Volume 5, Number 2, November 2021.
ISSN 2459-9484
http://seemedj.mefos.unios.hr

SEEMEDJ SOUTHEASTERN EUROPEAN MEDICAL JOURNAL

HAND STUDY MIHAJLO ŽIVIĆ, 1929
PLASTER, BLACK COLOR, 86 X 35 X 25 CM
INV. NO. MLU-K-130

SELECTED BY: DANIEL ZEC, PHD, MUSEUM ADVISOR

PHOTO: MARIN AND DOMAGOJ TOPIĆ

Josip Juraj Strossmayer University of Osijek
Faculty of Medicine

(Sikirevci, 23. IX. 1899. – Osijek, 14. IV. 1942.)

Mihajlo Živić graduated in sculpture at Kr. Academy of Arts and Crafts in Zagreb in 1928 (since 1926 he has been in a special sculpture school with Ivan Meštrović). He exhibited for the first time in Osijek in 1924 at a large exhibition of the Art Section of the Club of Croatian Writers and Artists in Osijek. After completing his studies, he returned to Osijek, where he remained until his death. He worked as a drawing teacher at the Osijek civic school. In 1928 he undertook a study trip to Paris, and in 1929 to Florence. In 1929, he had a large solo exhibition in Osijek, which represented a turning point in the establishment of Osijek interwar sculpture as the first Osijek exhibition to exhibit exclusively sculptural works, created by one, and domestic, Osijek, author. Thanks to the initiative of the Club of Croatian Writers and Artists in Osijek, he managed to realize several of his sculptural works as monumental sculpture - in the form of reliefs on memorial plaques. The most intense and fruitful period of his creation was from 1929 to 1935. He was influenced by Ivan Meštrović in his sculptural work. Only in some works, primarily relief portraits, a different stylistic expression can be discerned, moving away from Meštrović's recognizable stylistic morphology towards mild geometric stylization.

Southeastern European Medical Journal (SEEMEDJ)
Published by
University Josip Juraj Strossmayer Osijek
Faculty of Medicine Osijek
for publisher: Ivica Mihaljević, MD, PhD, - Dean of Faculty of Medicine Osijek, Croatia

Published online:
http://seemedj.mefos.unios.hr
ISSN 2459-9484

Since 2021 the journal is published with the financial support of the
Ministry of Science, Education and Sports of the Republic of Croatia

SEEMEDJ SOUTHEASTERN EUROPEAN MEDICAL JOURNAL

Dear colleagues,

Hereby, new 10th issue of SEEMEDJ is presented to you. This issue brings flaming topic of COVID-19 disease and some intriguing questions on transmission and mortality of COVID-19 in cancer patients in relation to blood group (Ebinc et al). Article by Bogović et al reviewed clinical outcomes of COVID-19. Anaemia of chronic disease is more common in COVID-19 positive patients and the clinical outcomes of COVID-19 disease is poorer. Also, an advanced inflammatory condition characterized with higher ferritin/transferrin ratio may be a predictive factor of intensive care unit admission in these patients. In line with wide discussion on pro and contra vaccination, article by Smajić et al. present a survey on university students and their attitudes towards responsible behavior and vaccination, finding interesting differences in favor to students form biomedical fields. Work in shifts significantly affects arterial blood pressure and higher ferritin levels in women, suggesting subclinical inflammatory process, possibly important in etiology of hypertension (Cvitkušić-Lukenda et al). Furthermore, Pavličević Tomas and Degmečić review data of 800 patients in psychiatry clinic and found out that almost one third of them suffered from hypertension which was related to recurrent depressive disorder, alcohol addiction and posttraumatic stress disorder.

Outcomes of deep vein thrombosis in emergency department with emphasis on treatments with novel oral anticoagulants (NOAC) is presented in article by Radilj et al. while chronic kidney disease related anemia is reviewed in study by Hrvačić et al. And finally, importance of effective minimization of blood usage and wastage in Guyana is presented in article by Kurupa et al.

The art work at the cover page is a sculpture from the first half of 20th century, a work by Mihajlo Živić, artist from Osijek, whose work was influenced by Ivan Meštrović.

I hope that readers will find relevant published articles for their work On a behalf of editorial board and my own, I warmly greet our readers and invite them to join us in the endeavor of publishing own scientific work in SEEMEDJ.

Ines Drenjančević, MD, PhD
Editor-in-Chief
Southeastern European Medical Journal (SEEMEDJ)

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Contents

Original article

Blood Group and COVID-19 Transmission and Mortality in Patients With Malignant Disease

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Abstract

Aim: The study aimed to investigate risk factors affecting the transmission of and mortality from COVID-19 in patients diagnosed with a malignant disease. In this context, ABO blood groups, gender, age, type of malignant disease, type of anti-tumoral agents, comorbidities and stage were examined.

Materials and Methods: Files of 1,256 patients who presented to our clinic between March and December 2020 were retrospectively reviewed. Patients diagnosed with a malignant disease who became infected with COVID-19 and those who did not were compared with regard to demographic, clinical characteristics and laboratory results (status of having been infected with COVID-19, ABO blood groups).

Results: Of 1256 patients in total, 72 (5.7%) were diagnosed with COVID-19. Median age of cancer patients infected with COVID-19 was 53 years (18-80). The most common types of cancer included gastrointestinal cancer (22.2%), breast cancer (20.8%), genitourinary cancer (20.8%) and lung cancer (16.7%). Of the patients diagnosed with COVID-19, 18.1% (n=13) died. Multivariate analysis identified disease stage as an independent prognostic factor for the risk of mortality [HR: 0.07, 95% CI (0.007-0.74), (p=0.02)]. A comparison of patients who became infected with COVID-19 and those who did not with regard to ABO blood groups (p=0.39) showed no statistically significant differences between the two groups. There was also no correlation between ABO blood groups and the risk of COVID-19-related mortality (p=0.83).

Conclusion: In patients suffering from malignant diseases, the ABO blood type exhibited no correlation with the risk of COVID-19 transmission and mortality. This study determined the presence of metastatic disease as a negative prognostic factor. Patients suffering from a metastatic malignant disease represent a high risk group for COVID-19 and should be treated using all necessary precautions.

(Ebinç S, Oruç Z, Kalkan Z, Urakçı Z, Kaplan MA, Küçüköner M, Işıkdoğan A. Blood Group and COVID-19 Transmission and Mortality in Patients With Malignant Disease. SEEMEDJ 2021; 5(2); 1-8)

Received: Apr 18, 2021; revised version accepted: Oct 10, 2021; published: Nov 26, 2021

KEYWORDS: COVID-19, abo blood group system, neoplasm

Introduction

SARS-CoV-2 infection, the first cases of which were reported in the People's Republic of China in late 2019, spread rapidly within a short period of time, marking the beginning of the COVID-19 pandemic. During this period, which has impacted almost all populations, patients diagnosed with a malignant disease were included among high-risk patient groups (1,2). Besides cancer, conditions such as immunosuppression, presence of comorbidities and advanced age resulted in these patients being included in groups impacted more severely by the infection (3). Frequent hospital visits are also among the factors elevating the risk of COVID-19 transmission in this population (4).

The genetically coded ABO blood group system is a phenotypic reflection of a genetic makeup. These antigens may serve as a protective factor against certain diseases and as a predisposing factor for others. Furthermore, the ABO blood group system was found to be associated with multiple infectious diseases. In some studies, it has been reported that anaemia is more common in A blood group in plasmodium falciparum and that HIV ag/ab is more common in A blood group (5, 6). Relationships between many infectious pathogens and blood group antigens and Anti-A/B antibodies have been investigated in extensive analyses (7). For example, some human immunodeficiency virus (HIV) and Gp120 isolates can react with blood group active monoclonal antibodies and lectins (8). Many studies have been conducted to evaluate the relationship between COVID-19 infections and the ABO blood group system. Some studies have found that women with A blood group are more susceptible to COVID-19 infections, while much lower COVID-19 infection rates were found in those with O blood group (9). In a study conducted during the Hong Kong epidemic, it was argued that O blood group is more resistant to the transmission of severe acute respiratory syndrome coronavirus (SARS-CoV) and that the risk of transmission is higher in A, B and AB blood groups (10). Like HIV, SARS-CoV targets the host cell via adhesion glycoproteins. It has been suggested that SARS-CoV targets the respiratory and gastrointestinal mucosa with its spike (S) protein and that high-titre Anti-A monoclonal antibody can block the S protein (11). Based on this information, the status of blood groups in the transmission of and mortality from COVID-19 was examined in patients suffering from malignant diseases.

Materials and Methods

Files of patients diagnosed with a malignant disease who presented to our Medical Oncology Clinic between March 2020 and December 2020 were retrospectively reviewed. Demographic, clinical characteristics of the patients, data about their treatment and laboratory results (status of having been infected with COVID-19, COVID-19 PCR test results, ABO blood group results) were obtained from the hospital records system. Patients in whom the presence of a SARS-CoV-2 infection was confirmed clinically and by laboratory results (positive PCR test) were considered COVID-19 cases. Patients diagnosed with COVID-19 were defined as the case group and patients not diagnosed with COVID-19 were defined as the control group. Clinical and laboratory characteristics of the groups and their survival outcomes were evaluated. Information about the blood group of 1,256 patients who presented to our clinic during the pandemic was available. Of these patients, 72 contracted COVID-19 and 13 patients in the patient group that contracted COVID-19 died. All statistical analyses were performed based on the specified numbers of patients. Patients were categorised based on age, gender, presence of comorbid diseases, type of cancer diagnosis, disease stage (metastatic/non-metastatic), treatment agents they received (chemotherapy, immunotherapy, tyrosine kinase inhibitors, anti-hormonal therapies) and blood groups (ABO, Rh). The case and control groups were compared according to these parameters. Also, the case groups were further categorised as survivors and non-survivors.

Mann-Whitney U test and logistic regression analysis were used for the analyses of non-normally distributed or non-parametric variables. A 95% confidence interval and significance value of p<0.05 were used.

Table 1. Mortality risk for patients with Covid 19 + according to disease and treatment characteristics

	N (%)	Non-survivor (N,%)	Survivor (N,%)	P value
All patients	72	13 (18.1%)	59 (81.9%)	
Age (median, yrs)	53 (18-80)	46 (18-80)	55 (18-75)	0.23**
Gender				0.41*
Male	37 (51.4%)	8 (61.5%)	29 (49.2%)	
Woman	35 (48.6%)	5 (38.5%)	30 (50.8%)	
Comorbidities				0.79*
Yes	30 (41.7%)	5 (38.5%)	25 (42.4%)	
No	42 (58.3%)	8 (61.5%)	34 (57.6%)	
Diagnosis				0.65*
Brain	3 (4.2%)	0 (0%)	3 (5.1%)	
GUS	15 (20.8%)	1 (7.7%)	14 (23.7%)	
Gİ	16 (22.2%)	5 (38.5%)	11 (18.6%)	
Soft tissue	5 (6.9%)	1 (7.7%)	4 (6.8%)	
Breast	15 (20.8%)	2 (15.4%)	13 (22%)	
Lung/pleura	12 (16.7%)	3 (23.1%)	9 (15.3%)	
Head and Neck	2 (2.8%)	0 (0%)	2 (3.4%)	
Others	4 (5.6%)	1 (7.7%)	3 (5.1%)	
Stage				**0.01***
Metastatic	46 (63.9%)	12 (92.3%)	34 (57.6%)	
Non-metastatic	26 (36.1%)	1 (7.7%)	25 (42.2%)	
Anti Tumoral agents (n:61)				0.79*
Chemotherapy	36 (59%)	5 (50%)	31 (60%)	
TKİs	9 (14.8%)	2 (20%)	7 (13%)	
İmmunotherapy	3 (4.9%)	1 (10%)	2 (3.9%)	
Hormonal therapy	13 (21.3%)	2 (20%)	11 (21.6%)	

*TKİ: Tyrosine kinase inhibitors, GUS: genitourinary system, Gİ: gastrointestinal truct, * chi-square test, ** independent samples T test.*

Statistical Anaylsis

Data were statistically analysed using the SPSS 18.0 package program. Descriptive statistics were used to evaluate patient characteristics and the frequencies of the parameters. Student's t-test was used for normally distributed numeric variables. A chi-squared test, Fisher's exact test,

Results

The study included 1,256 patients whose data could be obtained. During the pandemic, 72 (5.7%) patients were diagnosed with a COVID-19 infection. General characteristics of the patients are presented in Table 1.

Table 2: Covid-19 transmission and mortality status according to blood groups

		All patients	Blood groups (A-B-O)	O	A	B	AB	Rh group	Positive	Negative
All patients	N	1256		430 (34.2%)	488 (38.9%)	222 (17.7%)	116 (9.2%)		1092 (86.9%)	164 (13.1%)
	Covid(+)	72 (5.7%)		28 (38.8%)	21 (29.1%)	15 (20.8%)	8 (11.1%)		59 (81.9%)	13 (18.1%)
	Control	1184 (94.4%)		402 (33.9%)	467 (39.4%)	207 (17.4%)	108 (9.1%)		1033 (87.2%)	151 (12.8%)
	X²		0.38					0.19		
	HR (95%CI)			reference	0.64 (0.36-1.15)	1.04 (0.54-1.99)	1.06 (0.47-2.40)	0.66 (0.35-1.23)		
	p*		0.39		0.14	0.90	0.88	0.19		
Covid-19 +	N	72		28 (38.9%)	21 (29.2%)	15 (20.8%)	8 (11.1%)		59 (81.9%)	13 (18.1%)
	Non-survivor	13 (18%)		6 (46.2%)	3 (23.1%)	4 (30.7%)	0 (0%)		11 (84.6%)	2 (15.4%)
	Survivor	59 (82%)		22 (37.3%)	18 (30.5%)	11 (18.6%)	8 (13.6%)		48 (81.4%)	11 (18.6%)
	X²		0.40					0.78		
	HR (95%CI)			reference	0.61 (0.13-2.79)	1.33 (0.31-5.72)	0.00	1.26 (0.24-6.51)		
	p*		0.83		0.52	0.69	0.99	0.78		

*X2:chi-square test, *Binary logistic regression*

Median age of patients who contracted COVID-19 was 56 years. Male patients comprised 51.4% (n=37) of the cases. The most common types of cancer in COVID-19-positive patients included gastrointestinal cancer (22.2%), breast cancer (20.8%), genitourinary cancer (20.8%) and lung cancer (16.7%). Univariate and multivariate analyses showed that age, gender, comorbidity status and type of primary diagnosis had no effect on mortality in the patients infected with COVID-19. Of 61 patients in active treatment, 59% (n=36) received chemotherapy, 21% (n=13) received hormonal therapies, 14.8% (n=9) received tyrosine kinase inhibitor and 4.9% (n=3) received immunotherapy agents. A comparison of patients with regard to treatment they received showed no statistically significant differences between treatment agents in terms of mortality rates (p=0.79).

Of 1,256 patients evaluated with regard to ABO and Rh blood groups, 72 patients diagnosed with COVID-19 were defined as the case group and 1,184 COVID-19-negative patients were defined as the control group. In the case group, the rates of O, A, B and AB blood groups were 38.8% (n=28), 29.1% (n=21), 20.8% (n=15) and 11.1% (n=8), respectively. Regarding the case group, 81.9% of the patients (n=59) were Rh-positive and 18.1% (n=13) were Rh-negative. Meanwhile, in the control group, the rates of O, A, B and AB blood groups were 33.9% (n=402), 39.4% (n=467), 17.4% (n=207) and 9.1% (n=108), respectively. In the control group, 87.2% (n=1,033) of patients were Rh-positive and 12.8% (n=151) were Rh-negative. There was no statistically significant difference arising from ABO and Rh groups between the case and control groups with regard to the risk of COVID-19 transmission or among COVID-19-positive patients with regard to the risk of mortality. Details regarding blood groups are specified in Table 2.

The evaluation of COVID-19-positive patients in multivariate analyses according to the stage of disease showed that patients had a higher mortality risk in the metastatic stage compared with the non-metastatic stage [mortality rate of 26% in the metastatic stage, 3.8% in the non-metastatic stage (HR: 0.07, 95% CI (0.007-0.74), (p=0.02)]. Results of multivariate analysis are presented in Table 3.

Table 3. Multivariate analysis for mortality risk in patients with Covid 19 (+)

	Multivariate analysis	
	HR (95% CI)	**P value***
Age	0.93(0.87-1.00)	0.59
Comorbidities (no/yes)	1.76(0.23-13.0)	0.57
Stage (metastatic/non-metastatic)	**0.07(0.007-0.74)**	**0.02**
Blood groups (A-B-O)		0.80
O	Reference	
A	0.42(0.07-2.34)	0.32
B	0.76(0.15-3.90)	0.74
AB	0.99(0.00--)	0.99
Rh group (negative/positive)	1.66(0.25-10.7)	0.59

**Binary logistic regression.*

Discussion

It is known that patients diagnosed with a malignant disease are predisposed to infections due to immunosuppression arising from comorbidities and treatment they receive. During the COVID-19 pandemic, many unknown factors have become subjects of research, including, among other things, how and to what degree susceptible populations, such as those

suffering from malignant diseases, are affected by the pandemic and what the factors affecting disease transmission and mortality are. This study aimed to investigate the risk factors affecting the transmission of and mortality from COVID-19 in patients diagnosed with a malignant disease. The risk factors analysed included ABO blood groups, gender, age, type of malignant disease, type of anti-tumoral agents, comorbidities and stage.

Of 1,256 patients who were examined and treated at our clinic and whose blood groups could be determined exactly, 5.7% (n=72) were diagnosed with COVID-19 during the pandemic. Since the pandemic period is a dynamic period, variability in this rate across regions and an increase over time are expected. Previous studies conducted on patients diagnosed with a malignant disease have reported that advanced age, presence of comorbidities and receiving chemotherapy as opposed to other antitumor agents increase COVID-19-related mortality (12-14). In the evaluation of factors affecting mortality in patients infected with COVID-19 in this study, age, gender, presence of comorbidities and treatment received by the patients (chemotherapy, immunotherapy, TKI, hormonal therapy) were found to not influence disease-related mortality. COVID-19 is thought to be associated with a poorer course in lung cancers. However, in this study, the diagnosis of primary malignancy did not have a significant correlation with mortality. However, metastatic stage was found to be an independent risk factor predicting COVID-19 infection-related mortality (mortality rate of 26% in metastatic patients, 3.8% in non-metastatic patients (HR: 0.07, 95% CI (0.007-0.74), (p=0.02)). This can be explained by damage to natural barriers caused by cancer invasion and the patients' relative vulnerability to secondary infections. ABO blood group antigens are expressed in various tissues and cells, such as the epithelial, platelet, vascular endothelial cells and neurons. It is suggested that this system affects the spread of many pathogens. ABO antibodies are also a component of the innate immune system (15,16). Previous studies have found that susceptibility to viral infections is associated with ABO blood group. For example, susceptibility to Norwalk virus and hepatitis B was reported to vary depending on ABO blood type (17,18). Furthermore, individuals with O blood group were reported to have a lower likelihood of contracting SARS coronavirus (19). Do differences in blood group antigen expressions influence the risk of COVID-19 transmission and COVID-19-related mortality? Multiple epidemiological studies have been performed on this topic. Some studies have found that the number of patients with type-A blood was higher among patients infected with SARS-CoV-2 compared with healthy controls, while the number of those with O blood group was much lower. Some studies have also identified a correlation with the risk of mortality (9,20-22). In the study conducted by Zhao J. and colleagues, it was reported that A blood group was associated with a predisposition to COVID-19 infection, whereas the rate of infection was lower and the course of infection milder in O blood type individuals (21). In the study by Solmaz I. and colleagues conducted on a healthy population, COVID-19-positivity was reported to be higher in A blood group and lower in O blood group. However, it was stated that the need for intensive care did not vary across the groups (22). In another study, Arac E. and colleagues reported that there were no significant differences across the ABO blood groups, but that a significant difference existed within the Rh system, with Rh positivity predisposing persons to COVID-19 infection and Rh negativity exerting protective effects against it (23). The present study did not include a healthy population. Among the patients diagnosed with a malignant disease, those who did not become infected with COVID-19 were considered the control group and those who became infected with COVID-19 were considered the case group. A comparison of the group that contracted COVID-19 and the group that did not revealed no significant differences in terms of ABO blood groups (p=0.39). Moreover, it was found that ABO blood groups did not affect mortality in patients who became infected with COVID-19 (p=0.83). Similarly, it was also found that Rh antigen positivity was not a factor affecting COVID-19 transmission (p=0.19) and associated mortality (p=0.78). In this study,

ABO/Rh blood groups were evaluated with regard to susceptibility to COVID-19 infection and the related risk of mortality. The results of this study showed that COVID-19 and ABO/Rh blood groups did not have a statistically significant correlation in terms of the risk of transmission or the risk of mortality. However, metastatic malignant disease was an independent risk factor for COVID-19-related death. Limitations of this study include its single-centre, retrospective design and heterogeneity of the study population.

Conclusion

This study found that metastatic malignant diseases increased COVID-19-related mortality, while ABO blood groups and the Rh antigen status had no correlation with the risk of COVID-19 transmission and COVID-19-related mortality. According to the results of this study, patients suffering from a metastatic malignant disease represent a high risk group for COVID-19 and should be treated using all necessary precautions.

Acknowledgement. None.

Disclosure

Funding. No specific funding was received for this study.

Competing interests. None to declare

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Obtaining funding: Ebinç S, Oruç Z, Kalkan Z, Urakçı Z, Kaplan MA, Küçüköner M, Işıkdoğan A
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Statistical expertise (statistical analysis of data): Ebinç S, Oruç Z, Kalkan Z, Urakçı Z, Kaplan MA, Küçüköner M, Işıkdoğan A

Review article

Impact of Anaemia and Dysregulated Iron Metabolism on COVID-19 Clinical Outcome – Review Article

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Abstract

Coronavirus disease-19 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that can manifest in a wide range of forms, but the most common symptoms are fever, headache, fatigue, respiratory problems, lost sense of smell and taste, sore throat, muscle pain and malaise.

In patients with COVID-19, the inflammatory response of the organism affects iron homeostasis. Severe COVID-19 infections may lead to a hyperinflammatory condition, characterised by elevated ferritin levels that correlate with the severity of the clinical course, prolonged intensive care unit (ICU) stay, development of acute respiratory distress syndrome and a fatal outcome. As a result of iron metabolism disorders in inflammation, decreased erythropoiesis and reduced biological activity of erythropoietin, the erythrocyte half-life is shortened, leading to anaemia of chronic inflammation. Cytokine IL-6 plays the most crucial role in regulating iron concentration. It affects iron metabolism by producing hepcidin via STAT 3. Hepcidin produces regulatory effects on iron by binding with ferroportin, the only known transmembrane iron exporter.

Anaemia has long been characterised as a significant risk factor contributing to increased mortality and poorer clinical outcomes for various infections. The most severe forms of COVID-19 infection result in pneumonia, causing a reduced supply of oxygen to the circulation, ultimately leading to ischemia of vital organs. Anaemia of chronic disease is more common in COVID-19 positive patients and is associated with a poorer clinical outcome. A higher ferritin/transferrin ratio indicates an advanced inflammatory condition and may be a predictive factor of ICU admission.

