



A Prospective Observational Study to Determine Causes of Anemia in Intensive Care Unit Patients

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ABSTRACT

Anaemia is commonly seen in critically ill patients and is associated with considerable morbidity and worse outcomes. Common factors responsible for development of anemia during their stay in ICU are due to blood loss, nutritional deficiency, drug induced, phlebotomy and defective or decreased erythropoiesis etc. Aims: This study aimed to determine the causes of anemia and to analyze hematological, biochemical, and clinical pathological parameters from ICU patients. Methods and Material: Prospective observational study of 300 adult patients admitted to the ICU with stay of more than 7 days. Details such as age, sex, and clinical history (history of phlebotomy and blood transfusion) was obtained. Hemogram, PBS and other parameters (imaging, biochemistry, microbiology, serology) were studied. Results: Out of the 300 patients discharged with anemia, 266 had anemia at admission and 34 developed anemia during ICU stay. Most common cause of admission to ICU was medical followed by surgery and trauma. 65 patients had shock at admission. Lowest mean Hb was 7.13 g/dl seen in septic cases, most common type of morphological anemia at admission was NCNC. Anemia worsened in 101 patients, with male (64) predominance. 8 patients with worsened anaemia did not survive. Conclusions: Anemia is a significant cause of morbidity in critically ill patients specially in background of sepsis, post operative period and chronic renal diseases.

Key Words: Anemia of critical illness, shock, length of stay



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INTRODUCTION

Anaemia is characterised by a reduction of the total circulating red cell mass below normal limits [1]. According to the world health organization (WHO), anemia is defined as hemoglobin (Hb) levels <12.0 g/dl in women and <13 g/dl in men. Anaemia is commonly seen in critically ill patients and is associated with considerable morbidity and worse outcomes. Common factors responsible for development of anemia in critically ill patients during their stay in ICU:

- 1) Anemia due to blood loss: Many patients are admitted to the ICU because of bleeding due to surgery, trauma, coagulopathy, liver diseases and other causes. Patients admitted with other diseases may develop bleeding after admission.
- 2) Nutritional deficiency: Iron, folate, and vitamin B12 deficiency is typically common in our country and these deficiencies may get aggravated in the ICU because of inadequate nutritional support and increased utilization of these substrates in critical illness [2]
- 3) Drug induced: Certain drugs may cause anemia either by causing hemolysis or by suppressing bone marrow [3].
- 4) Phlebotomy: Diagnostic phlebotomy can result in a mean loss of up to 40 - 70 ml of blood per day in an ICU patient, which may be more than that can be naturally replaced in a critically ill patient and only a fraction of this blood is processed for laboratory tests [4].
- 5) Increased levels of Hepcidin: Hepcidin levels which reduces the absorption of iron from the GI tract and also traps the iron in its stores in the reticuloendothelial system (RES) and thus less iron is available to the bone marrow [5, 6].
- 6) Anaemia of defective or decreased erythropoiesis: Inflammatory cytokines such as interleukins released in response to sepsis or trauma reduce erythropoietin levels [7, 8].

MATERIAL AND METHODS

This observational study was conducted for a period of two years from 1st July 2020 to 30th June 2022 at Department of Pathology in a tertiary care hospital attached to a private medical college in western India. Total 300 patients admitted to ICU were analyzed. Demographic details such as age, sex and clinical history will be recorded. Hemogram of all

patients admitted to ICU at admission will be carried out and peripheral smears was studied. When anemia is detected, the classification is done based on morphology and a tentative cause is determined. The progress of anemia (improvement or worsening) will be recorded periodically during the ICU stay. The other investigative parameters (imaging, biochemistry, microbiology, serology) will be studied and correlated with the anemia. A record of frequency and volume of phlebotomy will be maintained. Any requirement of transfusion will be noted along with treatments instituted. A final cause of anemia will be determined at completion of stay in ICU.

