, the mean value of blood cell counts, reversible cytopenia and the cytopenia developed after ICU admission on the overall outcome. The results indicated that the overall outcome was significantly affected by Hgb concentration ( $p < 0.0001$ ), leucopenia ( $p < 0.0001$ ), neutropenia ( $p = 0.004$ ), lymphopenia ( $p = 0.002$ ), thrombocytopenia ( $p < 0.0001$ ) and pancytopenia ( $p < 0.0001$ ). The discharged group had a significantly higher rate of reversible lymphopenia than the expired group ( $p = 0.008$ ). However, the reversibility of other types of cytopenia had no significant association with the outcome ([Table 4](#)).

Longer duration of anemia, lymphocytopenia and thrombocytopenia was associated with longer ICU LOS ( $p < 0.001$  for all) and higher rate of mortality regarding overall outcome ( $p < 0.001$ ;  $p < 0.001$  and  $p = 0.004$ , respectively).

Discharged patients with lower amount of Hgb had a significantly longer ICU LOS ( $p = 0.022$ ); however, this association was not significant in expired patients ( $p = 0.614$ ). The outcome was not affected by anemia severity in both groups (discharged  $p = 0.472$  and 0.385 in discharged and expired patients, respectively). Patients with mild

**Table 1. Demographic and clinical data of the patients.**

Quantitative variable	Range	Mean (SD)
Age (years)	18–87	53.44 (18.80)
ICU LOS (days)	2–79	11.56 (13.79)
Serum creatinine (mg/dl)	0.5–9.1	1.37 (1.22)
Mg serum level (mg/dl)	0.2–9.1	2.12 (1.05)
P serum level (mg/dl)	1.8–7.1	3.85 (1.05)
CRP (mg/dl)	2–193	66.74 (38.73)
ESR (mm/hr)	0.5–122	45.44 (34.60)
Serum iron level (mg/dl)	12–46	30.83 (16.22)
Serum ferritin level (mg/dl)	106–772	483.83 (303.77)
Transferrin saturation (%)	8.20–57	25.87 (19.76)
The Child–Pugh score	5–11	8.13 (1.959)
Qualitative variable	N (%)	
Sex	– Male	48 (41%)
	– Female	69 (59%)
Reason for hospital admission	– Medical condition	88 (76.1%)
	– Surgery	13 (11.1%)
	– Trauma	15 (12.8%)
Underlying disease	– No	16 (13.7%)
	– Yes	101 (86.3%)
	– Cardiovascular disease	56 (47.86)
	– Cancers	46 (39.31%)
	– Endocrine disease	28 (23.93)
	– Infectious diseases	13 (11.11%)
	– Immune disorders	13 (11.11%)
	– Pulmonary disease	6 (5.12%)
	– Neurologic disease	6 (5.12%)
	– Urogenital	4 (3.41%)
– Gastrointestinal and liver diseases	4 (3.41%)	
History of medication use	– Cardiovascular system	30 (25.64%)
	– Systemic hormonal preparations	30 (25.64%)
	– Antineoplastic and immunomodulating agents	20 (17.09%)
	– Blood and blood forming organs	9 (7.69%)
	– Alimentary tract and metabolism	8 (6.83%)
	– Nervous system	5 (4.27%)
	– Musculo-skeletal system	5 (4.27%)
	– Anti-infectives for systemic use	4 (3.41%)
Prescribed drugs during pancytopenia	– Anti-infectives for systemic use	112 (95.72)
	– Alimentary tract and metabolism	111 (94.87)
	– Blood and blood forming organs	106 (90.59%)
	– Musculo-skeletal system	103 (88.03%)
	– Cardiovascular system	80 (64.37%)
	– Systemic hormonal preparations, excl. sex hormones and insulins	58 (49.57%)
	– Nervous system	29 (24.78%)
	– Antineoplastic and immunomodulating agents	7 (5.98%)
Urine culture	– Positive	13 (11.11%)
	– Negative	15 (12.82%)

CSF: Cerebrospinal fluid; ESR: Erythrocyte sedimentation rate; LOS: Length of stay; SD: Standard deviation.

