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INCREASED INCIDENCE OF HAEMOLYTIC ANAEMIA IN COVID-19 PANDEMIC TIME? A CROSS-SECTIONAL STUDY

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ABSTRACT

INTRODUCTION: After the global impact of the Coronavirus Disease 2019 (COVID-19) pandemic, which affects over 50 million individuals worldwide, the immune system has been reported hyperactivation and heightened autoantibody production. Post the COVID-19 pandemic, the diagnosis of hemolytic anemia has also exhibited a noteworthy escalation in emergency department admissions, capturing the attention of clinicians in this setting. Considering that autoimmune haemolytic anaemias are also classified under this group, the study investigated whether there was in fact a change in the incidence of haemolytic anaemia.

MATERIAL AND METHODS: The study included retrospective data from 591 patients admitted to the emergency department and diagnosed with anemia between September 2020 and September 2023. A retrospective review of patient records covered both pre- and post-diagnosis periods. The collected data comprised demographic information, laboratory values, primary diagnoses, and clinical outcomes. The classification resulted in three distinct groups: Chronic Anemia (CA), Anemia Due to Blood Loss (BLA), and Hemolytic Anemia (HA).

RESULTS: Between 2020 and 2023, the incidence of anemia notably decreased among patients in the CA group, whereas a significant increase in anemia incidence was observed among patients in the HA group over the same study period (p value < 0.05).

CONCLUSIONS: The study found that there was indeed an increase in the incidence of haemolytic anaemia. However with this, further detailed studies are needed to determine whether the rise in the incidence of hemolytic anemia during the COVID-19 pandemic is attributable to autoimmune disease.

KEYWORDS: incidence of anemia; hemolytic anemia; COVID-19; autoimmune diseases

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INTRODUCTION

Anaemia stands as the most prevalent haematological disorder, and the availability of comprehensive epidemiological and statistical data is hindered by divergent definitions. Nevertheless, the World Health Organization (WHO) provides the most reliable assessment of anaemia data. According to WHO, approximately 24.8% of the global population is affected by anaemia, with the highest prevalence observed among preschool children, pregnant women, and the elderly, in descending order [1].

Frequent encounters with patients presenting with anaemia in emergency departments underscore the significance of their thorough evaluation and

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management. Effectively addressing the aetiology, conducting further examinations, and initiating appropriate treatment in the emergency department play a crucial role in optimizing patient care for anaemia [2].

Patients with anaemia may present at the emergency department with symptoms directly attributable to anaemia, or they may manifest with asymptomatic or nonspecific complaints. Comprehensive data on the frequency of anaemia cases in the emergency department are currently limited [3].

Patients with anaemia admitted to emergency services may present with a variety of complaints, including weakness, fatigue, coldness, paleness, yellowing of the skin and eyes, chest pain, abdominal pain, and, in cases of acute blood loss, symptoms such as hypotension, tachycardia, and altered consciousness. Numerous tests essential for diagnosing anaemia are routinely utilized in emergency departments. However, for certain aetiological classes of anaemia, haematologists may require additional tests to be conducted to facilitate treatment planning [4].

Haemolytic anaemia is a condition characterized by the destruction of red blood cells. This can occur due to antibodies against red cell antigens or through non-immune-mediated breakdown of red cell membranes. When the antibodies are produced by the host, the resulting anaemia is termed autoimmune haemolytic anaemia (AIHA). The incidence of AIHA is approximately 1 in 100,000 people per year [5]. Haemolytic anaemia can be classified as secondary, resulting from an underlying cause, or primary, occurring as an independent phenomenon [6].

In haemolytic anaemias, there is a notable elevation in LDH values released into the circulation during erythrocyte destruction and haemolysis. Additionally, bilirubin levels increase indirectly as a result of haemolysis. Haptoglobin, an acute phase reactant that binds to free haemoglobin, plays a crucial role in the diagnosis of haemolytic anaemia; its serum values decrease when haemolysis occurs [7].

In the differential diagnosis of autoimmune haemolytic anaemia, Coombs tests include the direct antiglobulin test (DAT) and indirect antiglobulin test. A positive result in the DAT is indicative of autoimmune haemolytic anaemia [7, 8].

