Med Glas (Zenica) 2025;22(2)
https://doi.org/10.17392/1936-22-02

Med Glas (Zenica)

ORIGINAL ARTICLE

Fluoropyrimidine adjuvant chemotherapy leads to long-term impact on coronary arteries, blood cell profile and iron in colorectal cancer survivors

[1]Ivana Iveljić, [2]Lejla Alidžanović Nurkanović, [3]Alisa Krdžalić, [4]Dunja Aksentijevic

[1]Clinic for Invasive Cardiology, [2]Clinic for Oncology and Radiotherapy, [3]Clinic for Cardiovascular Surgery; University Clinical Centre Tuzla, Bosnia and Herzegovina, [4]William Harvey Research Institute, Barts and the London Faculty of Medicine and Dentistry, Queen Mary University of London, London, UK

ABSTRACT

Aim To assess whether colorectal carcinoma (CRC) survivors 5 years post-fluoropyrimidine (5-fluorouracil and capecitabine) chemotherapy (ChemT) has increased presence of subclinical coronary artery disease (CAD), lower iron and altered blood cell composition.

Methods This prospective, 2 year, single-centre study used invasive coronary angiography to detect the presence of CAD among ChemT (N=45) and control group patients (age, gender-matched, cancer-naïve (N=45). Full blood count and iron levels were compared between two groups.

Results Coronary angiography in 90 patients (mean age 65±7 years; 60% male) identified significantly higher presence of CAD in CRC ChemT patient group compared to control: 80% vs. 55 % (p=0.013). CRC ChemT patients had lower red blood cell count (4.45± 0.56 vs. 4.68± 0.50 x10^9/L; p=0.044), platelet count (214.18±50.99 vs. 251.00 ±156.40 x10^9/L; p=0.002) and white blood cell count (5.50 ±1.62 vs. 7.67±1.72 x10^9/L; p=0.000)**.** Mean corpuscular haemoglobin concentration was higher in CRC ChemT patients (342.11 g/L ±15.74 vs. 336.42 g/L ±10.29: p=0.046), and iron deficiency was more prevalent (ChemT20.40 µmol/L ±3.891vs. control 23.37 µmol/L ±4.10: p=0.001).

Conclusion Our study shows that among CRC survivors who underwent 5-FU and capecitabine therapy there is a significantly higher prevalence of CAD accompanied by long-term impairment in blood erythropoiesis.

Keywords: coronary artery disease, coronary angiography, erythropoiesis

INTRODUCTION

Colorectal carcinoma (CRC) accounts for 10% of all tumours. CRC is the third most common cancer-related cause of death claiming over 600,000 lives each year, with 5-year survival ranging from 30-60% in women, and 28-57% in men (1).

The typical course of treatment for non-metastatic CRC is surgical resection of the tumour aiding histopathological staging (2). For high-risk stage II and III CRC, treatment consists of adjuvant chemotherapy (ChemT), with the current standard of care consisting of a combination of fluoropyrimidine and oxaliplatin (3). The most commonly used fluoropyrimidine ChemT is a combination of 5-fluorouracile (5-FU) given intravenously, and capecitabine, which is an oral pro-drug that is enzymatically converted to fluorouracil in the tumour (4). However, this treatment has limited efficacy as within 5 years post-diagnosis CRC remains the most common cause of death in these patients (5). For the patients that survive the 5 year-window post-initial diagnosis and treatment, cardiovascular disease (CVD) is the most common cause of death (6, 7). The 10-year cumulative cardiovascular morbidity is significantly higher in CRC patients than in the general population, with the cumulative prevalence of CVD being 71% in the CRC population versus 22% in non- CRC population (8, 9). Recent studies have found that patients with CRC are at higher risk of developing new-onset morbidities related to CVD, with a 10-year cumulative incidence rate of 57% (10).

Prevalence of symptomatic cardiovascular toxicity during ChemT treatment ranges from 1% to 4 % presenting as atypical chest pain, ECG changes, coronary artery vasospasms, direct cardiotoxicity, and even acute myocardial infarction (11). Pre-clinical studies showed that possible acute cardiotoxicity mechanisms include cellular damage and ischemia (12) . However, CVD pathogenesis of the CRC survivors still remains unknown (13).