Table 1. Demographic and clinical data of the patients (cont.).

Quantitative variable	Range	Mean (SD)
Blood culture	– Negative	13 (11.11%)
	– Acinetobacter sp	3 (2.56%)
	– Klebsiella sp	2 (1.70%)
	– Staphylococcus sp	6 (5.12%)
	– Enterococcus sp	3 (2.56%)
	– Enterobacter sp	1 (0.85%)
Trachea culture	– Positive	3 (2.56%)
	– Negative	14 (11.96%)
CSF culture	– Positive	0 (0%)
	– Negative	5 (4.27%)
Thyroid hormone function	– Hyperthyroidism	1 (0.85%)
	– Hypothyroidism	0 (0%)
	– Euthyroidism	8 (6.83%)
Hepatitis C virus antibody	– Yes	4 (3.41%)
	– No	13 (11.11%)
Hepatitis B virus surface antigen	– Yes	1 (0.85%)
	– No	16 (13.67%)
Human immunodeficiency virus copy	– Yes	1 (0.85%)
	– No	15 (12.82%)
The Child–Pugh class	– Class A	1 (0.85%)
	– Class B	5 (4.27%)
	– Class C	2 (1.70%)
Mean body temperature	– Normal	74 (63.2%)
	– Above 37.9° C	43 (36.8%)

CSF: Cerebrospinal fluid; ESR: Erythrocyte sedimentation rate; LOS: Length of stay; SD: Standard deviation.

Table 2. The definition of each kind of cytopenia, the onset, the outcome, the mean value of duration and the mean value of blood cell counts.

Cytopenia	Definition	Severity	Frequency	Onset		Outcome		Mean value of related blood cell (SD)	Mean value of duration (SD)
				During ICU stay	On admission	Reversible	Irreversible		
Anemia	Female 9 < Hgb < 12 g/dl	Mild	91 (78.4%)	11 (9.48%)	105 (90.51%)	10 (8.62%)	106 (91.37%)	Hgb: 9.79 (1.07) g/dl	11.32 (13.64)
	Male 9 < Hgb < 13	Moderate	25 (21.6%)						
	7 < Hgb < 9 Hgb < 7 g/dl	Severe	0 (0%)						
Thrombocytopenia	70 < Plt < 100 X1000 cells/ $\mu$ l	Mild	12 (37.5%)	15 (46.87%)	17 (53.12%)	8 (25%)	24 (75%)	Plt: 0.59 (0.38) *1000 cells/ $\mu$ l	10.53 (9.35)
	20 < Plt < 70	Moderate	18 (56.3%)						
	Plt < 20	Severe	2 (6.3%)						
Lymphopenia	Lym < 1000 cells/ $\mu$ l	–	37	12 (32.43%)	25 (67.56%)	9 (24.32%)	28 (75.67%)	Lym: 0.61 (0.17) cells/ $\mu$ l	12.16 (11.96)
Leukopenia	WBC < 4000 cells/ $\mu$ l	–	8	4 (50%)	4 (50%)	4 (50%)	4 (50%)	WBC: 1.95 (1.05) *1000 cells/ $\mu$ l	10.50 (9.02)
Neutropenia	1000 < Neu < 1500 cells/ $\mu$ l	Mild	2 (33.3%)	3 (50%)	3 (50%)	3 (50%)	3 (50%)	Neu: 0.59 (0.38) cells/ $\mu$ l	9.17 (9.90)
	500 < Neu < 1000	Moderate	2 (33.3%)						
	Neu < 500	Severe	2 (33.3%)						

Hgb: Hemoglobin; ICU: Intensive care unit; Lym: Lymphocyte count; Neu: Neutrophil count; Plt: Platelet count; SD: Standard deviation; WBC: White blood cell.