RESULTS

Over the 2 years period, 300 patients were studied, who met the inclusion criteria. Among these 188 were male patients and 112 were females with mean age 51.2 years and 53.15 years respectively. 163 male patients out of 188 and 103 female patients out of 112 had anemia at the time of admission. Grading of anemia was done at the time of admission, 88(53.98%) of 163 male and 57(55.33%) of 103 female patients had moderate anemia (Table 1)

Table 1: Baseline details of cases

Sex	N=300	Not anemic At admission	Anemia at admission			Total
			Mild	Moderate	Severe	
Female	112 (37%)	9(3%)	10(9.7%)	57(55.33%)	36(34.95%)	103(34.33%)
Male	188(63%)	25 (15.33%)	29(17.79%)	88(53.98%)	46(28.22%)	163(54.33%)
Total	300	34(11.33%)	39(13%)	145(48.33%)	82(27.33%)	266(88.66%)

Out of the 300 patients discharged with anemia, 266 had anemia at admission. These comprised 32.4% of 820 total admissions to the ICU during this period.

Majority of the patients 90(30%) were in the age group of 30-45 years, out of which 77 patients had anemia at the time of admission and 88(29.3%) were in age group of 46-59 years out of which 77 patients had anemia at the time of admission. At discharge non-anemic patients also developed anemia (Table 2)

Table 2: Age distribution

Age distribution (years)	Number of patients	Percentage (%)	Anemia at admission		Anaemia at discharge
			Present	Absent	
18-29	23	7.7	20	3	23
30-45	90	30.0	77	13	90
46-59	88	29.3	77	11	88
60-75	77	25.7	72	5	77
>76	22	7.3	20	2	22
Total	300	100	266	34	300

145(48.33%) of 300 patients presented with comorbidities at admission, most common being DM (30.3%) and HTN (27.3%). 23 patients with worsened anemia had DM. Many patients had more than one co morbidity.

At the time of admission 34 patients were non-anemic with mean age of 48.9 years and 49.33 years in males and females respectively. 25 were male patients and 9 were female patients. 2 males and 1 female patient did not survive. Mean Hb in males was 14.2 g/dl and in females was 12.86 g/dl at the time of admission, whereas at discharge mean Hb dropped to 10.04 g/dl in males and in females 9.97 g/dl.

The most common cause of admission to ICU was medical followed by surgery and trauma. In medical most common cause was infection (covid and dengue were the most common ones), 55 cases and 2nd was renal disorders, 44 cases. The mean of total volume of blood taken during ICU stay for investigations was highest in trauma patients (238.52ml) with mean length of stay 19.05 days and second highest in CNS cases (187.68 ml) with mean length of stay 13.72 days. Patients admitted with GI tract diseases mainly comprised of GI bleeding had MCHC anaemia, whereas patients with chronic inflammation had NCNC anaemia. All patients presented with liver diseases had anaemia, among this anaemia worsened in 5 patients and improved in 7 cases (Table 3)

Table 3: Causes of admission to ICU

Cause of admission		No. of cases	Anemia present	Anemia worsened	Anemia improved	Developed anemia	Type of anaemia	Phlebotomy (ml)	Mean phlebotomy/day	LOS
Medical (n=230)	CVS	14(6%)	13	7	5	1	NCNC	135.21	14.1	10.5
	Lung	18(7.8)	14	5	5	4	NCNC	139.72	14.1	9.44

		(%)								
	CNS	25 (10.8%)	22	11	6	3	NCNC	187.68	14.73	13.72
	Renal	44 (19.1%)	42	23	12	2	NCNC	166.90	14.6	12.55
	Liver	19(8.2%)	19	5	7	0	NCNC	156.89	16	11.52
	Infection	55 (23.9%)	46	17	12	9	NCNC	177.2	14.11	12.69

The main cause of anaemia in ICU was blood loss of which trauma (35) and phlebotomy (29) contributed mainly. The next main causes were renal insufficiency and inflammation seen in 38 and 36 cases (Table 4).