Due to the plethora of definitions and the focus on populations with high prevalence, such as the elderly, preschool children, and pregnant women, studies on anaemia in the literature are often concentrated in these groups. Recognizing that the limitation of epidemiological and statistical data on anaemia is associated with this concentration, the study was designed to investigate the incidence and demographic characteristics of anaemia patients admitted to the emergency department over 3 years.

MATERIAL AND METHODS

Study setting and participants

This study was designed by retrospectively reviewing the data of patients who presented to the tertiary-level emergency department in Konya, Turkey and received a preliminary diagnosis of anaemia.

Sample size estimation

Since the study was retrospective and it was possible to reach all the data, the sample size was not calculated and it was aimed to reach the whole population.

Patients groups

Anaemia patients presenting to the emergency department and receiving a diagnosis were classified into three groups: 1) The CA group, encompassing cases related to iron deficiency, vitamin deficiencies, chronic kidney failure, and chronic liver failure; 2) The BLA group, including gastrointestinal system bleeding, genitourinary system haemorrhages, bleeding due to gynaecological pathologies, irregular menstrual bleeding, and oesophageal variceal bleeding; 3) The HA group, involving erythrocyte deformities, erythrocyte membrane disorders, membrane enzyme defects, immune and autoimmune diseases, viral infections (Mycoplasma, EBV, HIV), and drug-induced anaemias. The study compared the rates of all three patient groups within the 2020-2023 date range.

Exclusions were made for individuals under the age of 18 and over the age of 65 (n: 689), pregnant patients (n: 112), those with acute blood loss due to trauma (n: 292), early post-operative patients (n: 42), patients diagnosed with malignancy (n: 194), patients using neoplastic drugs (n: 82), and those with missing data (n: 79). Following these exclusions, the study comprised 591 patients who presented to the emergency department between September 2020 and September 2023 and were diagnosed with anaemia. The patient flow chart is presented in Figure 1.

As is well known, this period also includes the COVID-19 pandemic. Although the prevalence of infected individuals is high, not all patients with anaemia underwent COVID-19 testing, and routine COVID-19 tests were not conducted on anaemic patients. The comparisons made in the study pertain to the incidence of anaemia following the post-COVID pandemic period.

Data collection, and statistical analyses

For each of the CA, BLA, and HA groups, an analysis of variance (ANOVA) test was conducted to compare Hb (Normal range: 13–17 g/dL), Htc (Normal range: 40–49 %), MCV (Normal range: 80–94 fL), MCH (Normal range: 27–35 pg), MCHC (Normal range: 32–35 g/dL), PLT (Normal range:150–450 x $10^3/\mu$L), LDH (Normal range: 135–214 U/L), and indirect bilirubin values. The homogeneity assumption was assessed using the Levene test, and it was determined that the homogeneity assumption was violated in all analyses (p value < 0.05). Given the violation of the homogeneity assumption in the ANOVA analysis, the Welch correction was applied due to a lack of significance in the Levene test ($p > 0.05$) and ANOVA test ($p > 0.05$), while the Welch test yielded significance ($p < 0.05$).

Descriptive statistics, including mean, standard deviation, standard error, and confidence intervals for the mean, were calculated.

Statistical Packages for the Social Sciences (SPSS) 18.0 Windows software package (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of the findings obtained in the study.

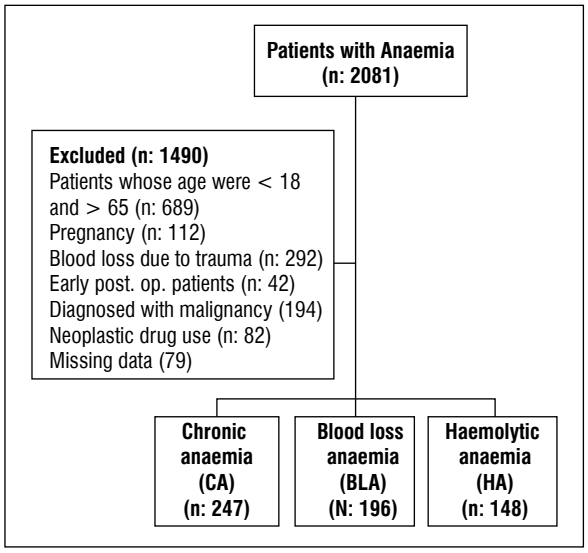

FIGURE 1. Diagram of inclusion and exclusion cases

RESULTS

The study comprised 591 patients, including 173 males and 418 females. A distribution analysis revealed that 44.3% (n: 262) of the patients fell within the 35–50 age range, 34.2% (n: 202) were over 50 years old, and 21.5% (n: 127) were under 35 years old (Tab. 1).