(Bogović M, Rončević R, Milanković SG. Impact of Anaemia and Dysregulated Iron Metabolism on COVID-19 Clinical Outcome – Review Article. SEEMEDJ 2021; 5(2); 9-17)

Received: Aug 25, 2021; revised version accepted: Nov 8, 2021; published: Nov 26, 2021

KEYWORDS: COVID-19, anaemia, iron metabolism, SARS-CoV-2

Introduction

In the Hubei Province of the People's Republic of China, in December 2019, a new type of virus emerged – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The world faced a new global issue, the pandemic of the coronavirus disease 2019 (COVID-19). Currently, there have been over 200,000,000 coronavirus cases recorded and most patients have presented with mild clinical symptoms (with over 180,000,000 patients recovered). However, 4,000,000 deaths from COVID-19 have been recorded up to this moment (1).

This pandemic has affected many aspects of our everyday life, from health to economy. In order to provide optimal treatment to patients, it is vital to identify the risk factors contributing to the development of severe forms of the disease so as to effectively use the limited resources available in the fight against the virus. Despite the progress that has been made, such as the development of the vaccine, the scientific community is still trying to understand the impact of the virus and its new variants on the clinical outcomes of patients with COVID-19. Infection with the SARS-CoV-2 virus can manifest itself in a wide range of clinical presentations: from asymptomatic vectors and milder forms to more severe ones, which require hospital care and respirators, and finally those ending in death. The infection affects various systems and the clinical presentation differs from patient to patient, but the most common symptoms include fever, headache, fatigue, respiratory problems, lost sense of smell and taste, sore throat, muscle pain and malaise (2).

A combination of symptoms, medical history information, epidemiological data, polymerase chain reaction (PCR) testing, serological testing, laboratory findings, chest X-ray or computed tomography (CT) findings results in a clinical diagnosis (3). Many agents are used in the treatment of COVID-19: antiviral drugs, corticosteroids, various antibiotics, anti-inflammatory drugs or immunomodulators. Over time, the scientific community has discovered alternative forms of treatment and prevention of the disease. At the moment, the best form of protection against infection and the development of more severe forms of the disease is vaccination, which is the most effective weapon in the fight against viruses.

In patients with COVID-19, the inflammatory response of the organism affects iron homeostasis and leads to a reduction in iron absorption in the intestine, which further reduces the availability of iron for erythropoiesis and haemoglobin production (4).

Iron is an important redox catalyst in several reactions. Due to the fact that a variety of pathogens need iron, one of many defence mechanisms is to limit the availability of iron to infectious agents. For example, iron is mostly found within cells, bound to haemoglobin in erythrocytes. Bacteria and viruses have developed mechanisms to steal iron from their hosts (5).

The aim of this review is to present the current knowledge from available papers and literature on the complex relationship between iron metabolism, anaemia and COVID-19 that affects the clinical course of the disease.

Regulation of iron metabolism

Maintenance of iron homeostasis is a complex process involving the regulation of (A) iron in duodenal enterocytes, (B) use in erythroblasts, (C) storage in hepatocytes and (D) macrophage recycling in the spleen. After being reduced with ascorbic acid and duodenal cytochrome b (DCYTB) on the apical membrane of enterocytes, iron is absorbed by divalent metal transporter 1 (DMT1) and transferred to the basolateral membrane, where it exits the cells with the help of ferroportin into the circulation, where it binds to transferrin (holo-Tf). Erythrocytes, the cells that require the most iron, bind holo-Tf to the transferrin receptor TfR1. After endocytosis, iron is used in the mitochondria to synthesise haem, which will be incorporated into haemoglobin. If the body absorbs more iron than it needs, it is stored in 6 ferritins, mostly in hepatocytes. The largest

source of iron are macrophages, which phagocytose stale erythrocytes and release iron from haem via haem oxygenase 1 (HO1). These processes are regulated by hepcidin, which binds to ferroportin and promotes its internalisation and degradation. In this way, it prevents the absorption of iron and the release of iron stored in hepatocytes and recycled in macrophages. (6) (Figure 1).

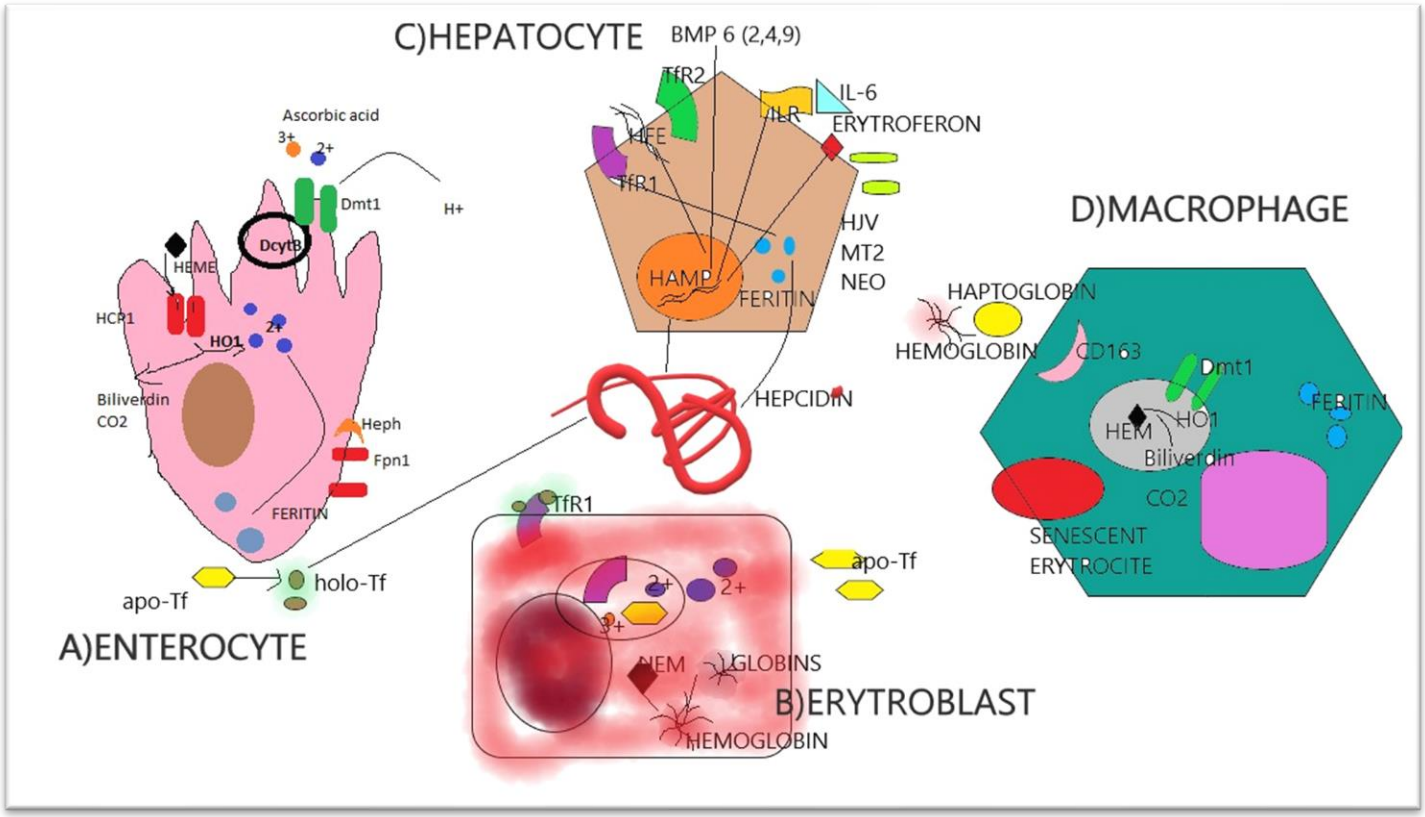

Figure 1. Maintenance of iron homeostasis

Inflammation leads to disbalanced iron homeostasis

Various comorbidities, such as obesity, hypertension, cardiovascular disease, hypercholesterolemia, chronic kidney disease and metabolic syndrome, as well as old age, are associated with higher mortality and poorer treatment outcomes of COVID-19 (7). Patients suffering from a more severe form of the disease, among other laboratory findings, had leukocytosis with low lymphocyte and platelet count. Inflammatory markers, such as C-reactive protein (CRP), interleukin 6 (IL-6) and ferritin were elevated (8). Viral infections, including SARS-CoV-2 infections, affect the haemoglobin molecule through ACE2, CD147, CD26 and other receptors on erythrocytes and/or blood cell precursors. Viral endocytosis can cause hemoglobinopathy through the connection between spike proteins and cellular receptors. ORF8 protein and surface glycoproteins on the virus can bind to porphyrin, attacking haem on the 1- β chain of haemoglobin. Consequently, SARS-CoV-2 promotes haemolysis and/or creates a haem release complex, forming dysfunctional haemoglobin with a reduced oxygen concentration and CO2 transport (9). More severe forms of COVID-19 are characterised by an excessive inflammatory response in the form of a cytokine storm, which is characterised by IL-6 hyper-expression and hyperferritinemia (Figure 2). IL-6 also affects iron metabolism by inducing the production of

hepcidin via STAT 3 (10), which is important in the regulation of iron homeostasis. According to the research published so far, cytokine IL-6 plays the most crucial role in regulating iron concentration, at least in humans and animals (11). Other cytokines, such as interleukin-1 and activin B, are also involved in regulating iron production, but their role has not been investigated sufficiently (12). Hepcidin produces its regulatory effects on iron by binding to ferroportin, the only known transmembrane iron exporter (13).

Increased hepcidin concentrations inhibit iron absorption in the duodenum, where ferroportin delivers the absorbed iron into the circulation. They also act on macrophages by blocking the release of iron recycled from older erythrocytes into plasma (14). Recent research suggests that in higher concentrations, hepcidin can directly block iron exports by occluding ferroportin, a mechanism that may be important in limiting the release of iron from endocytic-deficient cells machines (erythrocytes) or in conditions where endocytosis is slow (15). This mechanism leads to elevated intracellular ferritin. Excess intracellular iron reacts with free oxygen radicals, creating oxidative stress. The intracellular iron excess leads to ferroptosis, programmed cell death. Excess iron is also thought to cause mitochondrial dysfunction, microbiome diversity and hypercoagulability (16). New evidence suggests that IL-6 may have a secondary suppressive effect on erythroid precursors (17). In addition, loss of IL-6 and hepcidin results in milder anaemia and faster haemoglobin recovery in a well-established mouse model (18). IL-6 knockout animals showed faster bone marrow recovery compared to hepcidin knockout animals. Hepcidin downregulates the release of iron into plasma by binding to and functionally lowering ferroportin 1, the sole iron exporter (13,19). Persons with high iron levels are at an increased risk of developing various infections. Evidence suggests that better control of patients' iron levels could be a protective factor in the fight against the virus (20). It is still debatable whether an iron metabolism disorder is a result of a physiological response within an infectious disease or it leads to a worse disease outcome. However, recent research has shown that cell damage and inadequate immune response lead to iron disbalance. Therefore, we can conclude that iron metabolism disorders significantly contribute to the course of COVID-19 (4).

Impact of impaired iron metabolism on anaemia

Anaemia has long been characterised as a significant risk factor contributing to increased mortality and poorer clinical outcomes for various infections. It is well known that anaemia exacerbates the severity of respiratory problems, since various diseases and previous studies have shown a high prevalence of anaemia in patients with community-acquired pneumonia (21). Although it has not been documented explicitly, the underlying causes and patterns of inflammation, genetic composition and the patient's pre-disease condition, including iron concentration and erythropoietic capacity, could contribute to each pathophysiological pathway of inflammatory anaemia (22). Initially, systemic immune activation leads to significant changes in iron transport, causing iron retention in macrophages and reduced absorption of iron from food. Iron sequestration in macrophages is far more critical because 90% of daily iron requirements for haemoglobin (Hb) synthesis and erythropoiesis come from recycled iron originating from aged erythrocytes. Iron stores in tissues and in the circulation stimulate the expression of hepcidin (11,23) and inflammatory cytokines, hypoxia (12), iron deficiency and ineffective erythropoiesis. Inflammation adversely affects erythropoiesis by separating iron from erythroid precursors, thus causing iron-restricted erythropoiesis (24). Inflammatory anaemia, a condition involving elevated hepcidin levels, can conceptually be called functional iron deficiency. Due to this iron-restricted erythropoiesis, erythroferrone (ERFE) increases and is likely to provide some counter-regulation of elevated hepcidin. ERFE knockout mice treated with heat-killed Brucella abortus, a well-accepted model of inflammatory anaemia, showed delayed haemoglobin recovery because of inadequate hepcidin suppression

(25). Thus, suppressed erythropoiesis in inflammatory anaemia may allow a further increase in hepcidin expression.

Most COVID-19 infections have a milder clinical course and up to 20% of patients require hospital care, most often because of pneumonia, with admission to the ICU and a need for mechanical ventilation (26,27). The most severe forms of COVID-19 infection result in pneumonia, which leads to diffuse alveolar damage and gas exchange disorders (28). As a result, arterial oxygenation becomes impaired. Oxygen saturation depends on the concentration of haemoglobin, which is why reduced haemoglobin levels cause a decrease in the oxygen transfer capacity and oxygen saturation of arterial blood (29). Anaemia, as a separate condition, can cause ischemia of vital organs (30). The incidence of anaemia in patients hospitalised in the ICU is about 95% (31), while haemoglobin levels are lower in COVID-19 positive patients admitted to the ICU compared to hospitalised COVID-19 positive patients with a milder clinical presentation (32).

Increased levels of ferritin and hepcidin may be a predictive factor of a poorer clinical outcome. Severe COVID-19 infections are characterised by a hyper inflammatory condition, . including elevated ferritin levels that correlate with the severity of the clinical presentation, prolonged ICU stay, development of acute respiratory distress syndrome and a fatal outcome. As a result of iron metabolism disorders in inflammation, decreased erythropoiesis and reduced biological activity of erythropoietin, the erythrocyte half-life is shortened, leading to anaemia of chronic inflammation (33). A clinical study conducted in China has found that patients with a severe clinical course of COVID-19 infection had higher levels of hepcidin and ferritin compared to patients with a milder clinical course. It was concluded that hepcidin and ferritin could be predictive factors of the clinical outcome of coronavirus infection (34). Also, an elevated ferritin/transferrin ratio is a predictive factor of a worsening clinical condition and longer stay in the ICU (31) (Figure 2.)..

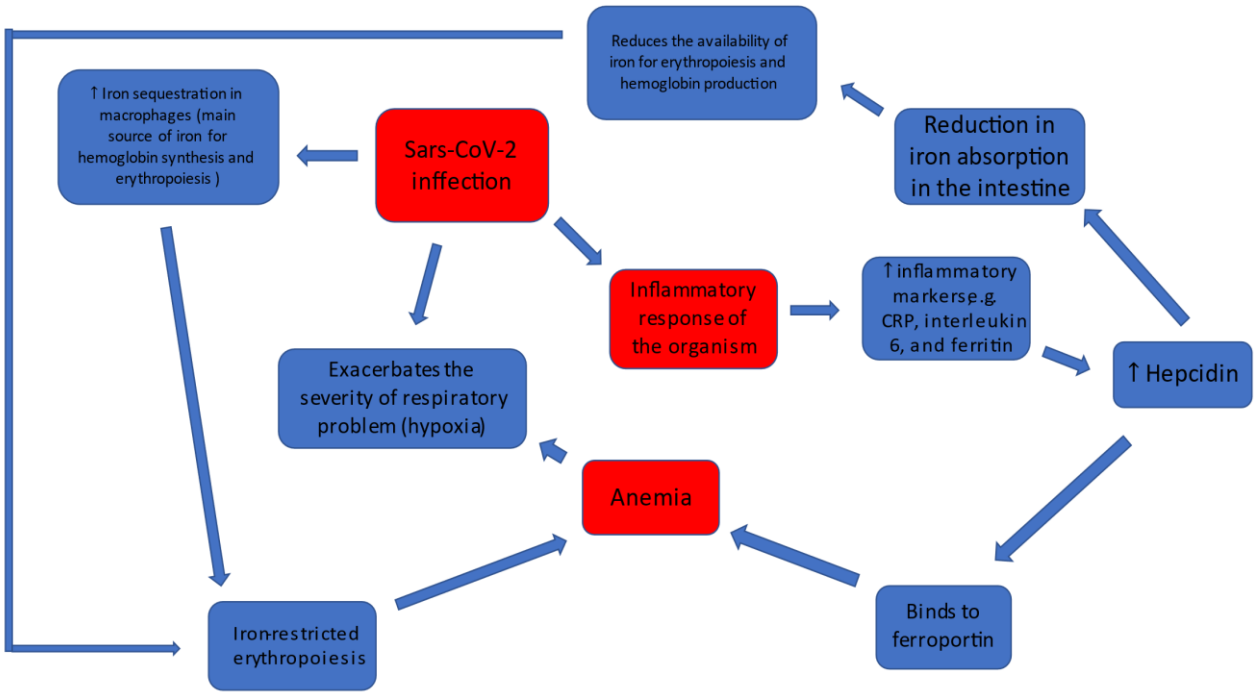

Figure 2. Increased levels of ferritin and hepcidin may be a predictive factor of a poorer clinical outcome

A review of the literature, including prospective studies monitoring the impact of anaemia on the clinical outcome of COVID-19 infections, shows that, of the total number of patients hospitalised due to COVID-19 infection, the proportion of patients with anaemia ranges between 25% and 65% (33,35,36). Studying the difference in the clinical outcome of COVID-19 infection in patients with and without anaemia, Tao, Z. et al. found that patients suffering from anaemia were older and more often had chronic kidney disease. The Chinese scientists classified patients with anaemia into three groups according to haemoglobin levels. Patients with severe anaemia (Hb < 80 g/L) had a higher incidence of dyspnoea and lower levels of O2 partial pressure and O2 saturation compared to patients with mild anaemia (Hb between 110 and 119 g/L for women and Hb between 110 and 129 g/L for men) and with moderate anaemia (Hb between 80 and 110 g/L) (35). Patients with severe anaemia were more likely to have coagulation disorders (elevated D-dimers) and increased inflammatory parameters compared to mild-to-moderate anaemia (35). A prospective study conducted in Iran by Dinevari et al. showed a high prevalence of COVID-19 infected patients with anaemia at admission to the hospital as well as an increased risk of admission to ICU, need for mechanical ventilation and mortality rates compared to COVID-19 positive patients without anaemia. It should also be emphasised that patients with anaemia were older and had more comorbidities, which also increased the risk of a poorer clinical outcome (36). In a study comparing hospitalised COVID-19 positive patients with other patients exhibiting the same symptoms, a higher prevalence of anaemia was found among COVID-19 positive patients, mainly due to inflammation with elevated ferritin levels and decreased saturated transferrin levels. Despite the higher prevalence, no statistically significant higher mortality was observed in anaemic patients compared to COVID-19 positive patients without anaemia (37). Elevated iron and ferritin levels in the circulation and in the lungs increase the risk of injury to the lung parenchyma (38). Severe forms of COVID-19 have been associated with disseminated intravascular coagulation and thrombosis, but the mechanism of thrombosis is unknown. Patients infected with COVID-19 have elevated transferrin levels, which may be associated with a hypercoagulable condition (39). It has long been known that transferrin is not only an iron transporter, but it also inhibits antithrombin and promotes the effect of thrombin and coagulation factor XIIa (40). The tendency to develop thrombosis is one of the most dangerous complications of COVID-19 infection. In order to protect the lungs from excessive free iron, treatment of COVID-19 positive patients with lactoferrin and iron chelators has been proposed to reduce circulating free iron (41). However, no clinical study has been published to date to show the effectiveness of this method. Regarding COVID-19 positive paediatric patients, no significant number of cases involving patients with anaemia have been reported, nor have they had a significantly worse clinical outcome (42).

Conclusion

In conclusion, anaemia of chronic disease is more common in COVID-19 positive patients and it is associated with a poorer clinical outcome. A higher ferritin/transferrin ratio reflects an advanced inflammatory condition and may be a predictive factor of ICU admission and the need for mechanical ventilation. Given the important role of iron metabolism in COVID-19 infection, future studies should evaluate the efficacy of treatment with iron chelators and lactoferrin and their impact on the clinical outcome of these diseases.

Acknowledgement. None.

Disclosure

Funding. No specific funding was received for this study.

Competing interests. None to declare

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Original article

Characteristics and Outcomes of Patients With Deep Vein Thrombosis Diagnosed in Emergency Department of Clinical Hospital Dubrava During 2019

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Abstract

Aim: Deep vein thrombosis (DVT) is a common clinical condition encountered in the emergency department (ED). The aim of this study was to compare the characteristics and outcomes of patients with respect to treatment using novel oral anticoagulants (NOAC).

Materials and Methods: In this retrospective observational study, we analyzed medical records of patients diagnosed with DVT during 2019 in the ED of the Clinical Hospital Dubrava. We identified 295 patients, who comprised 1.2% of all patients examined in the ED.

Results: Women were more frequently diagnosed with DVT (59%) and they were older than the men (median age 69 vs. 62 years, respectively). Patients with proximal deep vein thrombosis (71%) were admitted to the hospital. Two thirds of all patients were treated with NOAC. Rivaroxaban was the most commonly prescribed drug (52% of patients). Control Doppler ultrasound was performed in 58% of the patients, and complete resolution was observed in 63% of the cases. NOACs caused significantly fewer bleeding events than warfarin (3.2% vs. 13.6%, $p < 0.05$).

Conclusion: Our results demonstrate that patients with DVT can be safely treated with NOACs in an outpatient setting.

(Radilj I, Grabovac V, Mitrović Z. Characteristics and Outcomes of Patients With Deep Vein Thrombosis Diagnosed in Emergency Department of Clinical Hospital Dubrava During 2019. SEEMEDJ 2021; 5(2); 18-26)

Received: Aug 31, 2021; revised version accepted: Nov 8, 2021; published: Nov 26, 2021

KEYWORDS: deep vein thrombosis, emergency department, novel oral anticoagulants, rivaroxaban, warfarin, bleeding

Introduction

Deep vein thrombosis (DVT) is a clinical condition diagnosed in the emergency department (ED) on a daily basis. The average annual incidence rate of venous thromboembolism (VTE) in Europeans ranges from 1.04 to 1.83 per 1,000 person-years (1). Separately, pulmonary embolism (PE) with or without DVT varies from 0.29 to 0.78 per 1,000 person-years. DVT incidence rate ranges from 0.45 to 1.17 per 1,000 person-years. The total age-adjusted incidence rate is higher for men (1.3 per 1,000 person-years) than women (1.1 per 1,000 person-years) (1). The incidence rate in the population younger than 45 is 0.12 per 1,000 person-years, and 2.62 per 1,000 person-years in the population older than 65(2). In fact, DVT primarily affects older people.