Table 4: Causes of anaemia

Type of anaemia	causes	Number of patients	Total
Blood loss (n=91, 30.3%)	Phlebotomy	29	101
	GI bleeding	12	
	Trauma	35	
	surgery	25	
Erythropoietin insufficiency(n=74, 24.6%)	Renal insufficiencies	38	74
	Inflammation	36	
Nutritional deficiencies		32(10.6%)	32
Haemolysis		7(2.3%)	7
Coagulation abnormalities (n=55)(18.3%)	Sepsis	13	55
	Liver diseases	19	
	Viral infection	23	
Multifactorial		31(10.3%)	31

Total 65 patients presented with shock at admission, the most frequent was septic shock (9.33%) and hypovolemic shock (7%), of which only one patient was non-anaemic. This finding was statistically significant (Table 5).

Table 5: Details of shock at admission

		Anemia		Total	Chi-square value	P-value
Shock		Yes	No		7.92	0.005
	Yes	64	1	65		
	No	202	33	235		

Mean value of Hb in patients with shock was 7.51 g/dl and in patients without shock was 9.84 g/dl. This finding was statistically significant (Table 6)

Table 6: Mean Hb levels at admission and discharge

Independent t test							
Shock			N	Mean	SD	t-value	p-value
Hb (A)	Yes		65	7.51	2.56	6.79	<0.001
	No		235	9.84	2.42		

Highest volume of phlebotomy (206.57 ml) was found in patients with hypovolemic shock with mean length of stay 16.14 days, second was cardiogenic shock with phlebotomy volume 195.5 ml and mean length of stay 12 days. Patients with sepsis and hypovolemia had normocytic normochromic anaemia, whereas in haemorrhagic shock, MCHC anemia was seen.

Mean Hb in non anemic patients was 13.85 g/dl and in anemic patients it was 9.33 g/dl. At discharge all patients were anemic and mean Hb was 8.77 g/dl.

Out of 300 admissions, anaemia improved in 88(29%), worsened in 101(34%), anaemia developed in 34(11.33%) and there was no significant change in 77(26%) patients (Figure 1)

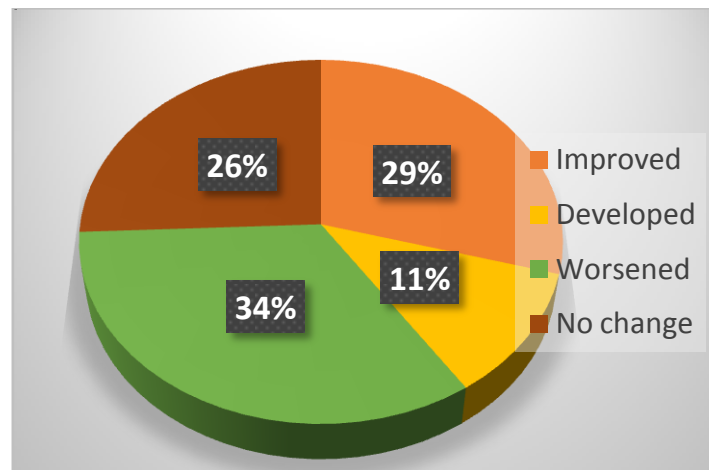


Figure 1: This chart shows progress of anaemia during ICU stay

Most common type of morphological anemia at admission was normocytic normochromic. 159 out of 176 patients remained normocytic normochromic at discharge and 22 out of 58 microcytic anemia cases, developed normocytic anemia at discharge (Table 7)

Table 7: Morphological classification of anemia in anemic patients at admission (n=266)

TYPE OF ANEMIA	AT ADMISSION (n=266)	AT DISCHARGE (n=266)		
		NCNC	MCHC	Macrocytic
NCNC	176(66.1%)	159	11	6
MCHC	58(21.85%)	22	35	1
Macrocytic anemia	32(10.6%)	17	0	15
Total		198	46	22

Out of 32 cases of macrocytic anemia. Vit B12 levels were done in 18 cases and 12 cases had low levels. S. iron levels were evaluated in 67 patients. Levels were low in 50 cases, of which 26 were normocytic normochromic cases and 23 were microcytic hypo chromic.