The comparative analysis of Hb, Htc, MCV, MCH, MCHC, PLT, LDH, and indirect bilirubin values among CA, BLA, and HA patients revealed significant differences (p value < 0.05). Descriptive statistics, including mean, standard deviation, standard error, and confidence intervals for the mean, are presented in Table 2.

Based on the results obtained from pairwise comparisons, it was observed that the BLA group exhibited lower, the CA group had intermediate, and the HA group demonstrated the highest Hb and Hct values. Furthermore, among the BLA, CA, and HA groups, a significant difference was identified in MCH and MCHC values (p value < 0.05). In the comparison of MCV values, it was found that the MCV values in the BLA and HA groups were significantly higher than the MCV values in the CA group (p value < 0.05). However, there was no significant

Table 1. Gender and age distribution of patients included in the study

		Frequency	Percent	Valid percent	Cumulative percent
Gender	Male	173	293	29.3	29.3
	Female	418	70.7	70.7	100.0
Age	35–50	262	44.3	44.3	44.3
	> 50	202	34.2	34.2	78.5
	< 35	127	21.5	21.5	100.0
Total		591	100.0	100.0	

Table 2. The comparative analysis of Hb, Htc, MCV, MCH, MCHC, and PLT values among chronic anaemia, blood loss anaemia and haemolytic anaemia patients

		Patients (n)	Mean	Standard Deviation	Standard Error	95% Confidence	
					Lower Bound	Upper Bound	
Hb	CA*	247	8.595	1.7475	0.1112	8.376	8.814
	BLA**	196	7.438	2.6109	0.1865	7.070	7.806
	HA***	148	11.189	2.1703	0.1784	10.836	11.541
	Total	591	8.861	2.6002	0.1070	8.651	9.071
Hct	CA	247	29.838	4.4692	0.2844	29.278	30.399
	BLA	196	27.041	9.1326	0.6523	25.754	28.327
	HA	148	38.547	5.2512	0.4316	37.694	39.400
	Total	591	31.091	7.9255	0.3260	30.451	31.732
MCV	CA	247	72.544	9.6804	0.6159	71.331	73.757
	BLA	196	82.331	13.985	0.9989	80.361	84.301
	HA	148	88.369	16.850	1.3851	85.632	91.106
	Total	591	79.699	14.749	0.6067	78.508	80.891
MCH	CA	247	22.145	5.5183	0.3511	21.453	22.836
	BLA	196	29.598	6.2080	0.4434	28.723	30.472
	HA	148	38.037	8.0400	0.6609	36.731	39.343
	Total	591	28.443	9.5154	0.3914	27.674	29.212
MCHC	CA	247	28.532	2.5674	0.1634	28.211	28.854
	BLA	196	34.514	3.3047	0.2360	34.049	34.980
	HA	148	41.647	7.0546	0.5799	40.501	42.793
	Total	591	33.810	7.1509	0.2941	33.133	34.288
PLT	CA	247	310.00	94.835	6.034	29811	321.89
	BLA	196	288.94	79.957	5.711	277.68	300.20
	HA	148	284.01	65.151	5.355	2273.42	294.59
	Total	591	296.51	83.993	3.455	289.72	303.29

*Chronic anaemia, **Blood loss anaemia, ***Haemolytic anaemia

difference between the BLA and HA groups in terms of MCV values (p value $>$ 0.05). While no significant difference was observed in PLT values between BLA and CA patients (p $>$ 0.05), it was noted that PLT values were lower in HA group patients (Tab. 2).

Patients in the BLA, CA, and HA) groups had a 4.6%, 6.1%, and 100% probability of elevated LDH levels, respectively. According to the results of the ratio test, the difference in the probability of high LDH was found to be statistically significant for all three groups (p value $<$ 0.05). This difference was further examined through pairwise comparisons for a detailed analysis.

In this context, no significant difference was identified in the probability of LDH and indirect bilirubin elevation between BLA and CA groups, and this probability was observed to be low. However, the probability of high LDH and indirect bilirubin in HA group patients was 1, indicating a complete likelihood, and this probability was found to be significantly different from other diagnoses (Tab. 2, 3).