DVT occurs as a result of three overlapping mechanisms, known as Virchow's triad: venous stasis, endothelial injury and hypercoagulability. The most important one is venous stasis, but it is not sufficient for thrombus formation in and of itself. Venous valve pockets are places of reduced blood flow in which thrombi develop. As a result of the blood flow slowing down, partial pressure of oxygen declines and consequently leads to local hematocrit increase. Higher expression of prothrombotic and lower expression of antithrombotic proteins further enhance the hypercoagulable microenvironment. Intact endothelial surface has antithrombotic and anticoagulant characteristics. Endothelial dysfunction or injury promotes contact of venous blood with tissue factor and thrombin, which activates the coagulation cascade (3, 4).

In Croatia, according to the study conducted by the Croatian Cooperative Group for Hematologic Diseases (KROHEM) in 2011, the estimated annual incidence of VTE was 1.185 per 1,000 people (5). The incidence of DVT was 0.79 per 1,000 people, with female predominance (56.3%). There were more patients with secondary VTE (57.3%), and malignant disease was the most frequent cause.

Since 2011, novel oral anticoagulants (NOAC) have emerged as a novel treatment option, in addition to low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKAs). Three NOACs were available in Croatia in 2019, however, only with partial reimbursement by national insurance: dabigatran (prothrombin inhibitor), rivaroxaban and apixaban (factor Xa inhibitors). Other than venous thromboembolism, indications for NOACs are atrial fibrillation and prevention of thromboembolic complications after a stroke or myocardial infarction. Their use is simpler, with fixed oral dosing, there is no need for laboratory monitoring and they do not depend on the diet. Patients can be treated with rivaroxaban and apixaban without LMWH as the standard initial therapy for DVT. Apixaban and dabigatran require dosing twice per day, as opposed to rivaroxaban, which requires use once per day (6).

The aim of this study is to determine the clinical characteristics, treatments and outcomes of patients who were diagnosed in the ED of the Clinical Hospital during 2019.

Patients and Methods

Study design

This study was designed as a retrospective analysis of electronic hospital charts of patients diagnosed with DVT in the Emergency Department of the Clinical Hospital Dubrava, Zagreb, Croatia, during 2019.

Patients and definitions

A total of 399 patients with VTE were diagnosed from 1 January to 31 December 2019. Patients that presented with PE without proven DVT were not included. Medical records of the remaining 295 patients with DVT were analyzed. Diagnosis was established based on clinical examination, D-dimer test and Doppler ultrasound. The following data were collected: age, sex, date of diagnosis, thrombosis type (proximal or isolated distal deep vein thrombosis; or other thrombosis), admission to hospital, treatment, idiopathic or secondary DVT. DVT was

considered secondary if some of the following risk factors were identified: malignant disease within 6 months of the event; recent trauma, surgery, immobilization/immobility; use of oral contraceptives; pregnancy; inflammatory bowel disease and thrombophilia. DVT was considered idiopathic if none of above factors were present. In our study, bleeding was considered significant if a patient required examination in the emergency department.

Statistical analysis

Categorical data are presented with absolute (N) and relative frequencies and compared using the $\chi 2$ test or Fisher's exact test, where applicable. Numerical data are presented with median and range values and compared using the Mann-Whitney U test. The probability value of < 0.05 was considered statistically significant. Estimated annual incidence per 1,000 inhabitants was calculated using the number of recorded new DVT cases divided by the population which gravitates to this hospital. Microsoft Excel was used for statistical analysis.

Ethics

Our research was conducted in full compliance with the Declaration of Helsinki and it was approved by the Ethics Committee of the Clinical Hospital Dubrava.

Results

A total of 295 patients were diagnosed with DVT, and 104 were diagnosed with PE (without concomitant DVT) out of a total of 23,899 patients examined in the ED in 2019 (Figure 1).

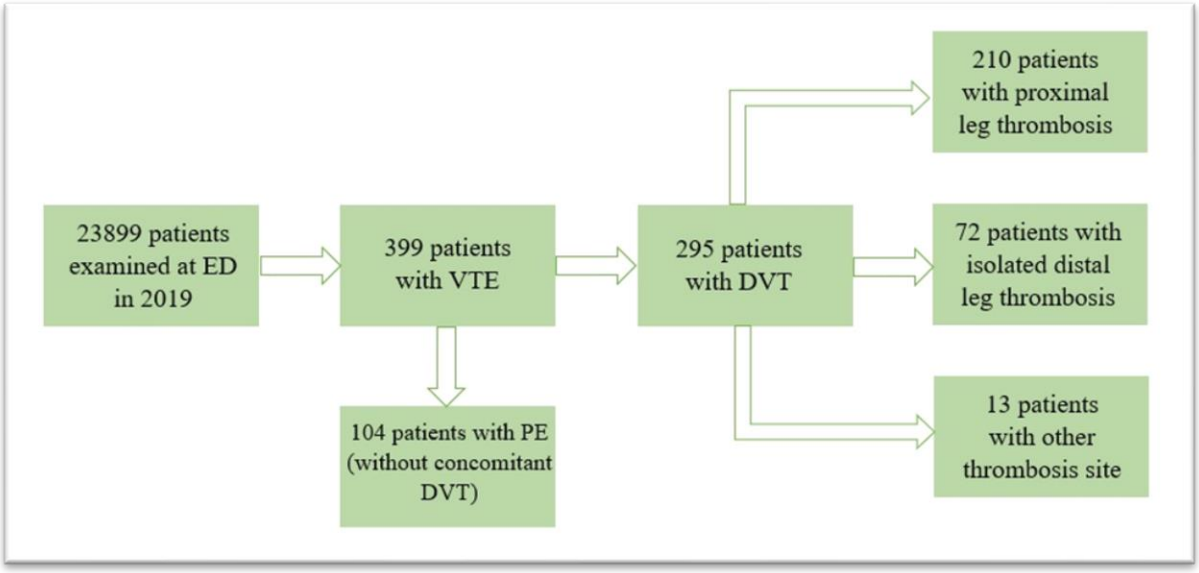

Figure 1. Patient flowchart (total N = 23,899)

ED = emergency department, VTE = venous thromboembolism, PE = pulmonary embolism, DVT = deep vein thrombosis

It should be noted that 55 DVT patients (13.8% of the total number) were diagnosed with concomitant PE. Thus, DVT frequency in our ED was 1.23% and PE frequency was 0.67%. Total VTE frequency was 1.67%. Considering the number of people gravitating to the Clinical Hospital Dubrava (which is about 330,000), the estimated annual DVT incidence was 0.894 per 1,000 people.

Median age was 65 years, ranging from 20 to 94 years. Women comprised 59% of patients (174 out of 295). Women were older (median 69 years; range 22 to 90) than men (median 62 years; range 20 to 94) ($p = 0.005$). However, in the younger age groups, the incidence of thrombosis was higher in men (Figure 2)..

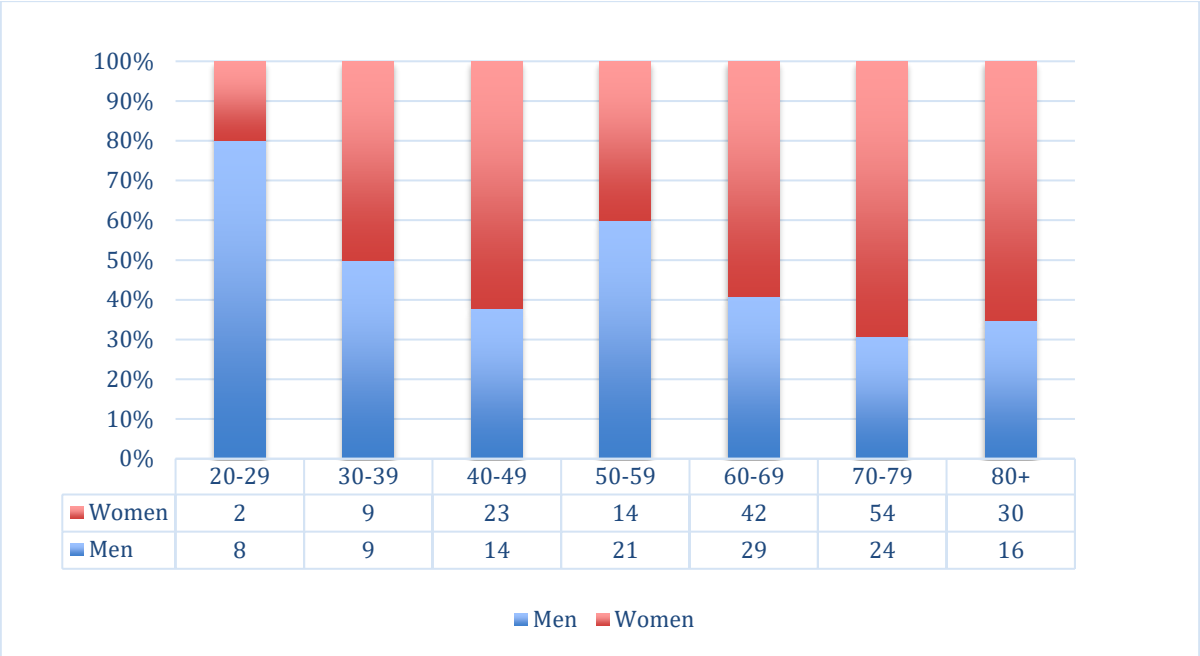

Figure 2. Proportion of men and women with deep vein thrombosis according to age groups (total N = 295)

Admission to the hospital was required for 206 patients (69.8%), and 73 patients (24.8%) were treated in an outpatient setting, while 16 (5.4%) refused hospitalization or were sent to another hospital. The patients who were admitted to the hospital were older compared to those who were discharged from the ED (median age was 69 years (range 20 to 94) vs. 60 years (range 25 to 88), respectively) (p = 0.0002).

Proximal DVT (thrombosis of the popliteal vein and of the femoral veins) was diagnosed in 210 patients (71.2%), while isolated distal DVT was diagnosed in 72 patients (24.4%) (Figure 1). Of the 13 patients with other thrombosis, IVC thrombosis was diagnosed in four patients (1.4%), internal jugular vein thrombosis in two patients (0.6%) and thrombosis of arm veins in seven patients (2.4%). Of the patients with leg thrombosis, left leg thrombosis occurred in 51.8% of patients compared to 46.5% of patients with right leg thrombosis (1.7% had thrombosis in both legs). A total of 67 patients (22.7%) had recurrent DVT. Divided by gender, there were 37 women (21.3%) and 30 men (24.8%) with recurrent DVT (p = 0.38).

Table 1. Secondary DVT* causes (total N = 170)

DVT CAUSES	N (%)
MALIGNANT DISEASE	69 (40.6%)
TRAUMA, OPERATION, IMMOBILIZATION	56 (32.9%)
IMMOBILITY	19 (11.2%)
HORMONAL CONTRACEPTION	4 (2.4%)
OTHER	22 (12.9%)

**DVT = deep vein thrombosis*

A provoking factor was identified in 170 patients (57.6%), while 125 patients (42.4%) did not have any factors in their medical documentation. Patients with idiopathic DVT appear to be older (median age 67 years) than those with secondary thrombosis (median age 64 years) (p

= 0.435). The most common provoking factor in the group of secondary DVT patients was active malignant disease in 69 patients (40.6%) (Table 1). Based on gender, there were 38 women (37.6%) and 31 men (44.9%) with malignant disease as a provoking factor (p = 0.34). Recent trauma, surgical procedure or limb immobilization was present in 56 patients (32.9%). There were 19 immobile patients (11.2%), while four patients (2.4%) were using oral contraceptives. The remaining 22 patients (12.9%) with secondary DVT had inflammatory bowel disease, thrombophilia, were pregnant, or failed to adhere to anticoagulant treatment after previous VTE.

Initial treatment with LMWH was started in 264 patients (90.7%). The most frequent treatment after initial LMWH was rivaroxaban in 130 patients (44.1%) (Table 2). Rivaroxaban without previous LMWH therapy was used in 24 patients (8.1%). The second most frequent therapeutic option was warfarin after LMWH, in 59 patients (20%). Long-term LMWH therapy was the option of choice for 46 patients (15.6%), mainly for patients with active malignant disease. Dabigatran or apixaban after initial LMWH treatment was used in 31 patients (10.5%). Acenocoumarol was the treatment option for one patient (0.3%). Therapy for four patients (1.4%) is unknown due to their transfer to another hospital.

Table 2. Treatment modalities (total N = 295)

THERAPY	N (%)
RIVAROXABAN AFTER STARTING LMWH*	130 (44.1%)
RIVAROXABAN WITHOUT PREVIOUS LMWH	24 (8.1%)
WARFARIN	59 (20%)
LONG-TERM LMWH	46 (15.6%)
DABIGATRAN/APIXABAN	31 (10.5%)
ACENOCOUMAROL	1 (0.3%)
UNKNOWN	4 (1.4%)

**LMWH = low-molecular-weight heparin*

We also compared the bleeding in patients on NOAC and warfarin. Of the 185 patients treated with NOAC, there were only six significant bleeding events (3.2%) that required medical attention in the ED. In comparison, of the 59 patients treated with warfarin, eight bleeding events were documented (13.6%). This is a statistically significant difference; p = 0.0067.

The median follow-up period for all patients was 260 days (range 3 to 648 days), with 45 (15.3%) patients lost to follow-up. Patients treated with warfarin had a similar median follow-up period compared to those treated with NOAC, 237 days (range 6 to 613 days) and 280 days (range 3 to 648 days), respectively. A follow-up Doppler ultrasound was performed in 170 patients (57.6%); 116 patients (39.3%) did not come for a follow-up examination in our institution, 6 (2.1%) were treated in another hospital and 3 patients (1%) died during or soon after hospitalization. Complete resolution was confirmed in 107 patients (62.9%), partial resolution was found in 60 patients (35.3%), and 3 patients (1.8%) did not show any improvement. Of the 129 patients treated with NOAC with available follow-up, 80 patients showed complete resolution (62%), whereas of the 31 patients treated with warfarin, 17 patients showed complete resolution (55%); p = 0.10.

Discussion

This study provided a valuable insight into the clinical characteristics and treatment of patients with DVT in Croatia in the era of NOACs. Estimated annual incidence of VTE from this research is consistent with other published studies (1, 2, 5). VTE frequency in the ED of the Clinical Hospital Dubrava is comparable to the

study conducted by KROHEM, and is almost identical to the Spanish study (1.67% vs. 1.65%) (7).

An interesting finding of this study is that DVT was diagnosed more frequently in women. In this study, we had 59% of women with DVT, which is comparable to other studies (JAVA, KROHEM) (5, 8). According to the estimation by the Croatian Bureau of Statistics, the proportion of women in the general population in 2018 was 51.7%, with increasing numbers in older age groups, and the average life expectancy of women in Croatia is 7 years longer than that of men (10). However, in patients younger than 65, there were only 48.6% of women (Figure 2). Overall, it seems that the female sex is not an independent risk factor for DVT.

Interestingly, there was a higher rate of simultaneous DVT and PE (13.8%) than in the study conducted by KROHEM (5.4%), while the Japan VTE Treatment Registry (JAVA) reported a rate of 14.4% (8). A reason for such difference could be the more frequent use of pulmonary angiography compared to the general hospitals included in the KROHEM study eight years prior to this study. It is known that with proximal DVT, asymptomatic pulmonary embolism can occur in 35% of the cases (9). Conversely, in patients with PE, deep vein thrombosis can be diagnosed in up to 71% of all patients (10). It is important to note that the ratio between proximal and distal DVT in our study is comparable to other studies, such as the Norwegian study, which reported 69.6% of patients with proximal DVT and 27.2% of patients with distal DVT (2).

Almost two thirds of the patients in 2019 were treated with NOACs, and one quarter of the patients were treated in an outpatient setting. Also, a substantial finding of this study is that NOACs cause fewer bleeding events compared to warfarin. Introducing NOACs into everyday clinical practice enabled a higher rate of outpatient management. For instance, in a Spanish study conducted in 2002, 99% of patients with PE and 85% of patients with DVT were admitted to the hospital (12). A more recent study from Spain, conducted in 2014 in 53 EDs across Spain, reported that 98.7% of patients with PE and 50.2% of patients with DVT were hospitalized (7). In our study, 71% of the patients were admitted to the hospital. This fully corresponds to the proportion of patients with proximal DVT. In other words, patients with distal DVT were treated in an outpatient setting using NOACs.

The prevalence of DVT on the left side (52.7% vs. 47.3%) found in our study was also observed in other studies (13, 14). The only valid explanation for that difference is compression of the left common iliac vein by the right common iliac artery (May-Thurner syndrome) (13). The proportion of idiopathic venous thrombosis in our cohort (42.4%) is consistent with other studies. Idiopathic thrombosis was diagnosed in 43.2% and 42.7% of the patients in the JAVA and the KROHEM studies, respectively (5, 8). Both the KROHEM study and this study report on the greater age of patients with idiopathic thrombosis compared to patients with secondary thrombosis. Venous thromboembolism is a well-known complication of malignant disease. In a recent study conducted on 1,041 patients with solid tumors, 7.8% of patients had a thromboembolic event (15). Both the KROHEM study and this study recognized malignant disease as the leading cause of secondary thrombosis. The second most common cause (trauma, surgical procedure and immobilization) was less frequent in this study (32.9%) compared to the KROHEM study (38.2%). Inability to move as a result of paralysis or frailty is considered to be the third most common risk factor. Oral hormonal contraception (OHC) is an important risk factor in the population of fertile women (15–45 years). Of the 16 fertile women with secondary thrombosis, 4 had OHC in their medical history (25%). The RIETE study reported that 36% of women with VTE younger than 50 years were using OHC (16). Other risk factors were less frequent (Table 1).

Initial treatment with LMWH was used in 94% of patients included in the Spanish study (7). That percentage is comparable to this study (90.7%). There were 12,585 patients with the first VTE episode included in a large Norwegian study, which excluded patients with malignant disease (17). Rivaroxaban was a treatment option in 46.3%

of patients, warfarin in 28.3%, apixaban in 24.5% and dabigatran in 0.7%. This study included patients with malignant disease, of whom two thirds were treated using prolonged LMWH therapy. Considering the entire DVT population, the most commonly used therapeutical option was rivaroxaban (52.2%) (Table 2). It is known that outpatient management using rivaroxaban can be efficiently performed in low-risk patients, with a low rate of bleeding and recurrent thrombotic events (18).

Other NOACs were less commonly prescribed (10.5%). This may be explained by the fact that dabigatran requires five days of prior LMWH treatment, which is complicated in an outpatient setting, as well as by the fact that apixaban was introduced in Croatia several years after rivaroxaban. On the other hand, warfarin was prescribed to 1 in 5 patients (Table 2). It is obvious that NOACs are the preferred choice for an increasing number of patients. In addition, patients report greater satisfaction with NOACs compared to warfarin (19). One of the reasons for that is the lower incidence of bleeding when using NOACs (20), which was confirmed in this study. We observed statistically fewer serious bleeding events in patients treated with NOACs compared to those treated with warfarin (Table 3).

Table 3. Bleeding during treatment with NOAC* and warfarin (total N = 244)

	N	Bleeding	Incidence
Warfarin	59	8	13.6%
NOAC	185	6	3.2%

**NOAC = novel oral anticoagulants*

Deep vein thrombosis is a disease which requires regular check-ups because of the high incidence of recurrent thrombosis. The five-year cumulative incidence of recurrent VTE events is 21.5% after the first DVT episode and 27.9% after the second (21). We had 22.7% patients with recurrent DVT after previous VTE. As a comparison, in the study conducted by KROHEM, recurrent VTE was diagnosed in only 11.9% of patients (5). However, as many as 39% of the patients diagnosed with DVT in our cohort in 2019 have had no further ultrasonographic check-ups in our institution. This could be explained by the fact that Clinical Hospital Dubrava was the national COVID-19 hospital during a few months in 2020 and 2021 and the patients were probably followed-up on in other institutions. Data about check-ups (and complications) observed in other institutions are not available. That is the main weakness of our study. Nevertheless, complete DVT resolution was documented in almost two thirds of our patients. There was a trend toward better efficacy of NOAC compared to warfarin; however, it did not reach statistical significance.

Despite the limitations of a retrospective study, we believe that our center's experience from 2019 shows the general characteristics of patients with DVT in Croatia. The incidence and characteristics of patients are comparable to those observed in the study conducted by KROHEM.5 However, the introduction of NOACs in the last few years has facilitated the outpatient treatment of such patients, at least those with distal thrombosis. We believe that even more patients will be treated with NOACs in the future.

Acknowledgement. None.

Disclosure

Funding. No specific funding was received for this study.

Competing interests. None to declare

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Drafting of the article: Radilj I, Grabovac V, Mitrović Z
Final approval of the article: Radilj I, Grabovac V, Mitrović Z
Provision of study materials or patients: Radilj I, Grabovac V, Mitrović Z
Statistical expertise (statistical analysis of data): Radilj I, Grabovac V, Mitrović Z

Original article

Relationship Between Serum Ferritin Levels, Arterial Hypertension and Shift Work in Women. A Cross-sectional Analysis

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Abstract

Introduction: The aim of this study was to use cross-sectional research to determine the relationship between serum ferritin levels and arterial hypertension in women who work in shifts and women with regular daytime working hours.

Methods: The respondents included 67 female nurses divided into two groups: nurses working in 12-hour shifts (7 am to 7 pm/7 pm to 7 am) were the test group, while nurses regularly working for 8 hours (7 am to 3 pm) were the control group. Data collection included information on associated diseases, chronic medication, last menstruation, duration of menopause, cigarette smoking, number of years of employment in shift work and regular daytime work, laboratory and anthropometric parameters and blood pressure levels.

Results: In all respondents, there was a significant and positive relationship between ferritin and CRP levels, i.e. the higher the CRP levels, the higher the ferritin levels (Rho = 0.401; P = 0.001). Among respondents who have regular daytime working hours, there was no significant association between ferritin and other indicators, while in the group of those who work in shifts, there was a significant and positive association between ferritin and CRP (Rho = 0.468; P = 0.002). Finally, a positive correlation was found between the number of years of employment in shift work and systolic blood pressure levels, i.e. higher systolic pressure was observed in those respondents who worked longer in shifts (Rho = 0.424, P = 0.03).

Conclusion: The study demonstrated a significant correlation between the number of years of employment in shift work and systolic blood pressure. A positive correlation between serum CRP and ferritin levels was also observed in all respondents, and especially in shift workers.

(Cvitkušić Lukenda K, Vučić D, Raguž A, Bitunjac I, Mišković D, Gabaldo K, Miškić B, Knežević Praveček M. Relationship Between Serum Ferritin Levels, Arterial Hypertension and Shift Work in Women. A Cross-sectional Analysis. SEEMEDJ 2021; 5(2); 27-37)

Received: Aug 12, 2021; revised version accepted: Oct 21, 2021; published: Nov 26, 2021

KEYWORDS: arterial hypertension, C-reactive protein, ferritin, shift work, women

Introduction

Iron is a trace element that is necessary for the normal functioning of numerous metabolic processes in living beings [1]. Accumulation of iron in organs such as the liver, heart and endocrine glands can lead to pathological changes and dysfunction of the organs [2]. Ferritin is an intracellular protein that serves to store and release iron, and by determining its serum level, insights into the body's iron stores are obtained [3, 4, 5]. In addition to storing and releasing iron, ferritin plays a role in cell proliferation, angiogenesis, immunosuppression and atherosclerosis [6]. Atherosclerotic lesions have been shown to contain ferritin; this means that iron is a potent catalyst for oxidation of lipids found in LDL cholesterol, which plays a major role in atherogenesis [7, 8].