Procalcitonin and CRP were raised in patients with anemia and these findings were statistically significant (Table 8).

Table 8: co-relation of various parameters with anemia

Mann-Whitney U Test				
Anemia at admission		N	Median (IQR)	p-value
Procalcitonin	Yes	117	1.85(0.34-8.23)	0.04
	No	19	1.00(0.20-1.10)	
D dimer	Yes	48	1042.00(466.75-2343.75)	0.61
	No	9	1425.00(553.00-1569.50)	
CRP	Yes	84	94.50(23.70-213.50)	0.02
	No	13	231.00(112.75-251.60)	
S. Ferritin	Yes	89	370.25(128.27-1053.80)	0.36
	No	5	231.00(112.75-251.60)	
LDH	Yes	74	407.00(270.25-781.00)	0.50
	No	6	508.00(365.00-765.00)	

Anemia worsened in 101 patients, with male (64) predominance with mean age 52.81 years and 37 were female patients with mean age 54.16 years. Mean Hb reduced from 10.63 g/dl to 8.52 g/dl in males and in females Hb reduced from 9.87 to 8.32 g/dl during ICU stay. 8 patients with worsened anaemia did not survive. Patients with longer stay in ICU had severe anemia at discharge/death. Blood transfusion was given in 32.33% patients with mean Hb 7.68 g/dl.

Patients who were transfused had more length of stay and phlebotomy volume. Of 89, 8 didn't survive (Table 9).

Table 9: Blood transfusion

Blood transfusion	Number of patients	LOS(day)	Phlebotomy(ml)	survivors	Non-survivors
Yes	97	12.75	176.7	89	8
No	203	11.8	160.2	191	12

Out of 300 patients, 20 didn't survive. Among 20 patients, 11 were males with mean age 71.45 years and 9 were females with mean age 65 years. Anaemia worsened in 4(36.3%) of 11 males and 4(44%) females during ICU stay. Out of 20, 16 patients had moderate anaemia and 4 had severe anaemia. Most common cause associated with death was COVID followed by trauma and cardiac arrest. In male patients mean Hb was 9.71 g/dl at the time of admission, which reduced to 9.15g/dl during ICU stay. In female patients mean Hb at admission was 9.25 g/dl which reduced to 8.42 g/dl during stay in ICU. 8(40%) out of 20 non-survivors, received blood transfusion.

The mean length of stay among non-survivors was 14.35 days with mean total phlebotomy volume 183.95 ml and in survivors it was 12.14 days with total mean phlebotomy volume of 166.37 ml (Table 10)

Table 10: comparison of length of stay and phlebotomy among survivors and non-survivors

	Number of patients	LOS	Phlebotomy(ml)
Survivors	280	12.07	166.37
Non-survivors	20	14.35	183.95