Poor cardiovascular outcome may result from long-term ChemT impact on blood cell profile and impaired erythropoiesis. About 60% of patients with CAD were found to have iron deficiency (14). Reduced red blood cell (RBC) count and iron deficiency are linked to higher mortality rates from coronary artery disease (CAD) (15). Increased haemoglobin concentration in RBCs, indicated by higher mean corpuscular haemoglobin concentration (MCHC), can lead to high blood viscosity

***Corresponding author:** Dunja Aksentijević
William Harvey Research Institute, Barts Faculty of Medicine and Dentistry, Queen Mary University of London
Chartherhouse Square, London EC1M 6BQ, United Kingdom
Phone: +44 (0) 20 7882 5555;
E-mail: d.aksentijevic@qmul.ac.uk
Ivana Iveljić ORCID ID: https://orcid.org/ 0000-0001-8927-5390

| Submitted: 04. Dec. 2024. Revised: 03 Mar. 2025. Accepted: 04 Mar. 2025.

and is linked to enhanced mortality from CVD (16, 17) . *In vitro* studies as well as clinical work have shown that acute treatment with 5-FU decreases blood viscosity. Furthermore, it was shown that increasing 5-FU concentrations, regardless of sheer rate, affects blood rheology (18).

Cardiovascular effects of 5-Fluorouracile (5-FU) and capecitabine adjuvant colorectal cancer chemotherapy vary from symptomatic electrocardiographic abnormalities to myocardial infarction. These changes are acute and present mostly during the ChemT administration (19). However, the long-term effect of fluoropyrimidine ChemT on blood composition and the subsequent impact on CVD remains to be elucidated.

The aim of this study was to assess CRC survivors 5 years post-adjuvant ChemT with 5-FU and capecitabine to identify whether they develop CAD and impaired erythropoiesis.

PATIENTS AND METHODS

Patients and study design

This prospective 2-year single-centre study was conducted at the University Clinical Centre in Tuzla, at the Clinic for Invasive Cardiology and Clinic for Oncology and Radiotherapy (Figure 1).

Records of the 142 patients who received 5-fluorouracile (5-FU) and capecitabine adjuvant colorectal cancer chemotherapy between 1 January 2015 and 1 January 1 2018 were screened for inclusion in the study. Eligible patients (ChemT group N=45) were selected using the following inclusion criteria: (1) diagnosed with CRC as the primary and only tumour; (2) diagnosed between 2015 and 2018 (3) patients with CRC that received treatment with adjuvant ChemT (5-FU and capecitabine) for a minimum 5 years and maximum 7 years before the study started (7) .

The control group (N=45) was selected from 1245 patients scheduled for coronary angiography between 1 August 2021 and 1 May 2024. The eligible patients for the control group were selected using the following inclusion criteria: (1) cancer naïve, (2) age-matched to the CRC group (3) gender-matched to the CRC group (4) selected for elective coronary angiography (7).

Exclusion criteria included: patients who did not give consent for the study, CRC patients with initially diagnosed metastatic cancer, those who had cancer recurrence within the time after ChemT until beginning of the study, CRC patients who had additional ChemT beside 5-FU and capecitabine, patients with acute coronary syndromes or those with previously diagnosed with CAD (Figure 1).

The study protocol was approved by the Ethics Committee of University Clinical Centre Tuzla (Ref. 02-09/2-40/24) and all methods were performed in accordance with their guidelines and regulations.

Methods

During hospitalization, after administration of heparin bolus (50 U/Kg) and 200 µcg of nitroglycerin, invasive coronary angiography was performed with the adoption of a standard right radial approach (20). After puncturing the anterior wall of the artery, a standard 5F-guiding catheter was introduced via an introducer sheet, over diagnostic 0.035inch guidewire and advanced into the ascending aorta. After gently retracting the wire, catheter was advanced first into the left followed by the right coronary cusp. Coaxial engagement of the left and right coronary ostia was made. Conventional coronary angiography cine images were acquired at 15 frames per second. Two orthogonal views were made of each vessel segment with no overlaps and sufficient contrast fillings. Presence and severity of coronary lesions was routinely established by visual screening by the operator. After the procedure, all patients were admitted to the Department of Interventional Cardiology.