It is known that the presence of ferritin is a result of the inflammatory response of the acute phase of systemic infections, because its synthesis is increased under the influence of cytokines and its serum level increases in inflammatory events [9]. Observational studies have shown a positive correlation between serum ferritin levels and the development of chronic diseases such as atherosclerotic coronary artery disease and cancers, while certain other studies have failed to show a correlation between high serum ferritin levels and chronic diseases [10, 11]. Arterial hypertension is one of the leading causes of morbidity and mortality in the population, with a continuous correlation between blood pressure levels and cardiorenal events [12]. Previous studies have found a higher prevalence of arterial hypertension in men who had higher iron stores and serum ferritin levels [13, 14, 15]. Likewise, a positive correlation has been shown between serum ferritin levels and the prevalence of arterial hypertension in shift workers [16]. Compared to regular daytime (morning and afternoon) work, shift work (day and night shifts) leads to circadian rhythm disorders and, additionally due to lifestyle changes, to an increase in stress levels, which can trigger an inflammatory response. Such an inflammatory response has an important role in all stages of atherosclerotic plaque formation and development [17].

Previous research has confirmed the association between increased arterial stiffness and the development of atherosclerotic plaque [18, 19]. A positive correlation between serum ferritin levels and arterial stiffness in adult men and women has also been confirmed [20]. Unlike in men, serum ferritin levels in women change before and after menopause. During the reproductive period, serum ferritin levels in women are low due to menstrual bleeding, but in menopause, after menstrual cycles stop, serum ferritin levels increase. Natural postmenopause is defined by the absence of menstrual bleeding over a period of 12 months (excluding exogenous factors such as hysterectomy) [21]. In addition, serum ferritin levels in women of childbearing age are difficult to assess because throughout life, a number of factors can affect the levels, such as pregnancy, hormone therapy and gynaecological diseases [22]. Consequently, the association between serum ferritin levels and arterial hypertension in women has been insufficiently investigated.

To our knowledge, there are no studies concerning the association between serum ferritin levels, arterial hypertension and shift work in women. Therefore, the aim of this article was to use cross-sectional research to determine the relationship between serum ferritin levels and arterial hypertension in women who work in shifts and those with regular daytime working hours.

Respondents and Methods

Respondents

Of the total number of healthcare professionals who underwent a health check-up at the "Dr. Josip Benčević" General Hospital in Slavonski Brod, Croatia, in the period from May to July 2021, 67 female nurses were included in this study.

The respondents were female nurses who were divided into two groups: nurses working in 12-hour shifts (7 am to 7 pm/7 pm to 7 am) were the

test group, while nurses regularly working for 8 hours (7 am to 3 pm) were the control group. The inclusion criteria were female gender, age of respondents between 18 and 65 for both groups, consent to participation in the survey and signed informed consent. Exclusion criteria included any form of iron replacement therapy, malignant disease, chronic renal failure, chronic liver disease, severe anaemia, acute illness, hormone replacement therapy, immunomodulatory therapy, reluctance to participate in the research.

The study was conducted in accordance with the Declaration of Helsinki. All participants in the survey signed a written informed consent form. The research was approved by the Ethics Committee of the "Dr. Josip Benčević" General Hospital in Slavonski Brod (Ethical Approval No. 04000000/21-46).

Data collection

The questionnaire was given and the physical examination was performed as part of the annual internal medicine examination. The questionnaire consisted of a report on medical history and primary health: it included data on chronic medication (for chronic conditions such as arterial hypertension, dyslipidaemia, diabetes, chronic obstructive pulmonary disease, osteoarthritis, depression), last menstruation, duration of menopause, cigarette smoking, number of years of employment in shift work and regular daytime work (at least one year for both groups). Regular cycles were the marker of premenopausal women, while absence of menstruation for the last 12 months or longer was a criterion for postmenopausal women [21]. Cigarette smoking habits were recorded as smoker, ex-smoker and non-smoker. Blood pressure was measured after 5 minutes of rest. Three measurements were performed at 1-minute intervals, with the respondents in a sitting position and using their right arm. Omron M6 Comfort® blood pressure monitor and Omron HEM-FL31® upper arm cuff with circumference of 22–42 cm were used to measure blood pressure. Levels of systolic pressure ≥ 140 mmHg and diastolic pressure ≥ 90 mmHg were used to define arterial hypertension, in accordance with the current guidelines for arterial hypertension of the European Society of Cardiology [12]. The blood pressure level of the respondents was calculated as the mean value of the second and third measurements. Respondents who had previously taken antihypertensive therapy were placed in the group with proven arterial hypertension. Height and weight were measured to the nearest 0.1 cm and 0.1 kg (using the SECA® scale and altimeter). During the measurement, the respondents were asked to take off their clothes and put on a disposable dress for the examination. Waist circumference (WC) was measured to the nearest 0.1 cm at the midpoint between the lower costal arch and the iliac crest. Body mass index (BMI) was calculated as weight/height ratio2 (kg/m2); values ≥ 25 kg/m2 indicated that the respondent is overweight, while values ≥ 30 kg/m2 indicated obesity.

Serum ferritin concentration was measured using the ALINITY® immunochemical analyser (Abbott). Laboratory parameters tested using fasting blood samples were as follows: erythrocytes (E), haemoglobin (Hb), haematocrit (Htc), mean corpuscular volume (MCV), leukocytes (L), platelets (Tr), iron (Fe), unsaturated iron-binding capacity (UIBC), total iron-binding capacity (TIBC), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (Tg), C-reactive protein (CRP), blood glucose (BG), haemoglobin A1c (HbA1c) and vitamin D. Complete blood count was determined using the SYSMEX XN-1000® haematology analyser by fluorescence flow cytometry. Vitamin D levels were determined by chemiluminescent immunochemical assay using the ALINITY® immunochemical analyser (Abbott). Haemoglobin A1c in venous blood was determined using the DxC 700 AU® biochemical analyser. Finally, biochemical parameters CRP, BG, TC, Tg, HDL, LDL, Fe and UIBC were determined using the biochemical part of the integrated ALINITY® system (Abbott).

Statistical analysis

General characteristics of the respondents, according to the groups (shift work/regular daytime work), were derived using a descriptive method for continuous variables and using the Chi-squared test for categorical variables after data weighting. The data were sorted into quartiles based on the respondents' serum ferritin concentrations: quartile 1 (Q1) ≤ 26.11 ng/mL, quartile 2 (Q2) 26.12–47.74 ng/mL, quartile 3 (Q3) 47.75–93.5 ng/mL, and quartile 4 (Q4) > 93.5 ng/mL. The respondents' basic characteristics according to ferritin levels in the quartiles were derived using the Chi-squared test and Fisher's exact test. By dividing data into quartiles, four groups were obtained with an almost equal number of respondents. Appropriate nonparametric tests were used to compare two or more independent groups. The Mann–Whitney U test was used to compare age, BMI, number of years of work and blood pressure levels between the test and control groups. The Kruskal–Wallis test (Conover post-hoc) was used to compare age, BMI, number of years of work, blood pressure levels in relation to groups, according to ferritin levels in the quartiles. The Chi-squared test was performed to divide the respondents according to ferritin levels and the presence of arterial hypertension. Spearman's correlation coefficient was used to assess the association of ferritin and other biochemical values between groups and to assess the association of shift work with arterial pressure and ferritin levels. The level of statistical significance was set at $p < 0.05$. Statistical analysis was performed using the SPSS for Windows 11.0.3 software (SPSS Inc., Chicago, IL, USA).

Results

The research was conducted on 67 respondents, of whom 43 (64%) work in shifts and 24 (36%) regularly work 8 hours. There were 45 (67.2%) obese or overweight respondents. There were 42 (62.7%) respondents in postmenopause, and in regard to comorbidities, arterial hypertension was recorded in 22 (32.8%) respondents, while diabetes was present in 3 of them (4.5%). Out of a total of 51 respondents who gave an answer about smoking, 19 (62.7%) respondents smoked cigarettes daily. Antihypertensive therapy was taken by 19 (37.3%), statins by 6 (9%), and vitamin D by 3 (4.5%) respondents. There were no significant differences in general characteristics between the groups (Table 1).

Table 1. Basic characteristics of the respondents

	Number (%) of respondents			
	Regular daytime work (n = 24)	Shift work (n = 43)	Total	*P**
BMI kg/m²				
< 25, normal	7 (29.2)	15 (34.9)	22 (32.8)	0.71
25–30, overweight	12 (50)	17 (39.5)	29 (43.3)	
> 30, obese	5 (20.8)	11 (25.6)	16 (23.9)	
Postmenopause	14 (58.3)	28 (65.1)	42 (62.7)	0.58
Smoking	6 (28.6)	13 (43.3)	19 (37.3)	0.28
Arterial hypertension	11 (45.8)	11 (25.6)	22 (32.8)	0.09
Diabetes mellitus	2 (8.3)	1 (2.3)	3 (4.5)	0.25
Antihypertensive therapy	10 (41.7)	9 (20.9)	19 (37.3)	0.07
Statins therapy	4 (16.7)	2 (4.7)	6 (9)	0.09
Vitamin D therapy	1 (4.2)	2 (4.7)	3 (4.5)	0.93

*χ^2 test

A statistically significant interquartile difference was observed in postmenopausal respondents (Table 2)..

Table 2. Basic characteristics of the respondents according to ferritin levels

	Number (%) of respondents according to ferritin levels					
	< 26.11 (n = 17) Q1	**26.12–47.74 (n = 17) Q2**	**47.75–93.5 (n = 17) Q3**	**> 93.5 (n = 16) Q4**	**Total**	*P**
BMI kg/m²						
< 25, normal	8 (47.1)	7 (41.2)	4 (23.5)	3 (18.8)	22 (32.8)	0.61
25–30, overweight	6 (35.3)	6 (35.3)	8 (47.1)	9 (56.3)	29 (43.3)	
> 30, obese	3 (17.6)	4 (23.5)	5 (29.4)	4 (25)	16 (23.9)	
Postmenopause	4 (23.5)	11 (64.7)	13 (76.5)	14 (87.5)	42 (62.7)	**0.001**
Smoking	5 (38.5)	5 (31.3)	5 (50)	4 (33.3)	19 (37.3)	0.79
Arterial hypertension	2 (11.8)	7 (41.2)	7 (41.2)	6 (37.5)	22 (32.8)	0.20
Diabetes mellitus	1 (5.9)	1 (5.9)	1 (5.9)	0	3 (4.5)	> 0.99†
Antihypertensive therapy	1 (5.9)	7 (41.2)	5 (29.4)	6 (37.5)	19 (28.4)	0.08†
Statins therapy	0	2 (11.8)	2 (11.8)	2 (12.5)	6 (9)	0.56†
Vitamin D therapy	0	0	2 (11.8)	1 (6.3)	3 (4.5)	0.32†

**χ2 test; † Fisher's exact test*

The median age of the respondents was 57 (interquartile range of 45 to 60 years), with respondents ranging from 25 to 65 years old and no significant difference between the groups. There were no significant differences in BMI, WC, postmenopausal duration, systolic and diastolic pressure and number of years of treatment for arterial hypertension with respect to the groups. Nurses working in shifts had more work experience, compared to nurses working only in the morning shift, with a median of 35 years (interquartile range from 25 to 39 years) (Mann–Whitney U test, P < 0.001) (Tables 3 and 4).

Table 3. Age, BMI, years of experience, blood pressure levels in relation to groups

	Median (interquartile range)				
	Regular daytime work (n = 24)	**Shift work (n = 43)**	**Difference ***	**95% CI**	***P†***
Age (years)	56.5 (44.5–60.75)	57 (45–59)	0	-4–4	0.98
BMI (kg/m²)	26.62 (24.33–29.43)	27.1 (23.9–30.1)	-0.11	-2.5–1.9	0.90
WC (cm)	95 (85–99.25)	89 (75–94)	-5	-11–2	0.18
Years of experience (years)	12.5 (4.25–24.75)	35 (25–39)	18	12–24	**< 0.001**
Duration of menopause (years)	9 (5–15.5)	8 (6–10)	0	-5–3	0.73
Systolic pressure (mmHg)	128 (118–137.25)	121 (115–130)	-5	-12–2	0.20
Diastolic pressure (mmHg)	79.5 (74.88–85.25)	78 (72–84)	-2	-6.5–2.5	0.41
Years of arterial hypertension	8 (2.8–11)	9 (6–13.5)	2.5	-	0.54

*CI – confidence interval, *Hodges–Lehmann median difference, †Mann–Whitney U test*

Table 4. Age, BMI, years of experience and blood pressure levels in relation to groups, according to ferritin levels (quartile)

	Median (interquartile range)				
	< 26.11 (n = 17) **Q1**	26.12–47.74 (n = 17) **Q2**	47.75–93.5 (n = 17) **Q3**	> 93.5 (n = 16) **Q4**	*P**
Age (years)	45 (37.5–53)	57 (49–61)	58 (48–61.5)	58.5 (53.5–61.8)	**0.006**‡
BMI (kg/m²)	26.4 (22.65–28.44)	27.3 (24.34–29.9)	26.8 (24.5–31.2)	27.3 (26–30.3)	0.70
WC (cm)	87 (72–94)	88 (77.5–96)	94 (85–102.5)	92 (80.8–97)	0.50
Years of experience (years)	21 (7–26)	26 (8.5–37)	35 (17.5–38)	31.5 (14.3–40)	0.08
Duration of menopause (years)	4.5 (2.5–8)	7 (4.5–12)	9 (7.3–15.8)	8.5 (7–10.3)	0.16
Systolic pressure (mmHg)	120 (106.5–126.5)	128 (119.5–133)	128 (118–141.8)	119.5 (114.3–131.8)	0.08
Diastolic pressure (mmHg)	73 (65–80.5)	81 (73–84.5)	80 (74.8–84.5)	79.8 (73.8–87.5)	0.16
Years of arterial hypertension	5 (n =1)	6 (2–11.8)	11 (9–12)	11 (8–15)	0.30

**Kruskal–Wallis test (Conover post-hoc)*
‡at the confidence level P < 0.05 there were significant differences in Q1 vs. Q2; Q1 vs. Q3; Q1 vs. Q4.

Arterial hypertension was present in 22 respondents, 2 of whom (9.1%) had ferritin concentrations in the lowest quartile (< 26.11 ng/ml). There were 45 respondents without arterial hypertension, of which 15 (33.3%) had serum ferritin concentrations in the lowest quartile (< 26.11 ng/ml). Likewise, there was no statistically significant difference between ferritin and the presence of arterial hypertension (Figure 1).

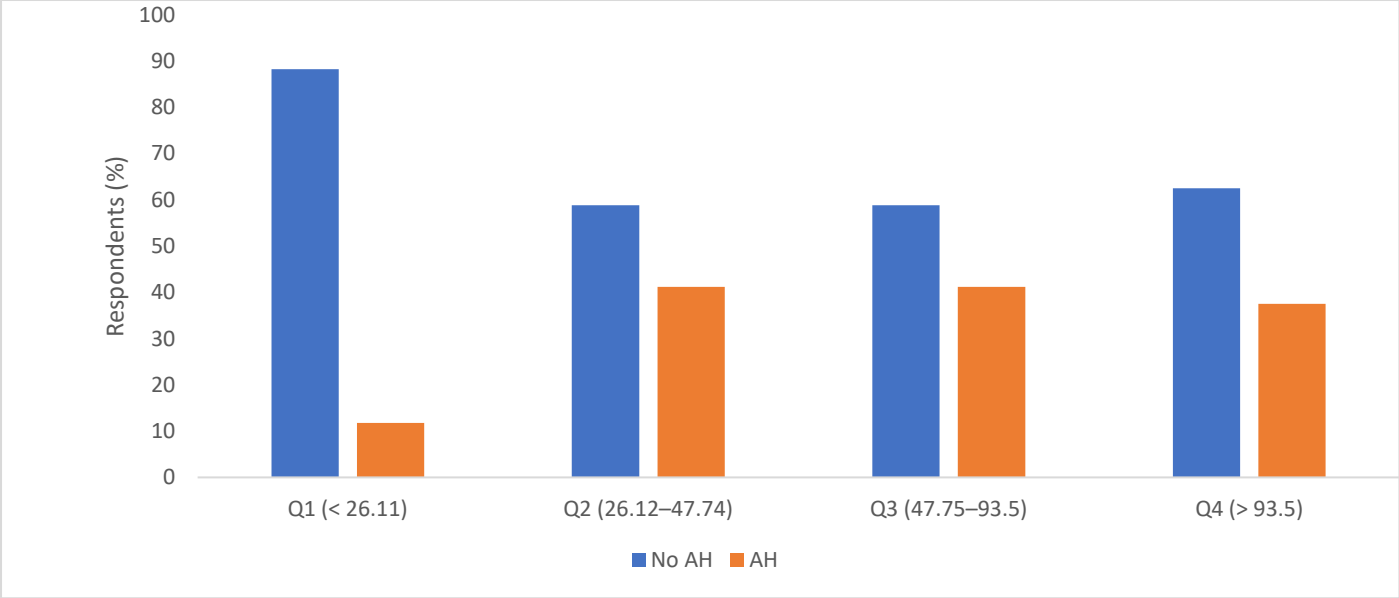

Figure 1. Distribution of respondents according to ferritin levels and the presence of arterial hypertension
AH – Arterial hypertension

The correlation coefficient of ferritin with other biochemical values was evaluated using Spearman's correlation coefficient. In the group of all respondents, there was a significant and positive relationship between ferritin and CRP levels, i.e. the higher the CRP levels, the higher the ferritin levels (Rho = 0.401; P = 0.001). Among respondents who regularly work 8 hours, there

was no significant association of ferritin and other indicators, while in the group of those who work in shifts, there was a significant and positive association of ferritin and CRP (Rho = 0.468; P = 0.002) (Table 5).

Table 5. Association of ferritin and other biochemical values between the groups

	Ferritin*	*P* value
All respondents		
TC (mol/L)	0.195	0.11
HDL (mmol/L)	0.103	0.41
LDL (mmol/L)	0.163	0.19
Tg (mmol/L)	0.161	0.19
BG (mmol/L)	-0.102	0.42
HbA1c (%)	0.072	0.56
CRP (mg/L)	**0.401**	**0.001**
Vitamin D (nmol/L)	-0.013	0.92
Regular daytime work		
TC (mol/L)	0.232	0.28
HDL (mmol/L)	0.039	0.86
LDL (mmol/L)	0.281	0.18
Tg (mmol/L)	-0.063	0.77
BG (mmol/L)	-0.119	0.58
HbA1c (%)	0.227	0.29
CRP (mg/L)	0.291	0.18
Vitamin D (nmol/L)	0.084	0.70
Shift work		
TC (mol/L)	0.178	0.26
HDL (mmol/L)	0.139	0.38
LDL (mmol/L)	0.109	0.49
Tg (mmol/L)	0.215	0.17
BG (mmol/L)	-0.086	0.59
HbA1c (%)	-0.027	0.86
CRP (mg/L)	**0.468**	**0.002**
Vitamin D (nmol/L)	-0.068	0.67

**Spearman's rank correlation coefficient (Rho)*

Spearman's correlation coefficient was used to assess the relationship between the number of years of employment in shift work with blood pressure and ferritin levels, and a positive correlation was found between number of years of employment in shift work and systolic pressure, i.e. higher systolic pressure was observed in those respondents who worked longer in shifts (Rho = 0.424, P = 0.03) (Table 6).

Table 6. Relationship of shift work length with blood pressure and ferritin

	Length of work in shifts*	*P* value
Systolic	0.424	**0.03**
Diastolic	0.202	0.34
Ferritin (ng/mL)	-0.005	0.98

**Spearman's rank correlation coefficient (Rho)*

Discussion

This study was conducted to determine the relationship between serum ferritin levels, arterial hypertension and shift work in women. This study demonstrated the persistent link between shift work and systolic blood pressure. A positive correlation between serum CRP and ferritin levels was also demonstrated in all respondents, and especially in shift workers. The reason for the expected higher levels of arterial pressure in shift workers, in addition to changes in the circadian rhythm, is increased exposure to psychophysical stress that leads to an inflammatory response [16, 23]. Due to the rapid modernization of many sectors, there is a growing need for 24-hour availability of the healthcare system, which creates the need for shift work. According to a 2010 European Union report, 23% of men and 14% of women work in shifts [24]. The consequences can be different, but the most significant ones are those that affect the cardiovascular system. Previous research has confirmed that shift workers, compared to regular daytime workers, have a higher incidence of ischemic heart disease and myocardial infarction, and more commonly develop arterial hypertension [25, 26]. Of noncardiac consequences, a higher incidence of gastric ulcer, obesity, and diabetes has been observed [27–29].

In previous studies, a proportional association between CRP levels and blood pressure was confirmed, i.e. higher levels of the inflammatory marker are associated with higher blood pressure levels [30–31]. In the Framingham Offspring Study, Rutter and colleagues showed that elevated CRP is associated with a higher risk of insulin resistance and metabolic syndrome in women [32].

Such a phenomenon can be explained by the fact that higher CRP levels are present in conditions that represent risk factors for development of arterial hypertension, such as obesity, metabolic syndrome, smoking and arterial stiffness [33–36]. CRP additionally reflects chronic low-grade inflammation of the arterial wall at the site of atherosclerotic plaque [37]. The mechanism of action is mediated by increased expression of adhesion molecules with receptor function, such as vascular adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), on endothelial cells of blood vessels [38]. Receptors have chemotactic function for macrophages which, by infiltrating the vessel wall, lead to an inflammatory reaction, mediated by proinflammatory cytokines – interleukin-1, interleukin-6 and tumour necrosis factor. Furthermore, CRP binds to the cell membrane of damaged cells, activating the inflammatory response, which leads to cell dysfunction and atherosclerosis by reducing the synthesis of nitric oxide [39, 40].

There is growing evidence that oestrogen depletion during menopausal transition promotes a systemic inflammatory condition. This condition is characterized by systemic proinflammatory cytokines derived from reproductive tissue, as well as by changes in the cellular immune profile [41].

An inverse relationship between oestrogen and ferritin concentrations is to be expected, i.e. a decrease in oestrogen concentration due to the weakening of ovarian function leads to an increase in ferritin levels in the absence of menstrual bleeding [42]. According to the results of the research by Milman and Kirchhoff, it follows that during the perimenopausal period, iron stores increase 2–3 times, i.e. an increase in

serum ferritin concentration by 1 μg/L corresponds to 120 μg of stored iron per kilogram of body weight [43]. Just like CRP, ferritin is a good indicator of the inflammatory response in the body, reflecting the degree of acute and chronic inflammation [44]. However, serum ferritin levels are directly linked to the occurrence of insulin resistance and diabetes mellitus, especially if it is accompanied by elevated CRP levels [45].