Images

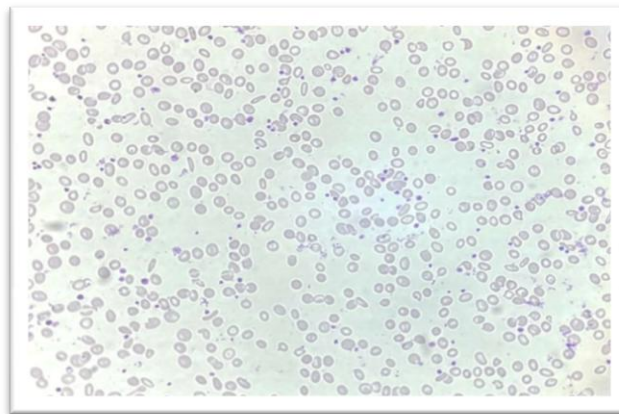


Image 1 (Leishman stain- 40x): Microcytic hypochromic anemia

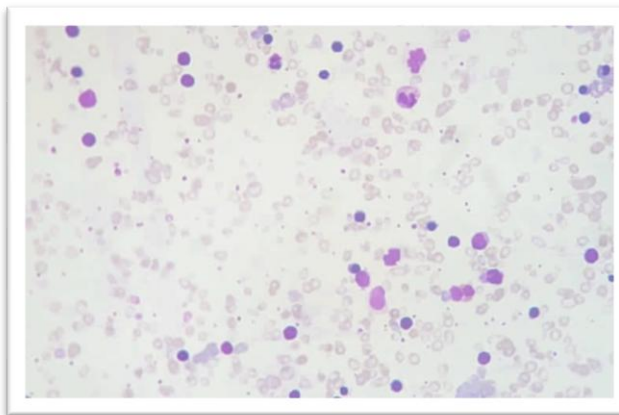


Image 2a (Leishman stain- 40x): Hemolytic anemia, image shows nRBCs

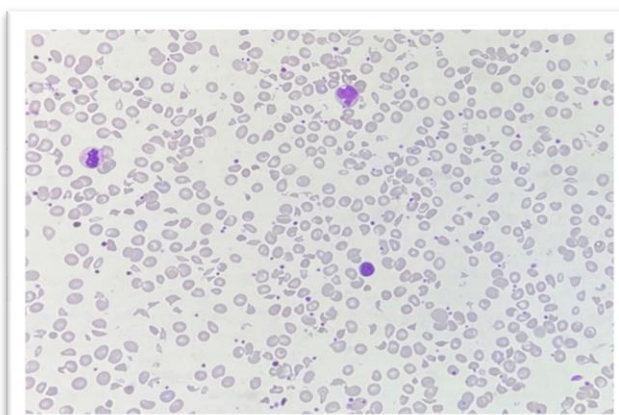


Image 2b (Leishman stain- 40x): Hemolytic anemia, image shows schistocytes

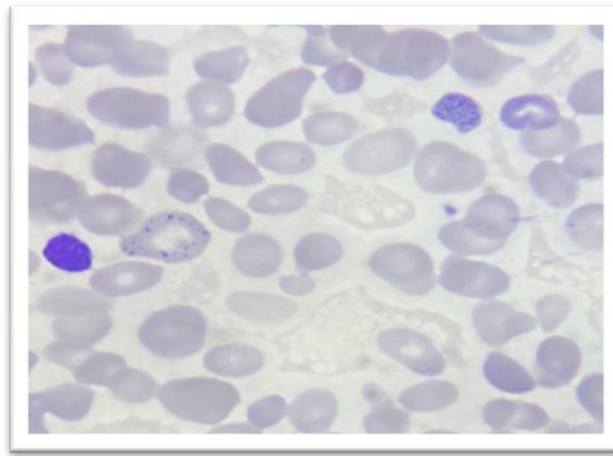


Image 4 (Leishman stain- 100x): Howell jolly body

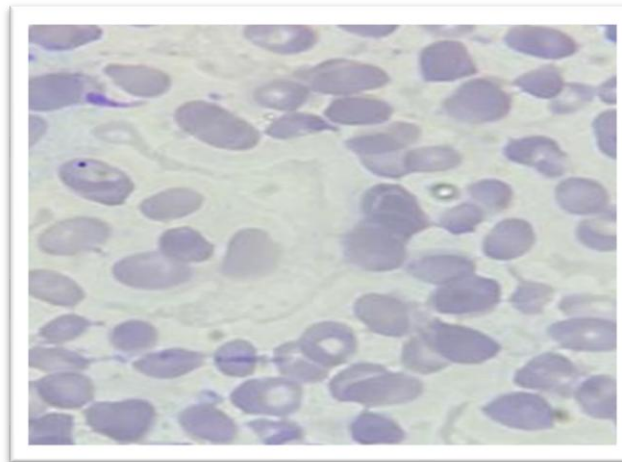


Image 5 (Leishman stain- 100x): Basophilic stippling

DISCUSSION

Anemia is commonly encountered problem in critical care units. Low Hb levels are associated with high mortality and longer stay in ICU. The first step in investigating anaemia is to study the haemogram and peripheral blood smear. Morphological type of anaemia provides valuable information and aids the clinician/haematologist to further investigate the patient to identify the cause of anemia so that it can be appropriately treated.