**Table 3. The causes, frequencies and probability of causality assessment for each type of cytopenia.**

Cytopenia	Causes	Frequency (percentage)			Causality assessment		
		Discharged patients	Dead patients	Total	Probable	Likely	Definite
Anemia	– Blood loss	50 (57.5%)	11 (37.9%)	61	1	45	15
	– Gastrointestinal cancers	16 (18.4%)	5 (17.2%)	21	2	19	
	– Chronic disease	7 (8.0%)	5 (17.2%)	12		8	4
	– Hematologic malignancy	1 (1.1%)	4 (13.8%)	5		5	
	– Sepsis and viral infection	2 (2.3%)	2 (6.9%)	4		3	1
	– Vaginal and nonvaginal delivery and abortion	11 (12.6%)	1 (3.4%)	12		7	5
	– Drug/radiotherapy induced	0 (0%)	1 (3.4%)	1		1	
	– Total	87 (75%)	29 (25%)	116			
Lymphopenia	– Blood loss	16 (88.9%)	6 (31.6%)	22	13	9	
	– Sepsis and viral infections	1 (5.6%)	5 (26.3%)	6	6		
	– Drug/radiotherapy induced	0 (0%)	3 (15.8%)	3	1	2	
	– Hematologic malignancy	0 (0%)	3 (15.8%)	3	3		
	– Disease related	1 (5.6%)	2 (10.5%)	3	2	1	
	– Total	18 (48.64%)	19 (51.36%)	37			
Thrombocytopenia	– Sepsis and viral infections	0 (0%)	4 (22.2%)	4	2	2	
	– Chronic disease	2 (14.3%)	4 (22.2%)	6	3	3	
	– Hematologic malignancy	0 (0%)	4 (22.2%)	4		2	2
	– Coagulopathy	5 (35.7%)	3 (16.7%)	8		6	2
	– Drug/radiotherapy induced	2 (14.3%)	3 (16.7%)	5	2	2	1
	– Massive blood loss	5 (35.7%)	0 (0%)	5		3	2
	– Total	14 (43.75%)	18 (53.25%)	32			
Leukopenia	– Sepsis and viral infections	1 (100.0%)	3 (42.9%)	4		3	1
	– Hematologic malignancy	0 (0%)	2 (28.6%)	2		1	1
	– Drug/radiotherapy induced	0 (0%)	2 (28.6%)	2		1	1
	– Total	1 (12.5%)	7 (87.5%)	8			
Pancytopenia	– Cancer chemotherapy	4 (66.6%)	0 (0%)	4	1		3
	– Sepsis/chronic infection	2 (33.3%)	0 (0%)	2	1		1
	– Total	6 (100%)	0 (0%)	6			
Neutropenia	– Hematologic malignancy	0 (0%)	2 (40.0%)	2		1	1
	– Drug/radiotherapy induced	0 (0%)	2 (40.0%)	2		1	1
	– Sepsis and viral infections	1 (100.0%)	1 (20.0%)	2		1	1
	– Total	1 (16.66%)	5 (83.34%)	6			

thrombocytopenia had relatively higher ICU LOS than patients with normal range ( $p = 0.033$ ). No significant relation was seen between the severity of neutropenia and ICU LOS in both discharged and expired patients.

According to multivariate logistic regression analysis and by adjusting for different variables (i.e., age, cause of ICU admission, hemoglobin amount, leukopenia, neutropenia, lymphopenia, thrombocytopenia and pancytopenia), only thrombocytopenia could independently predict mortality (OR: 0.485 and  $p = 0.016$ ).

## Discussion

Our results showed that 99.14% of cytopenic patients suffered from anemia and Hgb concentration below the lower limit of normal was the most common defect in blood cell counts among different types of cytopenia. Anemia is a common complication in ICU patients; almost 95% of our patients are anemic on day 3 of admission. As discussed in previous studies, the incidence of anemia and its management can affect the ICU LOS and mortality [29,30]. Culleton *et al.* followed up 17,030 older adults for 3 years and demonstrated that anemia is associated with a higher risk of mortality and hospitalization [20]. In patients who are predicted to have a longer duration of ICU stay, correction of nutritional deficiencies (iron, B12 and B9) must be considered to prevent anemia and consequent complications. Most of the critically ill patients demonstrate the pattern of anemia of inflammation and they are less sensitive to erythropoietin [31]. In our study, interventions and responses in anemic patients were not considered

Table 4. The association between different clinical and demographic variables and overall outcome.