Although the obtained results are in line with previous findings, the authors point out four important limitations of the research. First, of the respondents included in the research who were in the group of regular daytime workers, 91.7% had previously worked in shifts with a median duration of such work of 18 years (interquartile range 11.5–26.0). Second, cross-sectional testing cannot establish a causal relationship, which is why large population and prospective studies are needed. Third, as ferritin is an acute-phase protein, it may be elevated in inflammatory or other chronic events that may have remained unrecognized prior to the inclusion of respondents in the study. Finally, the uneven distribution of respondents, i.e. a higher share of postmenopausal women working in shifts, is possibly a consequence of personal financial circumstances.

Conclusion

The obtained data show a significant correlation between the length of work in shifts and systolic blood pressure levels, as well as a connection of shift work with higher ferritin and CRP levels. Further studies on a large sample are needed to determine the association between serum ferritin levels and arterial hypertension. To the best of the authors' knowledge, this is the first study conducted on women who work in shifts in the healthcare system. The question for further research remains whether the length of shift work should be limited and whether shift workers should undergo more frequent medical examinations due to the increased risk of adverse cardiovascular events.

Acknowledgement. None.

Disclosure

Funding. No specific funding was received for this study.

Competing interests. None to declare

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Short communication

Attitudes and Behavior of Biomedical Students in Comparison With Other Students During the COVID-19 Pandemic

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Abstract

Aim: Since its beginning, the COVID-19 pandemic has affected many people's usual activities and lifestyle, including Croatian students' lives. The aim of the study was to examine whether the attitudes and behaviour of students in the biomedical (B) field differed from those in other (O) fields at the Josip Juraj Strossmayer University of Osijek (JJSUO). The hypothesis was that B students would behave more responsibly.

Materials and Methods: A 10-question anonymous online survey on attitudes and behaviour related to the COVID-19 pandemic was designed and conducted. The research was carried out in November 2020 and it included a total of 348 students (46 % of B students) at the JJSUO. The data were statistically processed by the IBM ® SPSS ® Statistics 25.0 software at the statistical significance level of $P < 0.05$.

Results: Twenty-five percent of B students and 11.17 % of O students ($P = 0.001$) responded that they did not go to nightclubs, in accordance with the Civil Protection Headquarters' recommendations. Regarding their indoor socialising, 24.38 % of B students and 45.21 % of O students behaved the same as before the pandemic ($P < 0.01$). A total of 63.13 % of B and 39.36 % of O students ($P < 0.01$) responded that they would receive a vaccine against SARS-CoV-2.

Conclusion: B students behaved more responsibly than O students by reducing their socialising and going to crowded places, probably because of their education and awareness of the severity of COVID-19. Accordingly, more of them were willing to get the vaccine against SARS-CoV-2..

(Smajić M, Smajić P, Zibar L. Attitudes and Behavior of Biomedical Students in Comparison With Other Students During the COVID-19 Pandemic. SEEMEDJ 2021; 5(2); 38-43)

Received: Aug 25, 2021; revised version accepted: Nov 4, 2021; published: Nov 26, 2021

KEYWORDS: medical students; COVID-19; physical activity; vaccination

Introduction

Since the World Health Organization declared COVID-19 a pandemic in March 2020 (1), people's usual activities and lifestyle have fully transformed. Since social gatherings have been restricted ever since then (2), the pandemic has exerted a huge impact on everyone's day-to-day life, especially on young people's social life. In the summer of 2020, Croatia did not have high numbers of daily COVID-19 cases (3). However, by the beginning of October, the numbers started to rise once again (3). Due to alleviated restrictions in that transitory period (4), people in Croatia prevented the coronavirus transmission primarily by their own behavior. Therefore, we decided to examine the attitudes and behaviour of students at the Josip Juraj Strossmayer University of Osijek during the ongoing pandemic. The students were divided into two groups, biomedical students (B) and other (O) students, and the hypothesis was that B students would behave more responsibly.

Materials and Methods

In November 2020, a 10-question anonymous online survey on attitudes and behaviour related to the COVID-19 pandemic was designed and conducted using Google Forms. It included a total of 348 students at the Josip Juraj Strossmayer University of Osijek, with 45.98 % of B students and 54.02 % of O students. Of the total number of respondents, 70.11 % were female and 29.89 % were male. Respondents were aged 18 or above, opted in to the study voluntarily and were required to give their informed consent before starting the survey. Their habits during the pandemic were examined, including going to nightclubs, socialising indoors and going to a gym. We also considered whether they or their families had tested positive for COVID-19 on a polymerase chain reaction (PCR) test. In addition, we asked for their general opinion about the vaccine and checked if they would get a vaccine once available on the market.

Statistical Anaylsis

Chi-square test was used to examine the difference between the two groups. The data were statistically processed by the IBM®-SPSS® Statistics 25.0 software. Statistical significance level was set to $P < 0.05$.

Results

Twenty-five percent of B students and 11.17 % of O students ($P = 0.001$) responded that they did not go to nightclubs, in accordance with the Civil Protection Headquarters' (CPH) recommendations. A total of 65.8 % of both B and O students acknowledged that they went out less and more carefully (Table 1). There was no statistically significant correlation between going out and considering whether they or their families had tested positive for COVID-19.

Regarding their indoor socialising, 24.38 % of B students and 45.21 % of O students behaved the same as before the pandemic ($P < 0.01$). Only 8.05 % of all students claimed that they did not socialise indoors at all, in accordance with the CPH's recommendations (Table 1). Once again, there was no statistically significant correlation between the students' or their families' positive tests for COVID-19 and the students' decisions about socialising indoors.

A total of 35.34 % of B students and 54.74 % of O students stated that the level of their sports and recreational activities was the same as before the pandemic, while 64.66 % of B students and 45.26 % of O students answered that they performed recreational activities in accordance with the CPH's instructions and measures ($P < 0.01$). For the purpose of this comparison, 95 students who did not exercise were excluded (Table 1).

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Table 1. Going to nightclubs, socialising indoors and doing sports activities during the COVID-19 pandemic (N = 348)

Table 1.					
Question	**O students**		**B students**		
	n	**%**	**n**	**%**	***P****
GOING TO NIGHTCLUBS					
I do not go to nightclubs in accordance with the CPH's recommendations.	21	11.2	40	25	0.001
I go out less and more carefully.	128	68.1	101	63.1	
I go out the same as before the pandemic.	39	20.7	19	11.9	
INDOOR SOCIALISING					
I do not socialise indoors in accordance with the CPH's recommendations.	12	6.4	16	10	< 0.01
I socialise indoors less and more carefully.	91	48.4	105	65.6	
I socialise indoors the same as before the pandemic.	85	45.2	39	24.4	
SPORTS ACTIVITIES					
I do sports activities in accordance with the CPH's instructions and measures.	62	45.3	75	64.7	< 0.01
I do sports activities the same as before the pandemic.	75	54.7	41	35.3	

CPH – Civil Protection Headquarters, B – biomedical students, O – other students

A total of 63.13 % of B and 39.36 % of O students (P < 0.01) responded that they would get a vaccine against SARS-CoV-2 once it was available. General opinions about vaccination given by students who would not get the vaccine were mostly related to their doubts about the effectiveness of the vaccine and their thoughts on vaccinating only high-risk groups.

Discussion

As expected, there was a statistically significant difference between biomedical students and students from other fields in terms of following the CPH's measures. Even though there was a significantly higher proportion of B students who did not go to nightclubs in comparison with O students, it was still expected that the percentage of B students who would not go to nightclubs in accordance with the CPH's recommendations would be much higher than 25 %. It must be taken into account that the research was conducted between late October and early November 2020, when Croatia (population of 4 million) had over 15.000 COVID-19 cases per week (5). Nonetheless, cafés, restaurants and nightclubs were still open, although their hours of operation were limited (6). On 12 November, there were 3,082 COVID-19 cases recorded in Croatia, which was the largest number of daily cases up to that moment (7). On 20 December, exactly a month after all the cafés, restaurants and nightclubs had been closed, 1,975 new daily cases were confirmed (8). Following a slight drop in the number of daily COVID-19 cases after their closure, it was concluded that nightclubs were one of the riskiest places for the coronavirus transmission.

At the time of the research, only recommendations and moderate measures were imposed on indoor socialising (9). Considering that, it is not surprising that a total of 124 students (34.64 %) did not follow those recommendations. However, when it comes to this issue, B students were still much more responsible than O students. The results showed that three-quarters of B students were aware of the fact that the coronavirus spreads easily in enclosed spaces, as well as of the risk they would pose to mutual families visiting and gathering indoors with their own family.

The vast majority of B students exhibited responsible behavior as regards sports and recreational activities as well. More than half of B students claimed they performed recreational activities in accordance with the CPH's instructions and measures, meaning they worked out either at home or outdoors. The proportion of B (72.5 %) and O (72.8 %) students who were physically active (whether at a gym or at home/outdoors) at the time of the research was almost equal. These results differed from the results of a research by J. Steffen et al., who reported that medical students were much more physically active during the pandemic compared to non-medical students (10). Accordingly, the students in this study did not reduce their sports activities during the pandemic, unlike students of several other studies. In a survey by G. A. Zello et al., 90 % of the students reduced their physical activities during the pandemic (11). Moreover, in an international study by Ammar et al., it was noted that the frequency, duration and intensity of physical activities decreased by 35 %, 34 %, and 42.7 %, respectively (12). The differences noticed between this and other studies can be explained by the fact that gyms and fitness centres were not shut down at the time of this research, unlike in the two aforementioned studies.

As expected, a significantly larger number of B students expressed a positive opinion about being vaccinated against SARS-CoV-2. These results were mostly related to their education and knowledge about vaccine mechanism and effectiveness, which was confirmed by their opinions about the vaccine at the end of the survey. On the other hand, the most frequent reasons that O students pointed out as the reasons not to get vaccinated related to their fear of the short amount of time to develop the vaccine and their opinion about vaccinating only high-risk groups.

Conclusion

This is the first-ever study examining the differences between biomedical students and students from other fields based on their usual activities during the pandemic. In addition, other studies have not yet examined students' impression about the upcoming vaccine against SARS-CoV-2. As it was hypothesised, biomedical students adhered to the CPH's recommendations more and they were willing to get a vaccine against SARS-CoV-2 in a much higher proportion than students from other fields. The results could be associated with their long-term education in the field, along with their awareness of how easily the virus spreads among people.

Acknowledgement. This study was presented as an abstract and oral presentation at the International students' conference OSCON, Faculty of Medicine Osijek, Croatia 20.3.2021..

Disclosure

Funding. No specific funding was received for this study.
Competing interests. None to declare

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Review article

Chronic Kidney Disease Related Anemia - A Narrative Review

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Abstract

Iron is one of the most important essential elements, required by every cell in the body. Anemia is one of the most common medical conditions, defined as a decrease in blood's ability to transport oxygen to tissues, resulting in tissue hypoxia. However, anemia is not a disease, but rather the manifestation of an underlying disorder or disease and it is an important clinical marker of a disorder that may be basic or something more complex. Therefore, once anemia has been diagnosed, the physician must determine its exact cause.

Anemia is frequently associated with chronic kidney disease (CKD) as a consequential disorder of iron metabolism and erythropoiesis regulation. It is a result of a relative erythropoietin deficiency, functional iron deficiency, impaired iron absorption, or blood loss due to dialysis. CKD related anemia is associated with an increased risk of morbidity and mortality. Given the importance of public health, it is necessary to raise CKD awareness, and to encourage early diagnosis and treatment. The recommendations and guidelines of all professional societies of nephrology emphasize early diagnosis and timely treatment. It is important to ensure that patients have a good quality of life while also minimizing the risks of further complications associated with anemia.

(Hrvačić M, Penava M, Juras A. Chronic Kidney Disease Related Anemia- A Narrative Review. SEEMEDJ 2021; 5(2); 44-57)

Received: Jul 31, 2021; revised version accepted: Nov 4, 2021; published: Nov 26, 2021

KEYWORDS: chronic kidney disease, anemia, iron

Introduction

Iron is involved in many cellular processes and is one of the most important minerals in the body. Its absorption, transfer and metabolism are strictly regulated. Most of the ironin the human body, about 60-70%, is embedded into the erythrocyte hemoglobin, while ferritin and hemosiderin account for 20-30% of iron reserves in hepatocytes and macrophages of the reticuloendothelial system (1). Minimal content of iron is found in myoglobin or is embedded into various enzymes. Transferrin is a transport protein in plasma and approximately 3 mg of iron is bound to it. The body of an adult contains 3-5 g of iron, with the most of the circulating iron, about 18-20 mg per day, spent on the synthesis of hemoglobin in erythroblasts.This article is written as a narrative review that provides synthesis of knowledge and applicability of results of recent and significant studies to practice.

Disorders of iron homeostasis

Anemia is one of the most common medical conditions, because it is a symptom of another disease in more than 50% of the cases. The most common causes of anemia are: decreased production, increased deterioration or loss of erythrocytes. Decreased erythrocyte production is caused by weakened bone marrow, either due to a lack of bone tissue or due to suppressed inflammatory or tumor cells. Erythropoietin is a hormone that stimulates the production of erythrocytes and its low levels may result inanemia (2). The main causes of such anemia are decreased production and excretion of erythropoietin (EPO) from the kidneys and a reduced erythropoietic response to EPO (2).

What causes anemia development in CKD and what consequences does it bring?

CKD is a long-term condition with progressive impairment of renal function. Symptoms develop in stages, and they can generally include fatigue, nausea, vomiting, stomatitis, anorexia, muscle twitching, cramps, peripheral neuropathy, convulsions, and itching. Anemia occurs in addition to this wide range of symptoms. CKD develops as a result of any condition that causes functional kidneyimpairment of sufficient duration and intensity; thus the cause of its development can be diabetic nephropathy, hypertensive nephroangiosclerosis, primary and secondary glomerulopathiesinterstitial disease, etc.

Metabolic syndrome associated with arterial hypertension and type 2 diabetes is a major cause of renal dysfunction (3).

CKD involves five stages of kidney damage. In stage 1 CKD, eGFR > 90 mL/min/1.73 m2 signifies normal glomerular filtration, but there are other signs of kidney damage, such as proteinuria or erythrocyturia. In stage 2, the eGFR is between 60 and 89 mL/min/1.73 m2, and stage 3 includes 3.a.) a stagein which the eGFR is between 45 and 59 mL/min/1.73 m2, and 3.b.) a stage in which the eGFR is between 30 and 44 mL/min/1.73 m2, when severe symptoms appear, e.g., swelling of extremities, back pain, high blood pressure and anemia. In stage4 of the disease, the eGFR is between 15 and 29 mL/min/1.73 m2, which indicates severe kidney damage in addition to the previously described symptoms. Stage 5 CKD indicates end-stage renal failure and eGFR is <15 mL/min/1.73 m2 (4). Symptoms ofrenal failure are itching, nausea, vomiting, swelling of the extremities, pain and problems urinating, breathing and sleeping. In this stage of the disease, the patient is forced to undergo kidney dialysis or, if possible, a kidney transplant. Normocytic normochromic anemia occurs in the early stages of CKD, andit is an important factor in the development of cardiovascular disease. The cause of anemia is erythropoietin deficiency. As renal tissue function is slowly lost, erythropoietin secretion decreases, and advanced renal impairment contributes to the severity of anemia. Symptoms of anemia appear when GF drops below 60 mL/min in men and below 50 mL/min in women. Acute anemiaspresent more severe symptoms than chronic anemias, because there is less time for the organism to adapt. Significant symptoms, such as shortness of breath,

weakness, fatigue, headache, loss of concentration orpalpitations, occur when hemoglobin is less than 90 g/L.

Iron accumulation disorders, which represent a heterogeneous group of hereditary and acquired disorders, are at the opposite end of the spectrum of iron metabolism disorders. Iron overload can lead to the formation of reactive oxygen species (ROS), which can damage many cellular components (5).

Impairediron recycling, mediated by the liver hormone hepcidin, leads to the second most common anemia: inflammatory anemia (IA) or chronic disease anemia (CDA). Inflammatory anemia (IA, formerly referred to as chronic disease anemia or chronic disorder anemia) is usually a mild to moderate anemia (hemoglobin rarely below 8 g/dL) that develops as a result of an infection, inflammatory disease or cancer. It differs from iron deficiency anemia in that iron stores are preserved in the marrow of macrophages, in the spleen and in the liver, which recycle obsolete erythrocytes. Accordingly, inflammation anemia signifies a disorder of iron distribution. IA includes low serum iron levels despite adequate systemic iron stores (6). There are three mechanisms of inflammatory anemia, which include: a slight shortening of erythrocyte lifespan, a decrease in erythropoiesis due to a decrease in EPO secretion, a poorer bone marrow response to erythropoietin and impaired cellular iron metabolism.

Anemia in CKD patients

CKD diagnosisis based on laboratory indicators of renal dysfunction, imaging methods and renal biopsy. Anemia is very common in patients with CKD and is the result of dysregulation of iron metabolism and erythropoiesis. It occurs as the result of relative erythropoietin deficiency, functional iron deficiency, impaired iron absorption, or blood loss due to dialysis. Chronic renal patients with anemia have increased levels of serum hepcidin-25. Patients with CKD suffer from both absolute and functional iron deficiency. Absolute iron deficiency is defined by severely reduced or absent iron stores, while functional iron deficiency is defined by adequate iron stores but insufficient iron availability for incorporation into erythroid precursors, as a result of elevated hepcidin levels. Absolute iron deficiency is defined when transferrin saturation (TSAT) is ≤20% and serum ferritin concentration is ≤100 ng/mL among dialysis and peritoneal dialysis patients or ≤200 ng/mL among hemodialysis patients. Functional iron deficiency is characterized by TSAT ≤20% and elevated ferritin levels.

Treatment

The treatment of anemia in patients with CKD is based on guidelines. The KDIGO (Kidney disease: Improving Global Outcomes) group has published treatment guidelines for anemia in chronic renal patients, and the ERBP (European Renal Best Practice) group has reviewed those guidelines. The Croatian Society for Nephrology, Dialysis and Transplantation (HDNDT) has published its own guidelines based on the recommendations and experiences of European and international professional societies, as well as its own. In all cases of CKD or anemia, the following needs to be checked: erythrocyte count (E), hemoglobin concentration (Hb), erythrocyte mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH),mean corpuscular hemoglobin concentration (MCHC), leukocyte count (L), platelet count (Plt), absolute reticulocyte count (Rtc), serum ferritin concentration, plasma transferrin saturation (TSAT) and levels of vitamin B12, and folic acid (7).ESA should be used with caution by people who have a history of cancer or stroke. These conditions are not absolute contraindications to the use of ESA, and the decision should be made with the patient's consent, taking the risks and benefits of the treatmentinto account.

It is recommended that Hb levels are maintained between 100 and 120 g/Lin adults and between 110 and 120 g/Lin children (7).

Formula for calculating iron requirements:

Iron (mg) = body mass (kg) x desired Hb concentration (g/L) - current Hb concentration (g/L) x 0.24 +amount to replenish the iron stores

(adults 500 mg, children 15 mg/kg of body mass) (7).

Table 1. Main causes of CKD

Cause	Example
High blood pressure	Malignant glomerulosclerosis
(hypertension) and diabetes	Nephroangiosclerosis
Glomerulopathies	Primary focal glomerulosclerosis
	Idiopathic crescentic GN
	IgA nephropathy
	Membranoproliferative GN
	Membranous nephropathy with systemic diseases
	Amyloidosis
	Diabetes
	HUS
	Postinfectious GN
	SLE
	Wegener's granulomatosis
Chronic tubulointerstitial nephritis	
Hereditary nephropathies	Alport's syndrome
	Medullary cystic disease
	Nail-chip syndrome
	Polycystic nephropathy
Urinary tract obstructions by kidney stones, enlarged prostate or cancer	BPH
	Urethral obstruction (congenital, stones, malignancy)
	Vesicourethral reflux
Renal macrovascularopathy (artery and vein)	
Nephrotic syndrome	
Recurrent kidney infection (pyelonephritis)	
Lupus and other immune system diseases including polyarteritis nodosa, sarcoidosis, Goodpasture syndrome and Henoch-Schonlein purpura	

Table 1. lists the main causes of CKD (8)

Filtered erythrocytes should be used as needed. Blood transfusion should be used in case of inadequate response to ESA treatment and in cancer patients at risk for ESA treatment, in case the risk outweighs its benefit. It is not recommended to use blood transfusions based on Hb levels, but only in the presence of symptomatic anemia, and it is recommended in acute conditions in cases of bleeding, unstable angina pectoris and in perioperative patient care. Due to the very narrow therapeutic range in which the Hb concentration should be maintained and large individual differences between the patients and the methods of renal function replacement, it is very difficult to maintain the Hb concentration within the set limits.

Epoetin Therapy

The introduction of erythropoietin (EPO) into clinical practicefundamentallyaltered the care of patients with CKD.The extensive use of EPO and its analogues (erythropoietin-stimulating agents, ESAs) for the purpose of anemia correction has resulted in reducing associated morbidity and improving functionality, exercise tolerance, cognitive function, and overall quality of life(9).Patients who develop pure isolated red cell aplasia (PRCA) after treatment with any erythropoietin should not receive Epoetin alfa (10). Increased incidence of thrombotic vascular events (TVD) has been observed in patients receiving drugs to stimulate erythropoiesis. These include venous and arterial thrombosis and embolism (including some fatalities), such as deep vein thrombosis, pulmonary embolism, retinal vein thrombosis, and myocardial infarction. In addition, cerebrovascular events have been reported (including stroke, cerebral hemorrhage, and transient ischemic attacks) (11).

Darbepoetin alfa

Darbepoetin alfa is a second-generationESA that is a supersialylated analogue of EPO, possessing two extra N-linked glycosylation chains. This property confers a lower clearance rate in vivo, and the elimination half-life of the compound in humans after a single intravenous administration is 25.3 hours versus 8.5 hours for epoetin alfa. It has a 3-fold longer serum half-life compared to epoetin alpha and epoetin beta. It stimulates erythropoiesis (increases red blood cell levels) by the same mechanism as rHuEpo (binding and activating the EPO receptor) and is used to treat anemia commonly associated with CKD and cancer chemotherapy (12).

Methoxy Polyethylene Glycol – Epoetin Beta (CERA)

Alternative bioengineering techniques for extending the half-life of EPO resulted in the development of CERA, a continuous erythropoietin receptor activator. The drug stimulates erythropoiesis by interacting with the erythropoietin receptor on progenitor cells in the bone marrow.CERA has an elimination half-life in humans that is considerably longer than the half-life of either epoetin or darbepoetin alfa (13).Stage 4 studies suggest that many patients are able to be maintained with monthly administration of CERA, and a superiority study suggests greater efficacy with this frequency of administration compared with monthly dosing of darbepoetin alfa when administered intravenously to hemodialysis patients.