The rates of CA, BLA, and HA patients in the years 2020–2023 are presented in Table 3. A proportion test was conducted to assess whether the rates of patients in all three groups exhibited significant changes over the years. Holm correction was applied in pairwise comparisons for a comprehensive analysis.

According to the results of the proportion test, there was a significant difference in the rates of CA patients by year (p value $<$ 0.05). The difference in the rates of HA patients by year was found to be significant (p value $<$ 0.05). Furthermore, there was

Table 3. The crosstabulation of chronic anaemia, blood loss anaemia and haemolytic anaemia patients in the years 2020–2023

Date		Diagnosis Code			
		CA*	BLA**	HA***	Total
2020	Count	76	53	28	157
	% within date	48.4%	33.8%	17.8%	100.0%
	% within diagnosis code	30.8%	27.0%	18,9%	26.6%
2021	Count	58	42	15	115
	% within date	50.4%	36.5%	13.0%	100.0%
	% within diagnosis code	23.5%	21.4%	10.1%	19,5%
2022	Count	49	48	55	152
	% within date	32.2%	31.6%	36.2%	100.0%
	% within diagnosis code	19.8%	24.5%	37.2%	25.7%
2023	Count	64	53	50	167
	% within date	38.3%	31.7%	29.9%	100.0%
	% within diagnosis code	25.9%	27.0%	33.8%	28.3%
Total	Count	247	196	148	591
	% within date	41.8%	33.2%	100.0%	100.0%
	%within diagnosis code	100.0%	100.0%	100.0%	100.0%

*Chronic anaemia, **Blood Loss anaemia, ***Haemolytic anaemia

no significant change in BLA patient rates over the 2020–2023 period (p value $>$ 0.05).

In summary, over the three years from 2020 to 2023, a decrease was observed in the proportion of CA patients, while the rate of HA patients increased.

DISCUSSION

Patients with anaemia frequently present to the emergency department, and the evaluation and management of anaemia constitute a crucial aspect of emergency medical care. The epidemiology and statistical data related to anaemia face limitations due to the broad and diverse definitions and aetiologies associated with this condition [3]. Nevertheless, existing studies in the literature typically focus on populations where the prevalence of anaemia is widespread. Notably, in elderly patients, individuals with chronic kidney failure, chronic liver failure, additional malignancies, and those using medications for chronic diseases, the incidence of anaemia tends to increase [9]. The higher prevalence of anaemia in men compared to women could be attributed to the WHO definition, where anaemia is defined as haemoglobin levels below 13 g/dl for men and below 12 g/dl for women, as well as inherent physiological differences between genders [1]. Additionally, in pregnant women, the incidence of anaemia tends to increase due to gestational physiology, heightened metabolism, nutritional deficiencies, and lower socioeconomic status [2, 10]. Anaemia impacts 20% of children in the United States [11]. Similar to adults, anaemia in preschool children can arise from factors such as decreased production or destruction of red blood cells. Iron deficiency anaemia is a prevalent cause of anaemia in children. Additionally, hereditary anaemias, such as sickle cell anaemia and thalassemia, are common among children [12]. Acute blood loss secondary to trauma stands out as one of the most frequent causes of anaemia due to acute blood loss observed in the emergency department [13].

The present study aimed to investigate the incidence and demographic characteristics of anaemia, a condition less frequently encountered in emergency department admissions. To achieve this, deliberately excluded were populations with a higher incidence of anaemia, such as individuals over 65 years of age, those under 18 years of age, pregnant patients, individuals diagnosed with malignancy, patients using neoplastic drugs, and those diagnosed with anaemia secondary to trauma.

The patients included in the present study were categorized into three major groups: CA, BLA, and HA. Utilizing clinical and laboratory values from retrospective patient data as a basis, patients were classified based on Hb, Htc, MCV, MCH, MCHC, LDH, and indirect bilirubin levels.

Particularly in the HA group, there was a statistically significant difference in LDH and indirect bilirubin levels compared to the other two groups. This once again reaffirmed the conclusion that LDH and indirect bilirubin are crucial factors in determining the diagnosis of haemolytic anaemia. The values of LDH and Indirect Bilirubin were identified as diagnostically and predictively important for haemolytic anaemia.