Antecubital venous blood samples were collected for the analysis upon admission to the Clinic for Invasive Cardiology: red blood cells (3.86-5.08 x10^9/L), haemoglobin (119-157 g/L), haematocrit (0.356-0.470 L/L), MCV (83.0-97.2 fL), MCH (27.4-33.9 pg), MCHC (320-345g/L), white blood cells (3.4-9.7x10^9/L), platelets (158-424 x10^9/L), neutrophils (2.06-6.49 x10^9/L) and

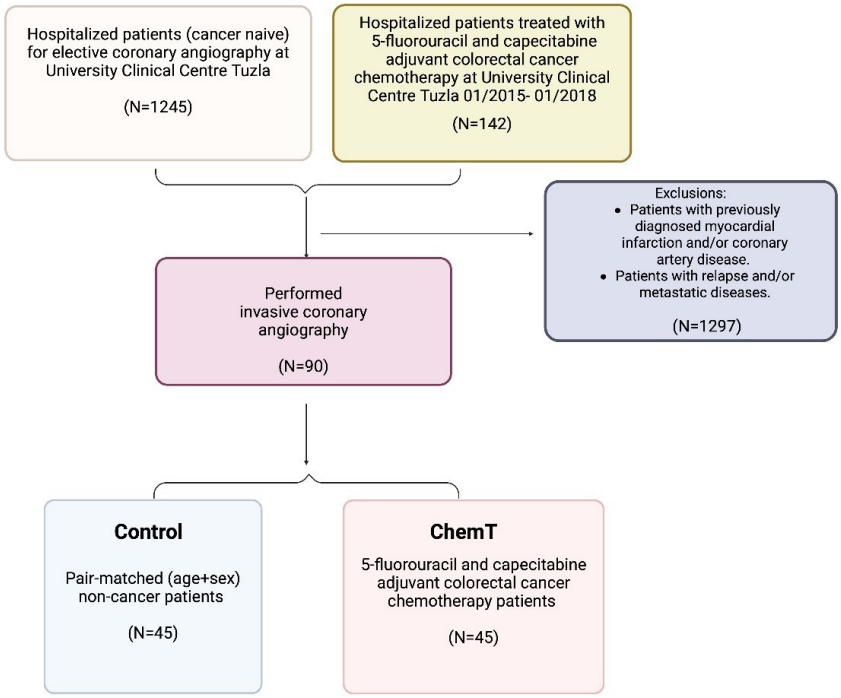

Figure 1. Summary of study design (Figure created with Biorender.com)

iron (8-30 μmol/L). All the blood samples were sent for analysis to the Polyclinic for Laboratory Diagnostic, University Clinical Centre Tuzla. The full blood count was determined by Sysmex XN 1000 laser flow cytometry-based haematological analyser (Sysmex Corporation, Cobe, Hyogo, Japan). The concentration of plasma iron was determined by the iron ferrozine colorimetric assay using Advia Centaur XPT biochemical-immunochemical analyser (Siemens, Dublin, Ireland).

Statistical analyses

Data are presented as mean±standard deviation (SD) unless otherwise stated. Normality of data distribution was examined using Shapiro-Wilk's normality test. Comparison between two groups was performed by Student's t-test (Gaussian data distribution). Qualitative variables were compared with Parson's $\chi 2$ test. Differences were considered significant when $p<0.05$.

RESULTS

Among 142 patients who were diagnosed with CRC between 2015-2018 and received adjuvant ChemT (5-FU and capecitabine), 45 patients (31.7%) fulfilled the inclusion criteria: mean age was 65±7 years; 27 (60%) were males (Figure 1). Among 1245 non-cancer patients hospitalized for elective invasive coronarography over the period 2021-2024, 45 (3.61%) patients met the eligibility criteria: mean age 65±7 years; 27 (60%) were males (Figure 1).

Both patient groups underwent coronary angiography to detect the presence of CAD. The prevalence of CAD was significantly higher in the CRC ChemT group, 36 (80%) compared to only 25 (55%) patients of control group ($p<0.01$).

Results of full blood count analysis showed significantly lower red blood count (RBC) count in ChemT group: 4.45 ±0.560 $x10^9$/L vs. control group 4.68±0.500 $x10^9$/L ($p=0.044$). There was a trend for lower mean corpuscular volume (MCV) in ChemT group: 92.14±4.336 fL vs. 90.40±4.136 fL) ($p=0.054$) (Table 1).