Demographic variable	Discharged	Expired	p-value
Age, years, mean (SD)	50.96 ± 18.6	60.93 ± 17.4	0.020
Sex (female), N (%)	53 (60.2%)	16 (55.2%)	0.631
Sex (male), N (%)	35 (39.8%)	13 (44.8%)	0.631
Presence of underlying disease, N (%)	75 (85.2%)	26 (89.7%)	0.547
Receiving medication before ICU admission, N (%)	48 (54.5%)	19 (65.5%)	0.3
Clinical variables			
Hemoglobin concentration, mg/dl, mean (SD)	9.99 ± 1.03	9.21 ± 0.9	<0.0001
Incidence of leucopenia, N (%)	1 (1.1%)	7 (24.1%)	<0.0001
WBC count, mean (SD)	1.30 ±	2.04 ± 1.10	0.661
Incidence of neutropenia, N (%)	1 (1.1%)	5 (17.2%)	0.004
Neutrophil count, mean (SD)	0.403	0.630 ± 0.421	0.770
Incidence of lymphopenia, N (%)	16 (21.9%)	16 (55.2%)	0.002
Lymphocyte count, *1000 cells/ $\mu$ l, mean (SD)	0.646 ± 0.121	0.581 ± 0.209	0.552
Incidence of thrombocytopenia, N (%)	14 (15.9%)	18 (62.1%)	<0.0001
Platelet count, *1000 cells/ $\mu$ l, mean (SD)	65.50 ± 19.54	56.27 ± 23.19	<0.0001
Incidence of pancytopenia, N (%)	0 (0%)	6 (20.6%)	<0.0001
Reversible anemia, N (%)	7 (8%)	3 (10.3%)	0.709
Reversible leucopenia, N (%)	1 (12.5%)	3 (37.5%)	0.9
Reversible neutropenia, N (%)	1 (100%)	2 (40%)	0.9
Reversible lymphopenia, N (%)	8 (21.6%)	1 (2.7%)	0.008
Reversible thrombocytopenia, N (%)	6 (18.75%)	2 (6.25%)	0.096
ICU stay anemia, N (%)	7 (8.0%)	4 (13.8%)	0.462
ICU stay leucopenia, N (%)	0 (0%)	4 (57.1%)	0.9
ICU stay neutropenia, N (%)	0 (0%)	3 (60.0%)	0.9
ICU stay lymphopenia, N (%)	3 (16.7%)	9 (47.4%)	0.079
ICU stay thrombocytopenia, N (%)	5 (35.7%)	10 (55.6%)	0.308

ICU: Intensive care unit; SD: Standard deviation; WBC: White blood cell.

but the Hgb level was used as an indicator of prognosis and outcome. Anemia was caused mostly by blood loss (trauma and surgery) in our patients (52.6%). In this regard, phlebotomy is assumed as a major modifiable cause in critically ill patients [32]. Von Ahsen *et al.* examined 96 patients treated in the ICUs for more than 3 days. They found out that 77% of patients suffered from anemia. Also, it was shown that overt bleeding or diagnostic blood sampling were not the main causes of anemia in these patients, but, rather, anemia resulted mainly from various other reasons, such as occult gastrointestinal bleeding and renal replacement therapy [33]. It is reported that in severe traumatic brain injury, anemia (Hgb < 9 g/dl) along with compromised brain tissue oxygen tension is associated with inappropriate outcomes [34]. We could not detect the benefit of anemia reversibility in patients' prognosis.

In our study, the patients were classified based on the severity of anemia. The results showed that a lower amount of Hgb was associated with a longer duration of hospitalization in discharged patients and just the incidence of anemia, independent of the severity, could affect the outcome in a statistically significant manner. Hgb concentration was statistically higher in discharged patients in comparison to expired individuals. Rasmussen *et al.* in their study showed that there is a relation between anemia (Hgb < 12 g/dl) and mortality in mechanically ventilated chronic obstructive pulmonary disease patients [35]. In the postoperative setting, the direct association between anemia and mortality was also observed [36–38]. There was a similar result regarding mortality and LOS with Hgb concentration of less than 9 g/dl [39].