In the CA group, consultation with the General Internal Medicine branch was sought by the emergency clinician to determine the chronic disease and aetiology of anaemia. For patients in the BLA group, the emergency clinician assessed the acute or chronic status and initiated blood transfusion and volume replacement, considering vital signs (hypotension, tachycardia), state of consciousness, and Haemoglobin values ($<$ 8g/dL) in 67 cases. All patients in the Anaemia Due to Blood Loss (BLA) group who were initially intervened in the emergency department underwent further evaluation. The focus of bleeding was identified, and patients were subsequently admitted to specialized clinics for additional examination and treatment. Specifically, 133 patients were referred to Gastroenterology-General Surgery for issues related to gastrointestinal bleeding and oesophageal variceal bleeding, while 63 patients were directed to Gynecology-Urology for myometrial and genitourinary haemorrhage. Due to the absence of routine tests such as haptoglobin, Coombs test, and serum protein electrophoresis in the emergency clinic where the study was conducted, cases with elevated LDH and indirect bilirubin levels in the HA group were identified. The emergency clinician was guided to consider haemolytic anaemia as the cause of anaemia in this group. Subsequently, consultation with haematology was sought to distinguish the aetiology of haemolytic anaemia, and these patients were hospitalized for further examination and treatment.

Given the exclusion of patients aged $>$ 65 and $<$ 18 from this study, the age range with the highest incidence of anaemia was identified as being between 35–50 years. The higher number of patients in this age range can be attributed to the presence of a significant female population within the childbearing age group. This explains why the number of female patients (n: 418) is higher than the number of male patients (n: 173). Consequently, it is reasonable to assert that genitourinary and gynaecological pathologies, characterized by conditions such as menorrhagia, metrorrhagia, ectopic pregnancy, and irregular menstruation, play a significant role in causing anaemia in women of childbearing age, excluding elderly and paediatric patients [14].

The substantial rise in the rate of Haemolytic Anaemia (HA) patients over the three years from August 2020 to January 2024 has prompted a reevaluation of the aetiology of haemolytic anaemia. Haemolytic anaemias can be categorized into two main groups: 1) hereditary causes, including erythrocyte deformities, membrane disorders, enzyme deficiencies, *etc*., and 2) acquired causes, such as immune reactions, autoimmune disorders, viral infections, mycoplasma, HIV, drug-induced reactions, *etc.* [15, 16].

The present study observed that all patients admitted to haematology with the diagnosis of haemolytic anaemia were newly diagnosed. Given that the age range with the highest number of patients is between 35–50, it would have been expected for patients to be diagnosed with hereditary haemolytic anaemia much earlier in life. Consequently, the increased incidence of haemolytic anaemia in this context is likely attributed to acquired haemolytic anaemias [17].

Taking into consideration the global impact of the COVID-19 pandemic between 2020–2023, it is evident from numerous cases and case series studies in the literature that there has been an increase in autoimmune diseases associated with COVID-19 [18–20]. Remarkably, among the autoimmune diseases that have seen an uptick after the pandemic, there is a notable increase in case series related to haemolytic anaemia, drawing significant attention in the medical literature [21, 22].

The principal limitation of the study lies in the fact that Emergency Clinicians were unable to ascertain the aetiology of haemolytic anaemia in patients diagnosed with this condition. This was primarily due to the absence of routine tests, such as haptoglobin, reticulocyte count, Coombs test, and serum protein electrophoresis, which are not typically conducted in emergency departments.

CONCLUSIONS

The incidence of patients diagnosed with haemolytic anaemia in the emergency department where the study was conducted increased between 2020 and 2023, corresponding to the COVID-19 pandemic period. There are studies in the literature indicating that the COVID-19 pandemic has led to an increase in autoimmune diseases. Further detailed studies are needed to determine whether the rise in the incidence of haemolytic anaemia during the COVID-19 pandemic is attributable to autoimmune disease.

Article information and declarations

Data availability statement

Workers have access to the data, provided that it is not disclosed to third parties.

Ethics statement

Ethics approval was obtained from the local ethics committee (date:04.01.2024, number: 01-40).

Author contributions

Demet Acar: conception, design, wrote the paper, supervision; Nazlı Kenan Karakuş: data collection and processing; Fatih Cemal Tekin: conception, design, wrote the paper, supervision.

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Conflict of interest

No conflict of interest between the authors.

Supplementary material

None.

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