In this study, prevalence of anaemia was 32.4%

Study	Year	Prevalence of Anaemia (%)
Thomas J. Jensen	2009	41
Juárez-Vela	2022	63.31
Vincent JL	2002	60-66
Piotr F. Czempik	2022	66
This study	2022	32.4

In this study, 300 patients were studied with mean age 51.93 years, who were admitted to ICU, with predominance of males 188(63%) and 112(37%) patients were females. A majority of patients 90(30%) were in the age group of 30-45 years, 88(29.33%) in 46-59 years, 77(25.66%) patients in age group 60-75 years. The mean age of females was 49.3 years and males were 48.9 years.

Juarez-Vela, collected data from a total of 387 patients. Only 142 patients were admitted to this study without a diagnosis of anemia with a median age of 58 years (IQI: 48–69), 71.83% male and 28.17% female [9].

In this study 34(11.3%) patients were not anemic at admission, with male predominance. Mean age of males was 48.9 years, mean Hb 14.2 g/dl and of females was 49.3 years with mean Hb 12.86 g/dl. Among 34 patients, 2 males and 1 female did not survive.

In this study at admission, the mean Hb level in anemic patients was 9.33 g/dl and in non-anemic it was 13.84 g/dl. The Hb level reduced to 8.77 g/dl during the stay in ICU. The mean Hb level among non anemic female patients was 12.86 g/dl and among male patients was 14.20 g/dl. The mean Hb level among anemic male patients was 8.94 g/dl and female patients was 8.45 g/dl.

Study done by Corwin et al showed, the mean hemoglobin level at baseline was 11.0 ± 2.4 g/dL. Hemoglobin level decreased throughout the duration of the study. Overall, 44% of patients received one or more RBC units while in the ICU (mean, 4.6 ± 4.9 units) [4].

In this study main reason for admission was medical 230(76.66 %), of which most common reason being infection 23.9% comprising of COVID, dengue mainly and renal diseases 19.1%. Surgical cases were 70(23.3%), of which trauma cases were 5.6 % and other surgical cases comprised of 17.6%. Other medical causes included chronic liver diseases, cardiac diseases, and respiratory diseases.

Smith ZA studied, 370 admissions to the ICU during the study period medical diagnoses accounted for 50.1% of admissions followed by surgery (43.2%) [10].

In 34 patients who were not anaemic at admission, developed anaemia during stay. Leading cause was blood loss followed by sepsis.

In this study, 65(21.6%) patients admitted with shock. Among these patients, the incidence of septic shock in patients admitted to an Intensive Care Unit (ICU) was 9.33%, 4.33% had hemorrhagic shock, 7% patients had hypovolemic shock and 1.33% had cardiogenic shock.

In a study done by Raul Juarez Vela, 38(26.76%) out of 142 presented with shock at admission, most common was septic shock (9.86%) followed by cardiogenic shock (8.45%) [9].

In this study, we found mean length of stay in mild anaemia cases was 7 days, in moderate anaemia 11.97 days and in severe cases 13.0 days. Overall, mean length of stay was 12.22 days, which is comparable to study done by Manal M. Kamal, in this study mean length of stay was $11, 87 \pm 12, 04$.

In this study mean volume per draw was 14.53ml which is comparable to the study done by Chant C, the patients had a mean daily phlebotomy volume of 13 ml. 97(32.3%) out of 300 patients received blood transfusion with mean length of stay and mean volume draw 12.75 days and 176.72 ml respectively, in whom who did not receive BT was it was 11.97 days and 160.28 ml respectively. The mean pretransfusion level of haemoglobin was 7.6 g/dl. Mean Hb level is comparable to the study done by Thomas, Jissy et al. [11] The RBC transfusion rate was comparable to Vincent JL and less as compared to Thomas Jissy and Chant C [2, 12].