Effects of therapy in CKD

In CKD, other causes of anemia must be corrected before initiating epoetin therapy. If the serum ferritin concentration falls below 100 ng/mL, it is necessary to introduce iron therapy. It is best to give intravenous iron, although oral administration can also be considered in patients not yet on dialysis. In Time to Reconsider Evidence for Anaemia Treatment (TREAT's) largest Essential Safety Arguments (ESA) study, initiating ESA therapy in patients with mild anemia underwent a benefit – risk assessment and was found to be unfavorable due to a small increase in quality of life, and high possibility of stroke (14). Based on research, The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the introduction of ESA therapy when the hemoglobin concentration falls below 9 g/dL. The commonly used target range of hemoglobin is

between 10 and 12 g/dL. The usual initial intravenous or subcutaneous dose of epoetin is about 25 to 50 IU/kg two or three times a week, of darbepoetin alfa 20 to 30 mcg once a week, and of C.E.R.A. 30 to 60 mcg once every two weeks. An increase in reticulocytes (RTC) is observed 3 to 4 days after startingthe therapy, and an increase in hemoglobin of about 1 to 2 g/dLis observed during one month. It is not recommended to increase the hemoglobin level to 13 g/dL; instead, the limit should be at 11.5 g/dL (15).

Hyporesponsiveness to ESA therapy

According to the latest recommendations, hyporesponsiveness to ESA therapy occurs when the Hb concentration does not respond by increasing in the first month of ESA treatment using modified weight-based dosages, or if, after treatment with stable doses, the patient's ESA dosage is changed two times up to 50% of the dose previously used, and that earlier dose achieved a stable condition. The usualcauses of hyporesponsiveness are iron deficiency, infection or inflammation and underdialysis. If possible, the causes of hyporesponsiveness must be treated and corrected. For example, if there is a possible iron deficiency, the patient should receive iron treatments intravenously. Using laboratory tests, it is possible to establish if a patient has severe hyperparathyroidism, or a deficiency of vitamin B12, folate and thyroxine. Hb electrophoresis should be performed to rule out hemoglobinopathies as causes of resistance to ESA therapy. Some patients taking angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers may be expected to require a higher dose of ESA treatment, but it is rarely necessary to stop taking these drugs. If a primary bone marrow disorder is suspected, a hematological examination of the bone marrow sample should be performed. A bone marrow test is also performed when antibody mediated PRCA are suspected, although a reticulocyte test and antibody to EPO measurement can be performed prior to this test. If a patient receiving ESA therapy has a high count of RTC, the bone marrow produces more new erythrocytes than necessary. Bleeding or hemolysis should be investigated by endoscopic examination or hemolysis test (serum bilirubin, Coomb's test,LDH - lactate dehydrogenase and haptoglobin levels).

The maximum dose of the drug is not precisely defined and doses of 60,000 IU EPO per week are commonly used in the United States. There are indications that high doses of the drug may increase the side effects regardless of Hb concentration. Experience has shown that very high doses can be effective even in critical patients, butRTC indicate no reduction in transfusion requirements and a rise in deep vein thrombosis. Given all that, it seems reasonable to continue with the same dose of ESA (16).

Pharmacotherapy using Roxadustat

Roxadustat, a new drug approved in Japan and China, is used in the treatment of anemia and it reacts as hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PH), thus increasing endogenouserythropoietin production, which stimulates the production of hemoglobin and erythrocytes. Roxadustat activates a response that occurs naturally when the body responds to reduced blood oxygen levels. Roxadustat promotes erythrocyte production by increasing endogenous erythropoietin production, improving the absorption, transport and utilization of iron and reducing hepcidin regulation, which helps overcome the negative impact of inflammation on hemoglobin synthesis and production of erythrocytes (17).

Studies

A list of studies conducted in CKD patients with anemia can be found on the website https://clinicaltrials.gov/(18). A total of 337 studies were found for Anemia in Chronic Kidney Disease, five of which are currently active and are listed in Table 2.A total of 243 studied were completed. Table 3. shows the first 30 completed studies involving different countries of the world (18). Insights provided by these medical research promises to lessen the impact of anemia in CKD patient by making sure that existing treatments are used in the best possible

ways. Research can find answers to things that are unknown, filling gaps in knowledge and changing the way that health care professionals work and ultimately improving CKD patient treatment and care.

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Table 2. List of studies conducted in chronic renal patients with anemia, ClinicalTrials.gov (16)

Row	Status	Study title	Conditions	Interventions	Locations
1.	Active, not recruiting	Study of HEMAX PFS Versus EPREX/ERYPO® in Predialysis Chronic Kidney Disease	Anemia in Chronic Kidney Disease	Biological: Erythropoetin alfa	• CEMEDIC Buenos Aires, Argentina • CEREHA Buenos Aires, Argentina • CIMEL Buenos Aires, Argentina • And 8 more…
2.	Active, not recruiting	Ascertain the Optimal Starting Dose of Mircera Given Subcutaneously for Maintenance Treatment of Anemia in Pediatric Patients With Chronic Kidney Disease on Dialysis or Not Yet on Dialysis	Anemia, Renal Insufficiency, Chronic	Drug: Mircera	• University of Alabama at Birmingham; Pediatric Nephrology Birmingham, Alabama, United States • Loma Linda University Health, Loma Linda, California, United States • Emory University School of Med; Pediatrics Atlanta, Georgia, United States • And 19 more…
3.	Active, not recruiting	Desidustat in the Treatment of Anemia in CKD	Chronic Kidney Disease Stage 3, Anemia, Chronic Kidney Disease Stage 4, Chronic Kidney Disease Stage 5	Drug: Desidustat oral tablet Drug: Darbepoetin Alfa	• Sunrise Hospital Vijayawada, Andhra Pradesh, India • Max Super Specialty Hospital New Delhi, Delhi, India • Thakershey Charitable trust Hospital Ahmadabad, Gujarat, India • and 29 more
4.	Active, not recruiting	Acute Effects of Intravenous Iron on Oxidative Stress and Endothelial Dysfunction in Non-dialysis CKD	Renal Anemia, Iron Toxicity, Oxidative Stress, Endothelial Dysfunction	Drug: Sodium Chloride 0.9% Intravenous Solution, Drug: Ferinject	• "Dr. Carol Davila" Teaching Hospital of Nephrology Bucharest, Romania
5.	Active, not recruiting	Prospective Observational Study of Erythropoietin- Iron Interaction in Anemia of Renal Disease	Anemia of End Stage Renal Disease	Other: Specimen collection	• University of Louisville, University Kidney Center Louisville, Kentucky, United States • Western New England Renal and Transplant Associates Springfield, Massachusetts, United States • Duke University Durham, North Carolina, United States

Table 3. List of completed studies, showing the first 30 completed studies involving different countries of the world.

Row	Study title	Conditions	Interventions	Locations
1.	Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients Not Requiring Dialysis	Anemia in Chronic Kidney Disease in Non-dialysis Patients	Drug: Roxadustat Drug: Placebo	Site BY37503 Brest, Belarus Site BY37504 Gomel, Belarus Site BY37501 Grodno, Belarus And 135 more…
2.	Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa	Anemia in Chronic Kidney Disease in Non-dialysis Patients	Drug: Roxadustat Drug: Darbepoetin alfa	Site AT43009 Vienna, Austria Site BY37503 Brest, Belarus Site BY37501 Grodno, Belarus (and 122 more…)
3.	ASP1517 Phase 2 Clinical Trial - Double-Blind Study of ASP1517 for the Treatment of Anemia in Chronic Kidney Disease Patients Not on Dialysis	Anemia in Chronic Kidney Disease Patients Not on Dialysis	Drug: ASP1517 Drug: Placebo	Chubu, Japan Hokkaido, Japan Kansai, Japan And 4 more…
4.	Study of FG-4592 in Subjects With Chronic Kidney Disease in China	Anemia in Chronic Kidney Disease	Drug: FG-4592 Drug: Placebo	Peking Union Medical College Hospital Beijing, China Peking University First Hospital Beijing, China Sichuan Provincial People's Hospital Chengdu, China (and 10 more…)
5.	Effect of Hemodialysis on the PK of JTZ-951 in Subjects With End-stage Renal Disease	Anemia in Chronic Kidney Disease	Drug: JTZ-951	Minneapolis, Minnesota, United States

6.	A Non-interventional Study of Diafer in Subjects With CKD on Haemodialysis for Treatment of Iron Deficiency	Anemia in Chronic Kidney Disease	Drug: 5% Iron Isomaltoside 1000	Heleneholmsdialysen Malmö, Sweden Morriston Hospital, Renal Department Swansea, Wales, United Kingdom
7.	Strategies Using Darbepoetin Alfa to Avoid Transfusions in Chronic Kidney Disease	Anemia in Chronic Kidney Disease Patients Not on Dialysis	Biological: Darbepoetin alfa Other: Placebo	Research Site Anniston, Alabama, United States Research Site Birmingham, Alabama, United States Research Site Huntsville, Alabama, United States And 246 more…
8.	TARGTEPO Treatment for Anemia in Chronic Kidney Disease (CKD) Patients and End-Stage Renal Disease (ESRD)	Chronic Kidney Disease, End-stage Renal Disease	Biological: MDGN201 TARGTEPO	Barzili Medical Center Ashkelon, Israel Meir Medical Center Kfar Saba, Israel Medical Center of the Galilee Nahariya, Israel (and 2 more…)
9.	A Study of FG-4592 for the Treatment of Anemia in Chronic Kidney Disease Patients Not Receiving Dialysis	CKD Anemia	Drug: FG-4592 Drug: Placebo	Investigational Site Huntsville, Alabama, United States Investigational Site Tempe, Arizona, United States Investigational Site Alhambra, California, United States (and 142 more…)
10.	Safety and Tolerability of FCM vs Standard of Care in Treating Iron Deficiency Anemia in Chronic Kidney Disease Patients	Anemia	Drug: Ferric Carboxymaltose Drug: Standard Medical Care (SMC)	Luitpold Pharmaceuticals Norristown, Pennsylvania, United States

11.	Comparison of Darbepoetin Alpha and Recombinant Human Erythropoietin for Treatment of Anemia in Children With Chronic Kidney Disease	Anemia of Chronic Kidney Disease	Drug: Recombinant human erythropoietin Drug: Darbepoetin Alfa	Sir Ganga Ram Hospital New Delhi, Delhi, India
12.	A Pilot Study of KRX-0502 (Ferric Citrate, Administered Without Food, in Treating Iron-deficiency Anemia	Anemia of Chronic Kidney Disease	Drug: KRX-0502	Barzilai Medical Center Ashkelon, Israel, Western Galilee Hospital Nahariya, Israel, Nazareth Hospital-EMMS Nazareth, Israel
13.	KRX-0502 (Ferric Citrate) for the Treatment of IDA in Adult Subjects With NDD-CKD	Anemia of Chronic Kidney Disease	Drug: ferric citrate Drug: Placebo	AKDHC Medical Research Services, LLC Phoenix, Arizona, United States Southwest Kidney Institute Tempe, Arizona, United States, California Renal Research Glendale, California, United States (and 33 more…)
14.	A Study to Evaluate Efficacy and Safety of JTZ-951 Compared to Darbepoetin Alfa in Korean Renal Anemia Patients Receiving Hemodialysis.	Anemia of Chronic Kidney Disease	Drug: JTZ-951 Drug: Darbepoetin Alfa	SMG-SNU Boramae Medical Center Seoul, Korea
15.	Vitamin D as a Modifier of Serum Hepcidin in Children With Chronic Kidney Disease	Anemia of Chronic Kidney Disease	Drug: Cholecalciferol	Johns Hopkins University Baltimore, Maryland, United States

16.	Phase 2a Study to Evaluate PRS-080 in Anemic Chronic Kidney Disease Patients	Anemia of Chronic Kidney Disease	Biological: PRS-080#022-DP Biological: PRS-080-Placebo#001	University Hospital Brno Brno, Czechia, HDS - Klaudian's Hospital, Mladá Boleslav, Czechia, Institute of Clinical and Experimental Medicine (ICEM) Prague, Czechia (and 3 more...)
17.	CKD-11101 Phase 3 IV Study in Patients Who Had Renal Anemia Receiving Hemodialysis	Anemia of Chronic Kidney Disease	Biological: CKD-11101 Biological: NESP	/
18.	Effect of Erythropoiesis-Stimulating Agent Therapy in Patients Receiving Palliative Care of Chronic Kidney Disease	Anemia of Chronic Kidney Disease	Drug: Erythropoiesis-Stimulating Agent	Prince of Wales Hospital, Chinese University of Hong Kong Shatin, New Territories, Hong Kong
19.	CKD-11101 Phase 3 SC Study	Anemia of Chronic Kidney Disease	Biological: CKD-11101 (Darbepoetin alfa) Biological: NESP (Darbepoetin alfa)	/
20.	Comparison Study of Two Iron Compounds for Treatment of Anemia in Hemodialysis Patients	Anemia of Chronic Kidney Disease	Drug: Supplementation of ferric carboxymaltose Drug: Supplementation of iron sucrose	Medical University of Vienna, Division of Nephrology and Dialysis Vienna, Austria, Wiener Dialysezentrum GmbH Vienna, Austria
21.	Safety, Tolerability, PK & PD Study of JTZ-951 in Anemic Subjects With End-stage Renal Disease	Anemia of Chronic Kidney Disease	Drug: JTZ-951 Drug: Placebo	Lakewood, Colorado, United States Miami, Florida, United States Orlando, Florida, United States (and 2 more...)

22.	Health Care Personnel Time for Anemia Management With Erythropoiesis Stimulating Agents in Hemodialysis Centers in Croatia	Renal Anemia of Chronic Kidney Disease	Other: No intervention	Bjelovar, Croatia Split, Croatia Zadar, Croatia Zagreb, Croatia
23.	A Study to Assess Hemoglobin Level Depending on the Comorbidity Index in Chronic Kidney Disease (CKD) Participants Not in Dialysis Treated With Methoxy Polyethylene Glycol-Epoetin Beta (COMETE)	Renal Anemia of Chronic Kidney Disease	Drug: Methoxy Polyethylene Glycol-Epoetin Beta	CHP Aix Aix En Provence, France Ch Notre Dame Misericorde; Hemodialyse Ajaccio, France Chi D Alencon; Nephrologie Hemodialyse Alencon, France (and 105 more…)
24.	Mass Balance Study of JTZ-951 in Subjects With End-stage Renal Disease on Hemodialysis	Anemia of Chronic Kidney Disease	Drug: JTZ-951, 14C-JTZ-951	Minneapolis, Minnesota, United States
25.	Does Oral Pentoxifylline Administration Improve Hemoglobin in Hemodialysis Patients?	Anemia of Chronic Kidney Disease	Drug: Pentoxifylline	Tanta University Hospital Tanta, Egypt
26.	Study to Evaluate Effect of Lapatinib on Pharmacokinetics of JTZ-951 in Subjects With End-stage Renal Disease	Anemia of Chronic Kidney Disease	Drug: JTZ-951 Drug: Lapatinib	Minneapolis, Minnesota, United States
27.	Periodic Versus Continuous IV Iron Supplementation in HD Patients	Anemia of Chronic Kidney Disease	Drug: Iron Sucrose Supplement	Papageorgiou General Hospital Thessaloniki, Greece

28.	Study of Anemia in Chronic Kidney Disease (CKD) Among High-Risk Hypertensive and Diabetic Patients in Pakistan	Anemia, Diabetes, Kidney Disease, Chronic, Hypertension	/	Islamabad, Pakistan Karachi, Pakistan Lahore, Pakistan
29.	Observational Study of MIRCERA in Users of Self-Application and Multidose Systems	Renal Anemia of Chronic Kidney Disease	Device: MIRCERA	Daun, Germany
30.	Paricalcitol Effect on Anemia in CKD	Anemia, Chronic Kidney Disease	Drug: Paricalcitol Drug: Calcitriol	Federico II University Naples, Italy

Completed studies

Conclusion

Given the importance of CHD for public health, it is necessary to raise awareness of CHD and encourage early diagnosis and treatment. Recommendations and guidelines of all professional nephrology societies are aimed at early diagnosis and timely treatment. When it comes to anemia, the goal is not to correct anemia, but to ensure that the serum hemoglobin level reaches approximately 100 g/L, which can provide the patient with a satisfactory quality of life and minimize the risks related to anemia. The treatment of anemia today represents a largely individualized. It is vital to consider all the current parameters of the disease and condition, the presence of comorbidities, the current method of treatment, as well as the patient's preference.

Acknowledgement. None.

Disclosure

Funding. No specific funding was received for this study.

Competing interests. None to declare

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Author contribution. Acquisition of data: Hrvačić M, Penava M, Juras A
Administrative, technical or logistic support: Hrvačić M, Penava M, Juras A
Analysis and interpretation of data: Hrvačić M, Penava M, Juras A
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Critical revision of the article for important intellectual content: Hrvačić M, Penava M, Juras A
Drafting of the article: Hrvačić M, Penava M, Juras A
Final approval of the article: Hrvačić M, Penava M, Juras A
Obtaining funding: Hrvačić M, Penava M, Juras A
Provision of study materials or patients: Hrvačić M, Penava M, Juras A

Original article

Connection between Mental Disorders and Hypertension In Patients Treated at the Psychiatric Clinic, Clinical Hospital Centre Osijek

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Abstract

Background: The objective of this study was to assess the type and frequency of psychiatric disorders associated with hypertension and to identify sociodemographic specifics and other comorbid diseases.

Materials and Methods: This was retrospective study to establish if there was a relationship between mental disorders and hypertension in patients hospitalized at the Department of Psychiatry from January 1, 2020 to August 15, 2021. Different mental disorders were correlated with hypertension comorbidity, with the emphasis on disease duration, mental disorder characteristics, diagnostic category such as age and gender, and other comorbidities.

Results: The study included data from 800 patients hospitalized at the Department of Acute and Biological Psychiatry and the Department of Integrative Psychiatry at the Psychiatry Clinic of the University Hospital Center Osijek. All of them were treated for various mental disorders in the period from January 1, 2020 to August 15, 2021. Special emphasis was placed on the patients who had been diagnosed with a mental disorder and hypertension in order to determine how many patients treated for a mental disorder also suffer from hypertension. The research shows that 230 (28.75%) out of 800 patients suffer from both a mental disorder and hypertension.

Conclusions: The study has shown that almost one third of the respondents treated at the Psychiatry Clinic for a certain period of time suffer from hypertension. The majority of hypertensive patients were treated for recurrent depressive disorder, alcohol addiction and posttraumatic stress disorder.

(Pavličević Tomas I, Degmečić D. Connection between Mental Disorders and Hypertension With Patients Treated at the Psychiatric Clinic, Clinical Hospital Centre Osijek. SEEMEDJ 2021; 5(2); 58-67)

Received: Sep 29, 2021; revised version accepted: Nov 8, 2021; published: Nov 26, 2021

KEYWORDS: mental disorder, hypertension, depression, comorbidities

Introduction

Mental disorders, such as anxiety and depression, are risk factors for mortality among cardiac patients, but this issue has received little attention when it comes to hypertensive individuals. Research suggests that the correlation between hypertension and total and cardiovascular disease mortality is higher when combined with a common mental disorder (1). Other studies have found significant correlation between depression, anxiety, impulsive eating disorders and substance use disorders and the subsequent diagnosis of hypertension. These findings highlight the importance of early detection of mental disorders, as well as of physical health monitoring in patients with those conditions. Social phobia and alcohol abuse were more strongly associated with hypertension in males than in females. The correlation between panic disorder and hypertension was particularly apparent in those with earlier-onset hypertension (2).

Among all mental disorders, depression must be recognized as the leading risk factor for hypertension and cardiovascular incidents. For patients suffering from depression, the risk of developing hypertension depends on: a) biological b) behavioral and c) psychological factors.

Biological factors

Certain pathophysiological factors favor faster development of hypertension and other cardiovascular diseases in patients suffering from mental disorders (particularly depression and stress-related disorders):

1. Hypothalamic-pituitary-adrenal axis (HPA axis) hyperactivity, which is in the pathogenesis of the mental illness, causes an increase in blood pressure and heart rate, as well as an acceleration of the atherosclerosis process.

2. Due to dysfunction of the autonomic nervous system in patients suffering from mental disorders, the activity of their sympathetic nervous system increases, causing catecholamine hypersecretion. This leads to vasoconstriction and enables ventricular irritability. The parasympathetic tone is reduced, which lowers the level of the ventricular ectopy occurrence. In addition to reduced heart rate variability, all of the above significantly increases the risk of sudden death.

3. The state of sub-chronic inflammation caused by hyperactivity of inflammatory cytokinins CRP, IL 1 and 6 in depressed patients leads to changes in sympathetic tone and influences serotonin and platelet aggregation and fibrinolysis affected by serotonin (3, 4).

4. Hypercoagulability, triggered by serotonin and the altered function of platelets affected by serotonin. Connecting itself to the platelets via the 5-HT 2A receptors, serotonin participates in the process of platelet aggregation, accelerates vasodilation with the help of preserved endothelium and maintains the flow of blood vessels. In addition to endothelium damaged by atherosclerotic changes, released platelet serotonin causes vasoconstriction and disrupts microvascular circulation. In addition to increased platelet aggregation, a serotonin-mediated increased activation of procoagulant factors (fibrinogen, von Willebrand factor and factor VII) and the reduction of fibrinolytic activity has been detected in patients suffering from depression (5, 6).

Behavioral factors

People suffering from mental disorders are not physically active enough. They tend to have unhealthy habits: they smoke, drink alcohol, consume food excessively and therefore gain weight, which accelerates hypercholesterolemia and indirectly leads to cardiovascular disease (7).

Psychological factors

Persons prone to vascular diseases are known as type A personalities. These are persons who are hyperactive and demanding, unable to relax, and who are aggressive and ambitious. However, from the psychodynamic point of view, they are insecure, with low self-esteem and primarily depressive. If such persons are

subjected to prolonged stress, it can be manifested both directly (the impact on the cardiovascular system via autonomous nervous system) and indirectly (the impact via the hypothalamic-pituitary-adrenal axis (HPA axis)), which can eventually lead to undesirable outcomes. The symptoms of mental illness may significantly interfere with the course and outcome of a cardiac disease, as well as with the recovery period.

The purpose of this study is to analyze the incidence of comorbidity of various mental disorders and hypertension among the patients treated at the Department of Psychiatry by using the retrospective analysis of medical history. The incidence of comorbidities was compared according to different diagnostic categories of mental disorders, as well as the duration of the disease. Incidence of other comorbid somatic diseases has also been studied in those with the aforementioned comorbid mental disorders and hypertension.

Material/Patients and Methods

The research was conducted at the Department of Psychiatry at the University Hospital Center Osijek. Medical histories and medical records of the hospital information system were used as data sources. Respondents were hospitalized at the Department of Acute and Biological Psychiatry and the Department of Integrative Psychiatry at the Psychiatry Clinic. This makes a total of 800 patients with different psychiatric diagnoses, who were hospitalized in the period from January 1, 2020 to August 15, 2021. The following factors were analyzed: the patients' age and gender, all psychiatric diagnoses for which they were treated, treatment duration and comorbidities. In our study, the emphasis was put on the comorbidity of mental disorders and hypertension, but other somatic disease comorbidities were also evaluated. Specific characteristics of the analyzed patient category were observed and recorded using the hospital IT system. The criterion for patient selection was the time period in which they were hospitalized at the Department of Psychiatry (from January 1, 2020 to August 15, 2021). The age and gender of all the patients, as well as their diagnostic categories, disease duration and comorbidities, were all recorded.