It has been shown that more than 50% of critically ill patients experience thrombocytopenia during their ICU stay and 5–20% of these patients suffer from severe thrombocytopenia (platelet counts below  $50 \times 10^9/l$ ) [40]. ICU patients usually have several comorbidities that affect platelet hemostasis and make this population prone to thrombocytopenia. Six major mechanisms have been introduced for thrombocytopenia induction, including hemodilution, increased platelet consumption, increased platelet destruction, decreased platelet production, improved platelet sequestration and pseudothrombocytopenia (laboratory artifacts) [41]. Defining the most common

causes of cytopenia in each setting can help clinicians make treatment choices. More than a fourth (27.82%) of our cytopenic patients suffered from thrombocytopenia. In Levi *et al.* study [8], sepsis was the most common cause of thrombocytopenia; however, we found coagulopathy as the main cause (25.0%), followed by chronic diseases (18.75%), particular drugs or radiotherapy (15.62%) and massive blood loss (15.62%).

Lower platelet count and longer duration of thrombocytopenia lead to higher mortality in ICU. A similar study in ICU patients found out that more severe thrombocytopenia and lower platelets are associated with a higher mortality rate. Thus, it can be used as a valuable prognostic marker [11,24,42]. Our results showed that among all of the variables (incidence, duration and severity of each type of cytopenia), the only incidence of thrombocytopenia was significantly associated with mortality. Some studies demonstrated that both the incidence and severity of thrombocytopenia contribute to higher mechanical ventilation requirement and mortality in critically ill patients [42,43]. Akca *et al.* implicated that late onset thrombocytopenia in ICU leads to higher mortality rates in comparison to early thrombocytopenia. The patients were categorized into two groups; groups 1 and 2 developed thrombocytopenia at the first and second weeks of admission, respectively. It was reported that the second group had a higher mortality rate [9]. Also, another study showed that late onset thrombocytopenia leads to a higher mortality rate [11]. Based on our results, the onset of thrombocytopenia had no significant effect on the overall outcome.

Near a third (32.17%) of our cohort were lymphopenic. Blood loss (e.g., trauma and surgery) was the main cause of lymphopenia (59.5%) in the present study. According to a retrospective review of a database of adult patients requiring ICU admission between 2002 and 2013 in the UK, 78% of patients had lymphopenia at admission and 91% of them developed at least one episode of lymphopenia during ICU stay [18].

Higher duration of lymphopenia can prolong the ICU LOS and negatively affect the outcome. Furthermore, the incidence of lymphopenia was associated with a higher mortality rate. A higher rate of reversible lymphopenia was observed among discharged patients. In contrast, prolonged and irreversible lymphopenia can lead to higher mortality. Lymphopenia developed during ICU-stay could not lead to higher mortality in comparison to that exists on ICU admission. Vulliamy *et al.* showed that the presence of lymphopenia on ICU admission and its persistence until day 3 could increase the risk of infection and just persistent lymphopenia, independent of onset, caused higher mortality [17]. Our current study also demonstrated that the longer length of lymphopenia was associated with increased mortality and ICU LOS. An increase in ICU LOS leads to an elevated overall hospitalization period. Our findings are consistent with those in which lymphopenia was considered as a predictor for poor outcome in terms of a longer hospital stay, in-hospital mortality and 1-year mortality after discharge [44].

Lymphopenia and neutrophil-lymphocyte count ratio can predict the possibility of bacteremia and somehow estimate the inflammation [45]. It has been shown that lymphopenia and an increase in the neutrophil count at the same time in critically ill patients with a prior history of diabetes is associated with poor prognosis [46]. However, based on our data, lymphocyte count did not affect mortality and length of stay.