Rahim Baghaei the mean hemoglobin level for onset of blood transfusion was 8.38 ± 1.17 g/dl. In study done by Corwin et al, the mean pretransfusion hemoglobin was 8.6 ± 1.7 g/dL [13].

Patients with chronic diseases had normocytic normochromic anaemia. The most common type of anaemia in renal patients 44(14.66%) was normocytic normochromic, which is comparable to study by Mohammed MR, 40 patients were included with chronic renal diseases, the most common types of anaemia was normochromic anemia (62.5 %) [14].

Vitamin B12 levels were studied in 18 patients out of 32 patients with macrocytic anaemia, out of those Vitamin B12 levels were reduced in 12 patients. S. ferritin levels were evaluated in 94 cases, it was raised in 55(58.5%) cases out of which 30 patients had NCNC anaemia and 14 patients with microcytic anaemia also showed raised levels, showing that it is not reliable marker for iron deficiency anemia. S. ferritin levels were decreased in 8 patients, of which 6 had MCHC anemia. Procalcitonin levels were evaluated in 136 patients. Levels were raised in 117(86%) patients with anaemia. Other parameter CRP was done in 97 cases, of which it was raised in 84(86.55) cases with anemia. Both CRP and procalcitonin are raised suggesting an important role of chronic inflammation in pathogenesis of anemia.

In a study by, Rodriguez RM researchers reported that 9% of ICU patients were iron deficient, 2% were vitamin B₁₂ deficient, and 2% were deficient in folic acid leading to anemia. In our study 4% cases were vitamin B12 deficient and iron deficiency was seen in 16.6%, both are high as compared to above study. [2]

The survivors were 280 and those who did not survive were 20, the mean Hb at admission was 9.32 g/dl for survivors group and 9.48g/dl for non survivors group which is higher than the mean Hb in the study done by Manal M. Kamal Shams Eldin [90]. In his study the survivors were 103 (62.5%), and those who did not survive were 62 (37.5%) the mean hemoglobin at admission was 8.28g/dl for survivors group and $8.27 (\pm 2.36)$ for non survivors. During the ICU stay anemia worsened in 8 (40%) patients and developed in 3 patients. The mean length of stay and mean phlebotomy volume in survivors was 12.07 days and 166.4 ml respectively, whereas in non-survivors it was 14.35 days and 183.95

ml respectively. This indicates longer stay and more blood volume draw may be related to increased mortality in critical patients. In 34 patients, who developed anemia during stay, the mortality rate was 8.8%, 2 were males and 1 female. Leading cause of death was blood loss (35%), followed by sepsis (30%), CNS (20%), CVS (10%) and renal (5%).

In this study 84 patients were admitted for more than 14 days, representing 28% of our study group, 11% of them died with mean Hb 8.9 g/dl.

Study conducted by Naglaa, showed post cardiac arrest, respiratory failure, neurologic problems, cardiogenic shock, septic shock, acute renal failure, and obstetrics catastrophes were associated with higher frequency of mortality among the total number of each reason; (85.7%, 77.8%, 66.7%, 60%, 55%, 45.5%, 60%) respectively. 78 patients were admitted for more than fourteen days in the ICU they represented 25% of this study group 39.7% of them died with haemoglobin 7g/dl which was chosen as a best predictor to outcome [15].

Poor outcomes were reflected by higher cases of worsening or development of new anemia as well as in the mortality figures. Clinician should minimize blood loss wherever possible and aggressively manage moderate or severe anemia to improve critical care outcome. Optimization of frequency and volume of blood drawn for tests is likely to improve clinical outcome.

CONCLUSION

Anemia is highly prevalent as well as most common hematological diseases associated with critical patients. Considering its multifactorial origin, it has great impact on morbidity and mortality of patient

Clinician should implement proactive measures to detect and prevent anemia as it is associated with poor patient outcome. Available therapies aim on maintaining adequate oxygenation. Future quality and patient safety improvements should be directed at modifiable risk factors such as phlebotomy and standardization of transfusion, because even small decreases in phlebotomy volumes appear to be associated with significant reductions in the number of RBC transfusions.

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