Statistical analysis

Data collected by reviewing specialist findings were processed using descriptive statistical methods. Categorical data are presented in absolute and relative frequencies. Numerical data are described by the arithmetic mean and standard deviation in the case of distributions following the normal distribution, and in other cases by the median and limits of the interquartile range. Differences or correlations of categorical variables were tested by $\chi 2$ test. A specific statistical program SPSS was used for statistical analysis. Significance level was set at $p<0.05$.

Results:

Special emphasis was placed on the patients who had been diagnosed with a mental disorder and hypertension in order to determine how many patients treated for a mental disorder also suffer from hypertension. The results of present study showed that 230 (28.75%) out of 800 patients suffer from both a mental disorder and hypertension. 1.3% of patients who suffered from both mental disorder and hypertension were between 20 and 29 years old; 2.6% ages 30 -39; 10% were 40 - 49 years old; 35.2% of patients were 50 – 59 years old; 36% were 60 – 69 years old; 12.6% were 70 – 79 years ol, and 2.1% of patients were over 80 years old. Other age categories were not recorded. The majority of patients with hypertension comorbidity were between the ages of 60 and 69, whereas the minority were between the ages of 20 and 29. 51.73% of patients with mental disorders and hypertension were women, and 48.26% were men. There is no statistical significance between the sexes.

Furthermore, the focus of the study was to determine which mental disorders the patients with hypertension comorbidity suffered from (Table 1). The highest percentage (30% (N=230) of the patients) suffered from recurrent depressive

disorder. 17.2% of psychiatric patients with hypertension were treated for alcohol addiction and 16% were treated for posttraumatic stress disorder. There were 14.3% of patients treated for recurrent depressive disorder with psychotic symptoms, and 11.7% of them were treated for schizophrenia. 9.5% of patients with hypertension were treated for psychoorganic symptoms and personality disorders, 7.3% of them were treated for bipolar affective disorder, 6.9% for first depressive episode and 4.7% for schizoaffective disorder. 3.4% of patients with hypertension were treated for mixed anxiety and depressive disorder, 3% for generalized anxiety disorder (GAD), 2.6% for inorganic psychotic disorder, 2.2% for adjustment disorder, 1.7% for delusional disorder and dementia. Finally, the smallest number of patients suffering from hypertension were treated for first psychotic reaction (1.3%).

Table 1. All psychiatric diagnoses of the patients with hypertension

ICD-10 Diagnosis	Description	n	%
F01-F09	**Mental disorders due to known physiological conditions**		
F03	Unspecified dementia	4	1.7
F06	Other mental disorders due to known physiological condition	22	9.5
F10-F19	**Mental and behavioral disorders due to psychoactive substance use**		
F10	Alcohol related disorders	41	17.8
F20-F29	**Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders**		
F20	Schizophrenia	27	11.7
F22	Delusional disorders	4	1.7
F23	Brief psychotic disorder	3	1.3
F25	Schizoaffective disorders	11	4.7
F28, F29	Other or unspecified psychotic disorder not due to a substance or known physiological condition	6	2.6
F30-F39	**Mood [affective] disorders**		
F31	Bipolar disorder	17	7.3
F32	Depressive episode	16	6.9
F33	Major depressive disorder, recurrent	71	30
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms	33	14.3
F40-F48	**Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders**		
F41.1	Generalized anxiety disorder	7	3
F41.2	Mixed anxiety and depressive disorder	8	3.4
F43.1	Post-traumatic stress disorder (PTSD)	37	16
F43.2	Adjustment disorders	5	2.2
F60-F69	**Disorders of adult personality and behavior**		
F60	Specific personality disorders	22	9.5

Depressive disorder and other mental disorders comorbidity were studied in more detail than any other mental disorders monitored and compared to hypertension comorbidity. The study showed that 9.5% of all the respondents had depressive disorder and posttraumatic stress disorder in comorbidity with hypertension, 6% of them suffered from depressive disorder and alcohol addiction, while 1.7% of depressed patients suffered from organic psychosyndrome and hypertension. The study also focused on the treatment period and the criterion included the long-term treatment of the mental disorder. The study showed that 81% of patients suffering from a mental disorder and hypertension had a chronic mental disease.

Other somatic comorbidities, particularly the most common somatic diseases, were monitored in addition to the mental disorder and hypertension comorbidities. 28.2% of patients suffering from various mental disorders and hypertension also suffered from chronic gastritis, 26.5% of them had diabetes mellitus, 1.8% had hyperlipidemia, and 8.7% had hypothyroidism.

Of the total number of the respondents with mental disorders and comorbid hypertension, 18.2% suffered only from hypertension and had no other physical disorders, whereas 81.8% also suffered from other physical illnesses (Table 2)..

Table 2. The most common physical comorbidities in patients with hypertension

ICD-10 Diagnosis	Description	n	%
E11	Type 2 diabetes mellitus	61	26.5
E78	Disorders of lipoprotein metabolism and other lipidemias	41	17.8
K29	Gastritis and duodenitis	65	28.2
E03	Other hypothyroidism	20	8.7

Discussion

The aim of the research was to establish the frequency of hypertension occurring in association with various mental disorders among all patients treated throughout this time period. According to the findings, 28.75% of the hospitalized patients had hypertension, which is consistent with the findings of other international studies. For example, in the study by Rantanen et al., the overall prevalence of depressive symptoms among respondents with hypertension was 22.8% (8). Furthermore, Li et al. found an even higher depression prevalence (29.8%), having conducted a meta-analysis of 10,194 hypertensive respondents in 27 studies using self-assessment scales (9). Predominantly conducted were screening studies of patients with hypertension and the level of their association with mood disorders.

In this study, the patients' age and gender were monitored separately among the respondents suffering from a mental disorder and hypertension. The results obtained indicate that the majority of patients (36%) were between the ages of 60 and 69, with the next most prevalent age group being between the ages of 50 and 59 (35.2%). Patients aged 20 to 29 had the lowest hypertension suffering ratio.

The age groups 70 to 79 and 30 to 39 had a comparable ratio, 12.6% and 10% respectively. The age groups 30 to 39 (2.6%) and above 80 (2.1%) had about the same percentage. Patients under the age of 20 were not represented.

There was no significant difference in terms of gender distinction: 51.7% were women while 48.3% were men. According to numerous literary sources, there is a difference in the affective disorder occurrence in terms of gender distinction. Depression occurs almost twice as often (2:1) in women than in men. The depression

incidence is estimated to be around 11% in men and 19% in women. The cause for that can be found in hormonal variations, primarily in serotonin, which affect patients' metabolism. An even greater difference in disorder incidence can be seen in anxiety disorders, with the frequency of anxiety disorders being more frequent in women than in men with a ratio of 3:2, and, according to some studies, of 2:1. As far as bipolar affective disorder and schizophrenia are concerned, it is estimated that the frequency is approximately equal (about 1%) (10). Since the predominant diagnostic category of this study was depressive disorder, the obtained results of female predominance were expected. However, in our study a smaller gender difference was observed, which can be attributed to the simultaneous analysis of all the represented diagnostic psychiatric categories. In one study, the most powerful predictor of depression and hypertension comorbidity was the female gender, which was followed by alcohol abuse and obesity. It seems that non-smokers and the moderately physically active people alleviate depression symptoms when compared with the people who are rarely physically active (8).

We were particularly interested in diagnostic categories of mental diseases that are in comorbidity with hypertension. Of the seventeen monitored diagnostic categories, the highest percentage of psychiatric patients were treated for recurrent depressive disorder (30%), which is also confirmed by other studies. The results of international meta-analysis suggest that when compared with the general population of the same age and gender, depressive patients have a 30% to 50% higher risk of developing cardiovascular disease and hypertension (11, 12). 2 out of 5 patients with coronary artery disease suffer from a clinically significant depressive disorder (12).

The mortality rate from cardiovascular diseases is 50% higher among depressive patients when compared to the general population (13). Depressive disorder doubles the risk of occurrence of major cardiovascular incidents (such as death caused by coronary heart disease, coronary incidence or myocardial reinfarction, heart failure, myocardial revascularization, fatal and nonfatal stroke) within a two-year-period after acute myocardial infarction (14). The prevalence of depressive disorder is three times higher in patients who have survived acute myocardial infarction in relation to the general population (15). Depressed patients have a 35% higher risk of having a stroke than the general population of the same age and gender (16).

Based on the data from a large population register of Sweden, Sandström et al. have shown that individuals with hypertension are more likely to suffer from depression than individuals who do not have hypertension (17). According to the US National Epidemiological Study of Monitoring Health and Nutrition, the comorbidity of hypertension with depression symptoms is associated with a 15% higher relative mortality risk than hypertension without depression symptoms, even after adjusting for lifestyle factors and comorbid diseases (18).

Higher level of psychological stress in patients treated for hypertension may partly be explained by the hypertension diagnosis (19, 20). The awareness of hypertension may have a labeling effect that causes mental distress, as suggested by Hamer et al. (19) On the other hand, Michal et al suggested that it could be a consequence of depressed persons' increased use of health care (20).

The second most common diagnostic category in our study was alcohol addiction (17.8%), even though there is a slight variation in terms of the frequency of our study's most common disorder. According to the data obtained in the study, we may conclude that the recurrent depressive disorder is mainly associated with hypertension, while the next most frequent disorder is 1.68 times less frequent. Posttraumatic stress disorder was represented in hypertension comorbidity with 16%. The fourth most frequent diagnostic category was recurrent depressive disorder with psychotic symptoms (14.3%). Schizophrenia was the fifth most frequent type of mental disorder (11.7%), followed by specific personality disorder (9.5%).

The least frequent diagnostic category was acute psychotic disorder, but because it is more

common in younger patients, this may also explain why it has the lowest prevalence of comorbidity with hypertension.

6.9% of patients suffering from illnesses with hypertension comorbidity were treated for the first depressive episode. We were especially interested in not only the duration of mental disorder and duration of treatment, but also in how the afore-mentioned parameters can affect the occurrence of hypertension and other somatic comorbidities. As regards the duration of the mental disorder in hypertensive patients, 81% of the respondents were receiving long-term psychiatric treatment. Their mental illness had lasted for several years, and the majority of them suffered from recurrent depressive disorder. In terms of frequency, alcohol addiction was the second most frequent, followed by post-traumatic stress disorder, both of which were categorized as chronic illnesses. We may conclude that chronic mental illnesses may be a risk factor for the incidence of somatic diseases such as hypertension.

Because recurrent depressive disorder was identified as the most prevalent chronic illness in patients who also suffered from hypertension, the connections with other mental disorders that occurred in comorbidity with recurrent depressive disorder were additionally analyzed (Table 2). The majority of patients (9.5%) suffered from both recurrent depressive disorder and chronic post-traumatic stress disorder. 6% of the patients had a comorbidity of recurrent depressive disorder and alcohol addiction, while 1.7% of patients with recurrent depressive disorder developed psycho-organic symptoms. All of the patients with two chronic mental disorders suffered from hypertension. 81% of patients were in a long-term psychiatric treatment.

The data obtained can be linked to the neuroendocrine theories, which are based on the fact that the hypothalamic-pituitary-adrenal axis (HPA axis) is dysregulated in 50% of depressed patients. Due to the absence of the negative feedback loop, the HPA axis is hyperactive, resulting in an increase in serum cortisol levels (in the range of 20% to 80%), which, in the biological sense, indicates a continuous state of chronic stress. Patients with HPA axis hyperactivity, on the other hand, are more likely to suffer from depression with psychotic symptoms or another mental illness, especially stress-related mental disorders (e.g., posttraumatic stress disorder). Thyroid disorders have also been reported in patients with depression (according to some studies, in about 25% of patients) (21, 22).

Only 18.2% of patients treated at the Department of Psychiatry had no physical illnesses other than hypertension, which is a modest proportion when compared to 81.8% of those who had multiple concurrent physical diseases. Given the large proportion of psychiatric patients with multiple physical comorbidities, the categories of the represented physical diseases were studied separately. The most prevalent diseases were also analyzed separately in terms of their incidence. Along with hypertension, chronic gastritis was the most common (28.2%). It can be concluded that almost one third of psychiatric patients suffered from both hypertension and chronic gastritis. The disease with an approximate incidence rate relative to chronic gastritis was diabetes mellitus (26.5%). Furthermore, a high percentage of psychiatric patients suffered from metabolic lipid disorders (17.8%). Finally, the incidence of hypothyroidism was also studied, and it was found that 8.7% of psychiatric patients with hypertension also suffered from this disease. It is possible to conclude that psychiatric patients belong to a vulnerable group with a high risk of developing chronic physical diseases with a progressive course.

According to numerous studies, psychiatric patients are at a higher risk of morbidity and mortality due to physical disorders (23-25). Serious and permanent mental disorders can shorten a patient's life by up to four years when compared to persons who do not have mental disorders.

A representative epidemiological study from the 2001-2003 U.S. National Comorbidity Survey (NCS-R) found that comorbidity between physical and mental diseases was the rule, not

the exception. (26, 27) More than 68% of adults with a mental disorder reported having at least one physical disorder, and 29% of those with a physical disorder had a comorbid mental disorder. Elderly patients and those diagnosed with organic psychosyndromes have been shown to be at the highest risk of comorbid physical illness. (28) In conclusion, a mental disorder is a risk factor for physical disorder and vice versa. In particular, physical illness is one of the strongest risk factors for depression and vice versa (29, 30). An epidemiological study found that the likelihood of being diagnosed with depressive disorder increased with each additional comorbid chronic somatic disease among its respondents (31). According to other studies, depression is comorbid with 26 disease categories and is most prevalent in combination with gastrointestinal disease, stroke, musculoskeletal disease, Parkinson's disease, respiratory disease and obesity (32). The study by Andres et al. (33) analyzes the association between post-infarction depression in patients with recurrence of acute myocardial infarction, where psychiatric disorders affected the risk of infarction recurrence in the same way that cigarettes, diabetes, and obesity did. Several authors reported that specialists could not recognize comorbid somatic diseases in nearly half of all the cases. (34, 35) In some cases, physical diseases lead to psychiatric disorders or they deteriorate the existing symptoms. In addition to mental disorder, the harmful effects of medications or some other treatments can result in serious physical pathology (36).

Conclusion

The study has shown that almost one third (28.75%) of the respondents who were treated at the Department of Psychiatry for a certain period of time suffered from hypertension.

The majority of patients suffering from hypertension were treated for recurrent depressive disorder, alcohol addiction and posttraumatic stress disorder. The least represented diagnostic category was acute psychotic disorder.

More than 80% of psychiatric patients with hypertension were in a long-term psychiatric treatment and that fact can be associated with a number of other physical comorbidities they suffered from.

Acknowledgement. None.

Disclosure

Funding. No specific funding was received for this study.
Competing interests. None to declare

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Original article

Effectiveness of Initiatives to Minimize Blood Usage and Wastage at a Public Hospital Setting in Guyana

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Abstract

Objectives: This is a cross-sectional descriptive follow-up study which analysed the pattern of blood usage and wastage after initiatives were taken following the initial study done in Guyana from 2012 to 2014. This study also assessed the healthcare personnel's knowledge regarding blood transfusion.

Methods: A study was conducted concerning blood product usage and wastage using data from the laboratory blood bank information system in 2016–2018 in the public hospital. Information on knowledge, attitude, practices and administrative guidance of healthcare personnel was assessed using a self-administered questionnaire on different areas of transfusion medicine. Usage of blood products was calculated as a percentage, and wastage of blood products was calculated as the number of units wasted due to each reason divided by the total number of units wasted. The data were entered and analysed in SPSS 21.0.

Results: A total of 29,577 units of blood were issued by the National Blood Transfusion Service. Each year, a blood unit collection of 9,745 (32.9%), 9,765 (33.0%), 10,067 (34.0%) units, respectively, was recorded. Data indicated that 3,851 units (13.0%) of blood were wasted at the Georgetown Public Hospital Cooperation due to various reasons. Packed red blood cells were the most commonly used blood product that was issued (52.5%) and platelets (47.8%) were the most commonly wasted product. In comparison to the previous study, blood wastage decreased from 25.4% to 13.0% after implementing simple interventions. Results of examination of knowledge, attitude, practices and administrative guidelines of health personnel were not satisfactory.

Conclusion: Simple and relatively cheap interventions introduced following the previous study had a dramatic impact on reducing blood wastage in the public hospital in Guyana.

(Kurup R, Anderson A, Bisnauth R, Pompey-Atkins S, Bostona C Mohamed-Rambarranb P. Effectiveness of Initiatives to Minimize Blood Usage and Wastage at a Public Hospital Setting in Guyana. SEEMEDJ 2021; 5(2); 68-76)

Received: Oct 16, 2021; revised version accepted: Nov 11, 2021; published: Nov 26, 2021

KEYWORDS: blood wastage, donors, effectiveness, Guyana

Introduction

Ensuring and practising safe and rational blood transfusion is important for high-quality and effective patient care in hospitals. The World Health Organization (WHO) defines blood management as "a patient-focused, evidence-based and systematic approach to optimize the management of patient and transfusion of blood products for quality and effective patient care. It is designed to improve patient outcomes through the safe and rational use of blood and blood products and by minimizing unnecessary exposure to blood products" (1). However, providing a safe and adequate supply of blood and blood products for transfusion is always expensive.

Appropriate clinical use of blood is an important aspect of blood safety and it reduces unnecessary exposure of patients to allogeneic blood and its associated risks (2). Despite extensive use in emergency settings, blood transfusion decisions are always made without reasonable training and with limited knowledge of the patients' situation. Overuse or inappropriate use of blood products leads to inadequacy of blood components and a substantial increase in the cost of care. Although blood components are a precious resource, their wastage is a critical problem in hospitals, especially in developing countries (3). Blood and blood components are extremely valuable and require careful allocation to maximize clinical benefits.

WHO reports that "[t]here are currently no global standards for the estimation of national requirements for blood and blood products. The need for blood and blood products is dynamic and is dependent on many factors related to health service coverage, the level of development and sophistication of the health care system and hospital blood usage" (2). There are multiple causes of blood wastage in hospitals, but the two major ones are: 1) delay in returning blood products after ordering and 2) exceeding shelf life (expiry) (3). As per the US Food and Drug Administration (FDA) and American Association of Blood Banks (AABB) guidelines, the criterion for accepting issued blood products is that the product was kept within a temperature range of 1–6 ˚C (4, 5). In most countries, including Guyana, blood banks follow a 30-minute rule for returning red blood cell (RBC) units. If the ordered RBC units are returned to the blood bank after 30 minutes without a controlled temperature, they must be discarded (6-8). Therefore, wastage occurs if the product has not been transfused or returned within 30 minutes of its issue.

In a previous study done in Guyana on blood wastage and usage, it was found that 25% of blood was wasted due to various reasons (9). This study identified a large percentage of blood wastage in the only tertiary hospital in the country. In an ideal setting, expiry and wastage of blood products should not occur, although a very low level of expiry of blood products could be expected due to blood product stocks and unpredictable demands on inventory (10).

Moral responsibilities of healthcare providers, along with strict interventions and awareness, could reduce wastage of blood products (11). Blood product wastage could be reduced through simple and cheap interventions (12). A study done on blood wastage by Heitmiller et al. indicated that RBC wastage could be decreased by 61% over 4 years, saving more than $800,000 (13). Simple interventions like strict management of blood stocks, tracking of released blood products and awareness of blood usage among clinical staff were introduced after the first similar study in the same setting. Transfusion guidelines among clinicians could also increase awareness of blood transfusion.

This study aimed to evaluate the efficiency of guidelines/interventions implemented after the previous study on blood usage and wastage. The interventions implemented after the first study helped in creation of awareness among hospital staff, creation of a proper electronic inventory and maintaining of proper temperature for blood and blood products. In order for the health professionals to make appropriate decisions in regard to proper management of blood products, it is very

important to educate them regarding the risks and benefits of transfusion. This study also aimed to investigate the adequacy in terms of knowledge, attitude and practices among doctors, nurses and laboratory technologists in the public hospital.

Materials and Methods

This was a cross-sectional, descriptive study conducted between 2016 and 2018 in the only referral hospital in Guyana. It was a follow-up study aimed at analysing the effectiveness of initiatives for minimizing blood usage and wastage in a public hospital setting in Guyana. Georgetown Public Hospital Cooperation (GPHC) is faced with high demand for blood for transfusion. National Blood Transfusion Service (NBTS), Guyana, is responsible for ensuring and providing an adequate supply of blood components. Blood collection, processing and screening of blood from donors is performed at the blood bank of the NBTS. It is a centralized blood centre which collects blood directly or through blood drives from voluntary blood donors. NBTS also collects blood through its blood facilities at the New Amsterdam, West Demerara, Suddie and Linden hospitals, along with mobile units for blood camps.

This study was conducted in three phases to meet the objective of the study: a) to assess the usage and wastage of blood and blood products; b) to investigate the knowledge, attitude and practices (KAP) of the health personnel; and c) to compare the usage and wastage of blood products with the data obtained in previous study.

Usage and wastage of blood and blood products

Wastage as a percentage of units issued (WAPI) was calculated for red blood cells (RBC), platelets (PLT), fresh frozen plasma (FFP), Pre-thawed FFP (PTFFP), Pediatric Packed Cell (PedPC), thawed fresh frozen plasma (TFFP) and packed red blood cell (PRBC):

$$\text{WAPI} = \frac{\text{sum of wasted units for each component} \times 100}{\text{sum of units issued for each component to the hospital}}$$

Percentage of blood and blood product wastage was calculated using the following formula:

$$\text{Percentage} = \frac{\text{number of units wasted} \times 100}{\text{total number of units wasted}}$$

KAP of health personnel

A carefully formulated multiple choice questionnaire, identifying areas of knowledge, attitude and practices (KAP) about blood usage and wastage, was prepared. The questions were adapted and modified from the AABB Technical Manual (17th Edition), AABB Standards for Blood Banks and Transfusion Services (27th Edition) and other literature to focus on local interests. The questionnaire was divided into four sections to meet the objectives. The first part was on knowledge assessment, the second on attitude assessment, the third on practice assessment and the last on assessing administrative guidelines. The questionnaire took less than 15 minutes to complete. Only doctors and nurses answered questions related to administrative guidelines.

A score was given for each correct answer and converted into a percentage. Mean scores were used to place each participant in a group: good or poor. Participants who scored above the mean were considered to have good KAP and those with a score below the mean were considered to have poor KAP. The same applied to the independent components of KAP. An overall average was calculated to compare the groups. A t-test and ANOVA were used to compare a statistically significant difference in mean KAP among the clinical staff involved. To validate and improve the questionnaire, a pilot study was conducted among a small group of clinicians and was not included in the actual study. Data were first entered in MS Excel and later analysed using SPSS 21.0.

Ethical considerations

Ethical approval for the study was obtained from the Institution Review Board, Ministry of Public Health, Guyana and from the Director of GPHC before proceeding with the research. A signed

consent form was obtained from all participants prior to their participation in the study.