Pancytopenia is related to poor prognosis, as all of pancytopenic patients expired in our study. However; one cannot make a definite statement in this regard due to the small population size (only 6 patients). All of these patients were anemic. On the other hand, the most common cause of pancytopenia was probably nutritional megaloblastic with concurrent iron deficiency [47]. Low doses of methotrexate can induce pancytopenia [48] and one of our cases had received this medication as an abortive therapy. Therefore, drug-induced pancytopenia is probable. We had three patients who had received induction therapy for acute myeloid leukemia and their pattern of cytopenia was compatible with chemotherapy-induced pancytopenia described by other studies [49].

The major strength of our investigation is the comprehensive study of the frequency of different types of cytopenia, related risk factors and its impact on clinical outcome in critically ill patients in the ICU.

Our study had some limitations which should be considered. We had no access to information before or after ICU admission. In addition, only random cytopenic patients were evaluated, and we had not the control group concurrently. Therefore, we cannot report the definite prevalence and also possible risk factors of cytopenia at our center. This negatively impacts the generalization aspect of the obtained results. The number of neutropenic and leukopenic patients was too small to detect any probable statistical differences. Thus, further studies with larger sample sizes are required.

## Conclusion

Our results demonstrated that the rate of cytopenia, especially anemia, is relatively high in critically ill patients. Among all assessed variables, only thrombocytopenia could significantly and independently predict ICU mortality

in our cohort. Knowing causes of cytopenia and its pattern, helps the clinicians to prevent cytopenia or choose the best treatment plan for cytopenic patients and reduce the cost imposed on patients and the healthcare system.

### Future perspective

Assessing the effect of treatment and efficacy of managements of cytopenia along with determining relevant and possible risk factors of cytopenia in ICU patients are the era for further studies.

#### Summary points

- Cytopenia can increase the mortality and intensive care unit length of stay in critically ill patients.
- This study was conducted to evaluate the incidence and pattern of different types of cytopenia in critically ill patients.
- During a 10 months period, critically ill patients presenting with any kind of cytopenia for more than 2 days were evaluated.
- Anemia was the most common type of cytopenia in the patients (99.14%), followed by lymphocytopenia (32.17%), thrombocytopenia (27.82%) and leukopenia (19.13%).
- Mortality rate was significantly higher in patients with anemia ( $p < 0.0001$ ), thrombocytopenia ( $p < 0.0001$ ), leukopenia ( $p < 0.0001$ ), neutropenia ( $p = 0.004$ ), lymphopenia ( $p = 0.002$ ) and pancytopenia ( $p < 0.0001$ ).
- Knowing causes of cytopenia and its pattern, helps the clinicians to prevent cytopenia or choose the best treatment plan for cytopenic patients and reduce the cost imposed on patients and the healthcare system.

### Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

### Data sharing statement

Research data are available per request.

### References

1. Valent P. Low blood counts: immune mediated, idiopathic, or myelodysplasia. *Hematology Am. Soc. Hematol. Educ. Program* 2012(1), 485–491 (2012).
2. Walsh TS, Saleh EE. Anaemia during critical illness. *Br. J. Anaesth.* 97(3), 278–291 (2006).
3. Nguyen BV, Bota DP, Melot C, Vincent JL. Time course of hemoglobin concentrations in nonbleeding intensive care unit patients. *Crit. Care Med.* 31(2), 406–410 (2003).
4. Bateman AP, Mcardle F, Walsh TS. Time course of anemia during six months follow up following intensive care discharge and factors associated with impaired recovery of erythropoiesis. *Crit. Care Med.* 37(6), 1906–1912 (2009).
5. Hayden SJ, Albert TJ, Watkins TR, Swenson ER. Anemia in critical illness: insights into etiology, consequences, and management. *Am. J. Respir. Crit. Care Med.* 185(10), 1049–1057 (2012).
6. Beutler E. Drug-induced anemia. *Fed. Proc.* 31(1), 141–146 (1972).
7. Vincent JL, Baron JF, Reinhart K *et al.* Anemia and blood transfusion in critically ill patients. *JAMA* 288(12), 1499–1507 (2002).
8. Levi M, Opal SM. Coagulation abnormalities in critically ill patients. *Crit. Care* 10(4), 222 (2006).
9. Akca S, Haji-Michael P, de Mendonca A, Suter P, Levi M, Vincent JL. Time course of platelet counts in critically ill patients. *Crit. Care Med.* 30(4), 753–756 (2002).
10. Baughman RP, Lower EE, Flessa HC, Tollerud DJ. Thrombocytopenia in the intensive care unit. *Chest* 104(4), 1243–1247 (1993).
11. Moreau D, Timsit JF, Vesin A *et al.* Platelet count decline: an early prognostic marker in critically ill patients with prolonged ICU stays. *Chest* 131(6), 1735–1741 (2007).
12. Frontiera M, Myers AM. Peripheral blood and bone marrow abnormalities in the acquired immunodeficiency syndrome. *West J. Med.* 147(2), 157–160 (1987).
13. Kaushansky K, Lichtman MA, Prchal JT *et al.* *Williams Hematology (9th Edition)*. McGraw-Hill Medical, NY, USA (2016).
14. Hotchkiss RS, Tinsley KW, Swanson PE *et al.* Sepsis-induced apoptosis causes progressive profound depletion of B and CD4<sup>+</sup> T lymphocytes in humans. *J. Immunol.* 166(11), 6952–6963 (2001).