Statistical analysis

The data related to usage and wastage of blood products were presented as number, percentage, and standard deviation. The hi-2 test was used for statistical analysis and a p-value less than 0.05 was considered statistically significant.

Results

Status of blood usage

A total of 29,577 units of blood were collected in the referral hospital from the blood bank during the period from 2016 to 2018. For each year, a blood unit collection of 9,745 (32.9%; 95% CI 32.4–33.5), 9,765 (33.0%; 95% CI 32.5–33.6), 10,067 (34.0%; 95% CI 33.5¬–34.6) units, respectively, was recorded. Mean (± SE) blood products collected annually were 331 ± 3.91 (95% CI 323.4–338.7), 335 ± 4.43 (95% CI 326.3–343.7), 359 ± 4.33 (95% CI 350.5–367.5) for 2016, 2017 and 2018, respectively. Compared to 2016, there was an increase in collection (by the referral hospital) of PRBC, FFP, platelets and PedPC in 2018 by 4.7%, 6.1%, 16.6%, and 16.1%, respectively (Figure 1).

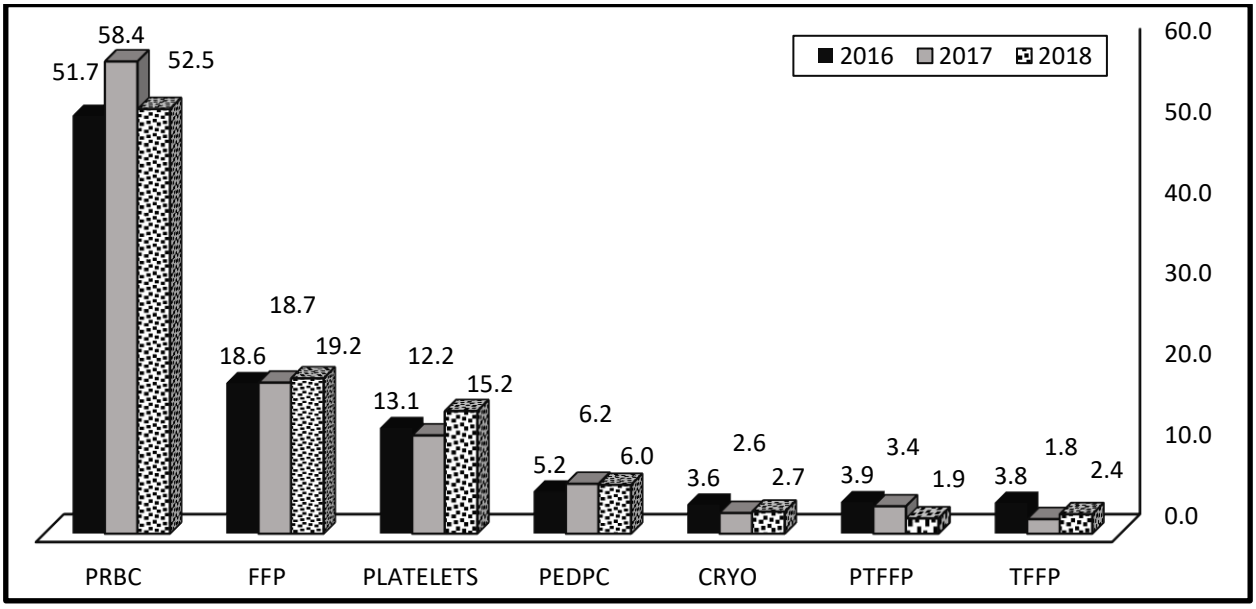

Figure 1: Distribution of blood products during the study period (2016–2018)

Of the blood products collected collectively and annually, the most frequent blood type was O+ with 50.6% (95% CI 50.0–51.2), followed by B+ (20.2%, 95% CI 19.7–20.6) and A+ (18.9%, 95% CI 18.4–19.3) (Figure 2). Usage of blood components during each quarter of the study period is shown in Figure 3..

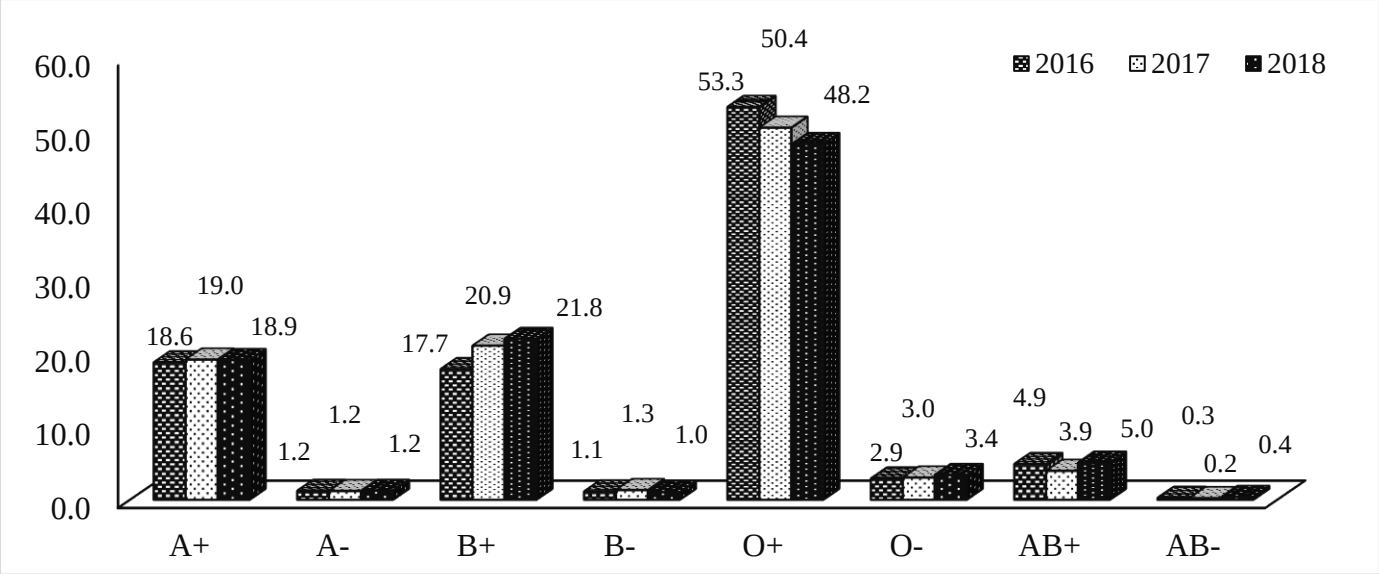

Figure 2: Distribution of blood groups during the study period (2016–2018)

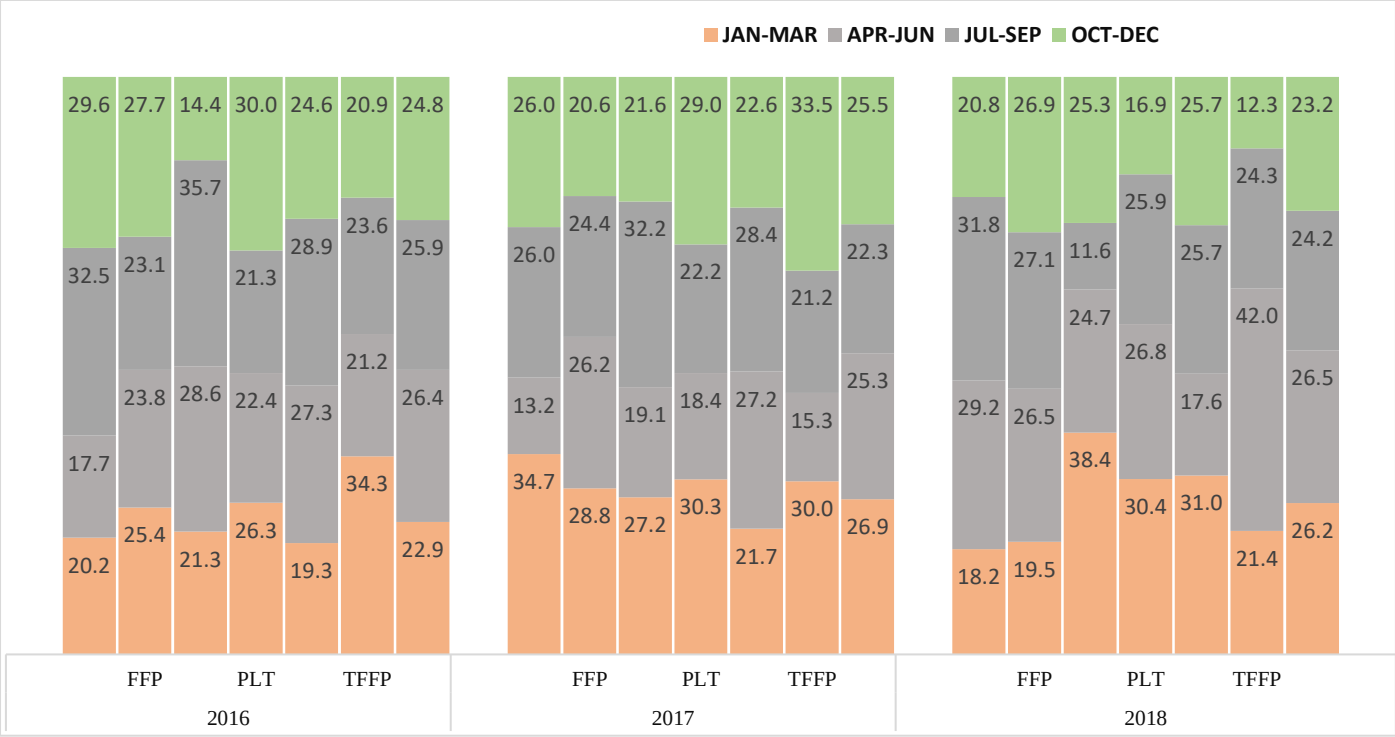

Figure 3: Blood components and their usage every quarter (2016–2018)

Status of blood wastage

The WAPI rates of Cryo, FFP, PTFFP, platelets, PedPC, TFFP, and PRBC were 17.2% (95% CI 14.7–19.9), 15.9% (95% CI 14.9–16.9), 42.9 (95% CI 39.6–46.2), 46.6 (95% CI 45.0–48.2), 5.0 (95% CI 4.0–6.1), 23.3 (95% CI 20.4–26.4) and 2.1 (95% CI 1.9–2.3), respectively. The highest wastage was observed with platelets, followed by PTFFP and TFFP.

Table 1 shows the various causes of blood wastage during the study period. The major reasons for significant blood wastage during the study period were expired blood unit (91.4%; 95% CI 90.4–92.2), broken bag (3.8%; 95% CI 3.2–4.4), unit returned after 30 minutes (1.0%; 95% CI 0.7–1.4).

Table 1: Reasons for blood component wastage during the study period (2016–2018)

Reason for blood wastage	2016	2017	2018	TOTAL	difference (%)	p-value
Expired unit	1301 (90.5)	1190 (91.6)	1028 (92.2)	3519 (91.4)	1.7	0.00
Broken bag	72 (5.0)	34 (2.6)	40 (3.6)	146 (3.8)	-1.4	0.0002
Broken cold chain	21 (1.5)	28 (2.2)	19 (1.7)	68 (1.8)	0.2	0.4
Return after 30 minutes	21 (1.5)	16 (1.2)	3 (0.3)	40 (1.0)	-1.2	0.0
Clotted blood	10 (0.7)	9 (0.7)	5 (0.4)	24 (0.6)	-0.3	0.4
Broken seal	8 (0.6)	9 (0.7)	2 (0.2)	19 (0.5)	-0.4	0.1
Component with RBC	3 (0.2)	4 (0.3)	0	7 (0.2)	-0.2	0.2
Expired transfusion unit	1 (0.1)	4 (0.3)	13 (1.2)	18 (0.5)	1.1	0.002
Transfusion reaction	0	5 (0.4)	5 (0.4)	10 (0.3)	0.4	0.1

Comparison of blood wastage with previous study

Figure 4 compares the blood wastage percentage recorded in the current three-year study and in the previous three-year study. Each year showed a gradual decrease in blood wastage in the current study. Year 1 of the previous study, showed a decrease in blood wastage by 15.4% (95% CI 13.0–17.7, $p \leq 0.05$), year 2 a decrease of 13.1% (95% CI 11.9–14.3, $p \leq 0.05$), year 3 a decrease of 12.3% (95% CI 11.2–13.4, $p \leq 0.05$). Overall, the current study recorded a significant decrease in blood wastage of 12.4% (95% CI 11.6–13.1, $p \leq 0.005$).

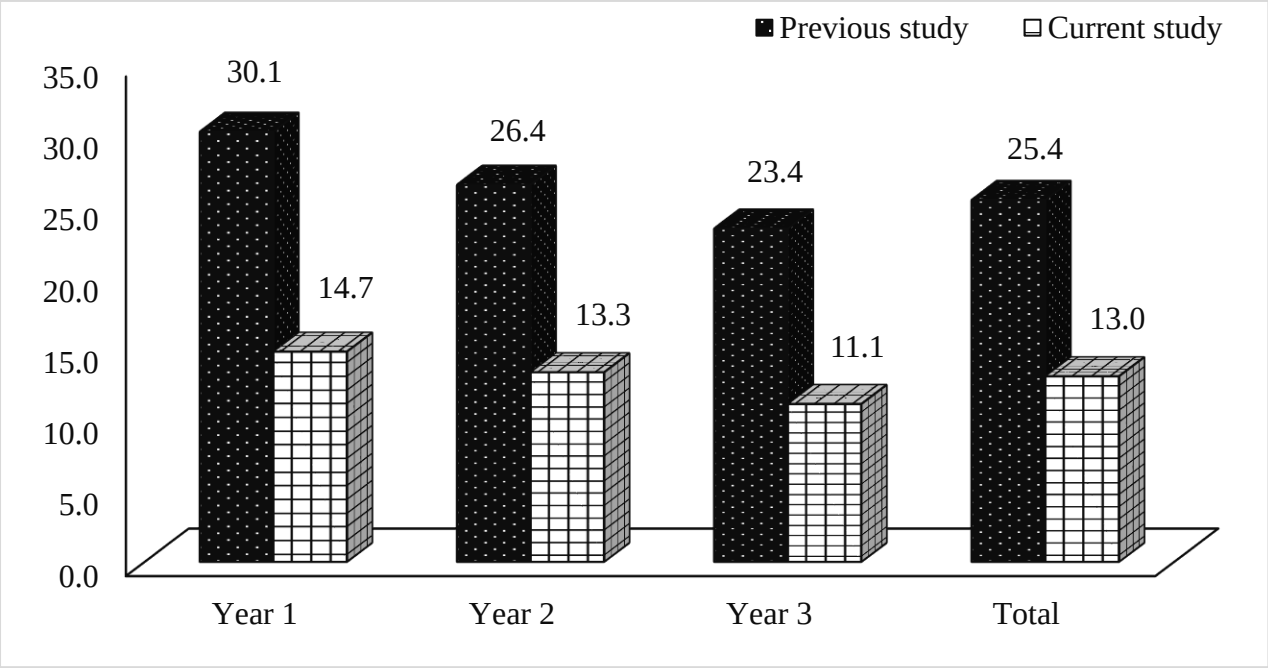

Figure 4: Percentage of blood wastage recorded in the current study (2016–2018) and in the previous study (2012–2014)

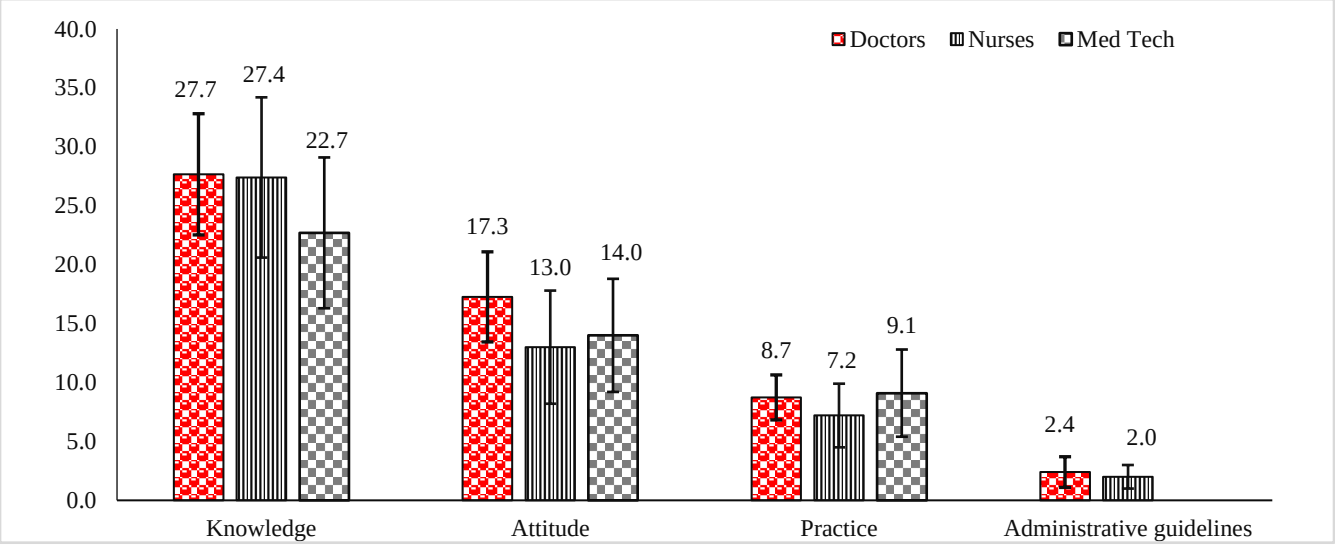

Figure 5: Mean ± SD of KAP and AG of health personnel regarding blood transfusion

(SD = standard deviations; KAP = knowledge, attitude and practices; AG = administrative guidelines)

KAP scores of medical personnel

The study included 30 doctors, 31 nurses and 12 medical technologists. The mean (± SD) age of doctors, nurses and medical technologists was 28.9 ± 5.1, 28.5 ± 4.9 and 26.3 ± 4.0, respectively, and the average number of years of experience was 2.9, 4.9 and 4.0, respectively. Only the group of doctors included male (30%) and female (70%) participants, while all nurses and medical technologists were female. The mean ± SD (95% CI) scores of KAP-AG among doctors, nurses and medical technologists were 27.7 ± 5.1 (95% CI 25.5–29.9), 17.3 ± 3.8 (95% CI 15.7–18.9), 8.7 ± 1.9 (95% CI 7.7–9.7), 2.4 ± 1.3 (95% CI 2.0–2.8); 27.4 ± 6.8 (95% CI 25.2–29.5), 13.0 ± 4.8 (95% CI 11.4–14.5), 7.2 ± 2.7 (95% CI 6.3–8.2), 2.0 ± 1.0 (95% 1.6–2.5); 22.7 ± 6.8 (95% CI 19.2–26.2), 13.0 ± 4.8 (95% CI 11.5–16.5), 9.1 ± 3.7 (95% CI 7.6–10.6) (Figure 5).

A significant difference was observed among health professionals in regard to knowledge ($F = 3.2$, $p < 0.05$), attitude ($F = 7.6$, $p < 0.001$) and practices ($F = 3.5$, $p < 0.05$); however, no significant difference was observed in regard to administrative guidelines ($t = 1.3$, $p > 0.05$). No significant difference was observed between the genders in terms of knowledge ($t = -0.5$, $p > 0.05$).

Discussion

This study aimed to investigate the pattern of usage and wastage of blood products before and after simple interventions. Likewise, this study aimed to assess the KAP of the health personnel regarding blood transfusion. This study was a follow-up study of the study on blood usage and wastage done in a public hospital in Guyana in 2012–2014 (9). The previous study indicated a wastage of 25% of blood units (9). To prevent such wastage, several initiatives were introduced in the public hospital under the supervision of the laboratory director, keeping on par with the findings of the previous study. Some of the initiatives included increased awareness among hospital staff, encouraging them to maintain the temperature of blood units and to return them before expiry if not used. Further, to control expiry of blood products, component identification modalities were included in an electronic registry in order to accurately review and monitor the release of blood units according to the expiry date. A similar study done by Collins et al. demonstrated that relatively inexpensive interventions can have a prompt and dramatic impact on reducing blood wastage with regard to both cost and resource savings (14).

The present follow-up study showed an increase in blood and blood products collection when compared to the previous study done in the same setting (9). This could be assumed to be the result of meeting the demands of the referral hospital and improved management. Similar to the previous study, the current study also showed a higher collection of PRBC, followed by FFP and PC (9, 15). However, the previous study showed a 25% blood unit wastage, which was greatly reduced to 12.3% blood unit wastage in the present study. The most common causes of blood wastage were expired unit, broken bag, broken cold chain, returning after 30 minutes.

Similarly, wastage of blood units has also been reported in other studies. In developing countries like Iran, blood product wastage of about 9.8% in the Qazvin Province and of 12% in Ahwaz hospitals was reported. Blood wastage in developed countries was also reported; 4.4% of issued RBC was wasted according to a study conducted in the United States (US), while a similar study in the UK reported 2.1% to 4.8% blood wastage (13, 16). Expiry of blood products was the main cause of wastage in our both current study and in the previous study (9). Expiry of blood products also remains the main reason for blood wastage in other studies (3).

Different intervention strategies have been introduced in various hospitals to reduce blood wastage. Educational interventions and simple review and documentation of blood products were introduced after the previous study. This study also included a KAP study to understand the basic knowledge, attitude and practices of the health personnel. Nurses had good knowledge, attitude and administrative skills concerning blood transfusion, while doctors had good practice scores. The KAP study results were not satisfactory and suggested a lack of knowledge and training among doctors, nurses and laboratory technologists regarding transfusion medicine. The results indicated a big gap in the health personnel's knowledge about transfusion medicine. Interns indicated that there was a lack of dedicated teaching or training in the undergraduate curriculum. However, an effective training program for all healthcare personnel would be an essential step in creating good knowledge and effective transfusion practice in any hospital setting. Every hospital should work on formulating a hospital transfusion policy and establishing a transfusion committee. This committee should be responsible for providing training to health personnel, implementing policies on blood usage and management of transfusion reactions. Such policies hope to reduce unnecessary wastage of blood, as well as provide good knowledge and awareness regarding blood transfusion.

Conclusion

This study showed a decrease in blood wastage from 25% to 13.0% since the introduction of interventions in the public hospital laboratory, Guyana. This study therefore represents a model for reducing blood wastage in hospitals worldwide. Prevention of blood wastage in hospitals can be achieved with simple, easy and inexpensive interventions, as well as with an efficient inventory system. Awareness and training of all healthcare personnel should be encouraged for the purpose of effective blood usage and management in hospitals.

Acknowledgement. None.

Disclosure

Funding. No specific funding was received for this study.

Competing interests. None to declare

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[1] **Author contribution.** RK, AA, RB, SA, CC, PR contributed equally to this paper. RK did the statistical analysis and the first draft of the paper. RK and AA contributed to the conception of the study. All of the authors read and approved the final manuscript.