15. Castellino DJ, McNair P, Kay TW. Lymphocytopenia in a hospital population—what does it signify? *Aust. NZ J. Med.* 27(2), 170–174 (1997).
16. Adrie C, Lugosi M, Sonnevile R *et al.* Persistent lymphopenia is a risk factor for ICU-acquired infections and for death in ICU patients with sustained hypotension at admission. *Ann. Intensive Care* 7(1), 30 (2017).
17. Vulliamy PE, Perkins ZB, Brohi K, Manson J. Persistent lymphopenia is an independent predictor of mortality in critically ill emergency general surgical patients. *Eur. J. Trauma Emerg. Surg.* 42(6), 755–760 (2016).
18. Hsieh MM, Everhart JE, Byrd-Holt DD, Tisdale JF, Rodgers GP. Prevalence of neutropenia in the US population: age, sex, smoking status, and ethnic differences. *Ann. Intern. Med.* 146(7), 486–492 (2007).
19. Felix-Getzik E, Murray YA, Nigro SC. Interpretation of Clinical Laboratory Tests. In: Koda-Kimble MA, Young LY (Eds). *Applied Therapeutics: The Clinical Use of Drugs (11th Edition)*. Lippincott Williams & Wilkins, PA, USA, 33 (2018).
20. Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. *Blood* 107(10), 3841–3846 (2006).
21. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer* 106(10), 2258–2266 (2006).
22. WHO Collaborating Centre for Drug Statistics Methodology Guidelines for ATC classification and DDD assignment, 2018. Oslo, Norway (2017). [www.whocc.no/atc-ddd-index-and-guidelines/guidelines/](http://www.whocc.no/atc-ddd-index-and-guidelines/guidelines/)
23. Drews RE, Weinberger SE. Thrombocytopenic disorders in critically ill patients. *Am. J. Respir. Crit. Care Med.* 162(2 Pt. 1), 347–351 (2000).
24. Levi M, Löwenberg EC. Thrombocytopenia in critically ill patients. Presented at: *Seminars in Thrombosis and Hemostasis*. 34(5), 417–424 (2008).
25. WHO. *Iron Deficiency Anemia. Assessment, Prevention, and Control. A Guide for Programme Managers*. WHO/NHD/01.347–62 (2001). [www.who.int/nutrition/publications/micronutrients/anaemia\\_iron\\_deficiency/WHO\\_NHD\\_01.3/en/](http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/WHO_NHD_01.3/en/) Publisher: WHO
26. Laupland KB, Shahpori R, Kirkpatrick AW, Ross T, Gregson DB, Stelfox HT. Occurrence and outcome of fever in critically ill adults. *Crit. Care Med.* 36(5), 1531–1535 (2008).
27. O’Byrant CL, Glode AE, Thompson LA. Anemias. In: Koda-Kimble MA, Young LY (Eds). *Applied Therapeutics: The Clinical Use of Drugs (11th Edition)*. Lippincott Williams & Wilkins, PA, USA, 1927 (2018).
28. The use of the WHO–UMC system for standardised case causality assessment (2018). [www.who-umc.org/media/164200/who-umc-causality-assessment\\_new-logo.pdf](http://www.who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf)
29. Corwin HL, Krantz SB. Anemia of the critically ill: “acute” anemia of chronic disease. *Crit. Care Med.* 28(8), 3098–3099 (2000).
30. Hecht D, Boujoukos A. Anemia in the ICU: are your patients needin’ erythropoetin? *Crit. Care* 14(6), 332 (2010).
31. Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG. Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. *J. Crit. Care* 16(1), 36–41 (2001).
32. Chant C, Wilson G, Friedrich JO. Anemia, transfusion, and phlebotomy practices in critically ill patients with prolonged ICU length of stay: a cohort study. *Crit. Care* 10(5), R140 (2006).
33. Von Ahsen N, Muller C, Serke S, Frei U, Eckardt KU. Important role of nondiagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients. *Crit. Care Med.* 27(12), 2630–2639 (1999).
34. Oddo M, Levine JM, Kumar M *et al.* Anemia and brain oxygen after severe traumatic brain injury. *Intensive Care Med.* 38(9), 1497–1504 (2012).
35. Rasmussen L, Christensen S, Lenler-Petersen P, Johnsen SP. Anemia and 90-day mortality in COPD patients requiring invasive mechanical ventilation. *Clin. Epidemiol.* 3, 1–5 (2010).
36. Martinez FJ, Foster G, Curtis JL *et al.* Predictors of mortality in patients with emphysema and severe airflow obstruction. *Am. J. Respir. Crit. Care Med.* 173(12), 1326–1334 (2006).
37. Chambellan A, Chailleux E, Similowski T. Prognostic value of the hematocrit in patients with severe COPD receiving long-term oxygen therapy. *Chest* 128(3), 1201–1208 (2005).
38. Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion* 42(7), 812–818 (2002).
39. Corwin HL, Gettinger A, Pearl RG *et al.* The CRIT Study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit. Care Med.* 32(1), 39–52 (2004).
40. Greinacher A, Selleng S. How I evaluate and treat thrombocytopenia in the intensive care unit patient. *Blood* 128(26), 3032–3042 (2016).
41. Greinacher A, Selleng K. Thrombocytopenia in the intensive care unit patient. *Hematology Am. Soc. Hematol. Educ. Program* 2010, 135–143 (2010).

42. Vanderschueren S, De Weerd A, Malbrain M *et al.* Thrombocytopenia and prognosis in intensive care. *Crit. Care Med.* 28(6), 1871–1876 (2000).
43. Crowther MA, Cook DJ, Meade MO *et al.* Thrombocytopenia in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *J. Crit. Care* 20(4), 348–353 (2005).
44. Rubio-Rivas M, Formiga F, Grillo S, Gili F, Cabrera C, Corbella X. Lymphopenia as prognostic factor for mortality and hospital length of stay for elderly hospitalized patients. *Aging Clin. Exp. Res.* 28(4), 721–727 (2016).
45. de Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, Van Der Poll T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. *Crit. Care* 14(5), R192 (2010).
46. Jimenez-Ibanez EO, Castillejos-Lopez M, Hernandez A, Gorocica P, Alvarado-Vasquez N. High mortality associated with hyperglycemia, neutrophilia, and lymphopenia in critically ill patients. *Toboku J. Exp. Med.* 226(3), 213–220 (2012).
47. Sankepally KR, Saikrishna K. Etiological Profile of Pancytopenia. *Int. J. Innov. Res. Dev.* 4(3), 42–46 (2015).
48. Preet Singh Y, Aggarwal A, Misra R, Agarwal V. Low-dose methotrexate-induced pancytopenia. *Clin. Rheumatol.* 26(1), 84–87 (2007).
49. Glucksberg H, Cheever MA, Farewell VT, Fefer A, Sale GE, Thomas ED. High-dose combination chemotherapy for acute nonlymphoblastic leukemia in adults. *Cancer* 48(5), 1073–1081 (1981).