Table 1. Full blood count and iron levels in patients receiving ChemT therapy for colorectal carcinoma (CRC)

Variable (reference value)	Control (N=45)	ChemT (N=45)	p
	Mean±SD		
Red blood cells (3.86-5.08 x109/L)	4.68 ± 0.50	4.45 ± 0.56*	0.040
Haemoglobin (119-157 g/L)	139.87 ± 14.01	138.71 ± 12.09	
Haematocrit (0.356-0.470 L/L)	0.41 ± 0.046	0.40 ± 0.039	
MCV (83.0-97.2 fL)	90.40 ± 4.13	92.14 ± 4.33	
MCH (27.4-33.9 pg)	30.89 ± 3.66	32.02 ± 1.92	
MCHC (320-345g/L)	336.42 ± 10.29	342.11 ± 15.74*	0.046
White blood cells (3.4-9.7x109/L)	7.67 ± 1.72	5.50 ± 1.62*	0.0001
Platelets (158-424 x109/L)	251.00 ± 156.40	214.18 ± 50.99*	0.002
Neutrophils (2.06-6.49 x109/L	3.20 ± 0.77	3.58 ± 1.52	
Iron (8-30 μmol/L)	23.37 ± 4.10	20.40 ± 3.89*	0.001

*p<0.05 vs. control
MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration

Moreover, ChemT patients had significantly lower platelet count, 214.18±50.99 vs. 251.00±156.40 $x10^9$/L) ($p=0.002$) and lower white blood cell count, 5.50±1.62 $x10^9$/L vs. 7.67±1.72 $x10^9$/L ($p=0.0001$). Cancer survivors had higher mean corpuscular haemoglobin concentration (MCHC) (342.11±15.74 g/L vs. 336.42±10.29 g/L ($p=0.046$). Lower iron concentration was detected in ChemT group (20.40±3.89 μmol/L vs. 23.37± 4.10 μmol/L ($p=0.001$).

DISCUSSION

Patients diagnosed with common cancers have unexpectedly higher prevalence of CVD than the general population, and the concurrent incidence of both diseases relates to risk factors, side effects of cancer therapy, and direct cardiovascular effects of the cancer itself (21). Here, we investigated long-term impact of ChemT consisting of 5-FU and capecitabine in colorectal cancer survivors. To our knowledge, this is the first clinical study to use coronary angiography, a gold standard for diagnosing CAD, to examine this patient population. Furthermore, we examined the long-term impact of the therapy on full blood count parameters including iron. Among CRC survivors who underwent 5-FU and capecitabine therapy, a significantly higher prevalence of CAD accompanied by long-term impairment in blood erythropoiesis was found in our study.

Previous studies have shown higher CVD mortality in CRC patients in comparison to cancer-naïve individuals (6, 22). Reportedly, no single mechanism responsible for cardiotoxicity from these drugs (5-FU and capecitabine) has been reported as underlying mechanisms are multifactorial (23). Preclinical work on rats has demonstrated that 5-FU can cause short-term effect on the heart: haemorrhagic infarction, proximal spasm of the coronary arteries and concentric fibrous thickening of the intima of the small arteries (24). Histopathological studies in rabbits have shown arterial endothelial damage after administration of 5-FU (12).

In vitro studies on cultured myocardial and endothelial cells showed that toxic effects of 5-FU may not be lethal, but may reflect reversible interference with cellular function (25). Our results of higher prevalence of CAD in ChemT patients versus the control group could explain the enhanced CVD mortality associated with post-adjuvant therapy with 5-FU capecitabine (26).

Some of the pathophysiological mechanisms of cardiotoxicity of 5-FU could be due to its influence on blood rheology. *In vitro* studies have shown that 5-FU interacts with the cell membrane, induces echinocytosis and vesiculation, and affects blood rheology, which may contribute to CVD (27). In our study, higher MCHC in ChemT CRC patients was found. Higher MCHC correlates with increased rigidity of RBCs and can negatively impact microcirculatory blood flow. It can contribute to higher blood viscosity, which may contribute to a lack of myocardial perfusion, ischemia and bigger infarct size in acute myocardial infarction (AMI) (28). Higher MCHC can be a prediction factor for poorer prognosis in several cardiovascular conditions like acute myocardial infarction and congestive heart failure (16). Our results showed significantly lower red blood cell count in ChemT group, which can also contribute to increased cardiovascular mortality (15).

We have also found lower platelet and white blood cell count in ChemtT CRC patients. Low platelet counts in patients with AMI have been associated with a higher incidence of major adverse cardiovascular events and shorter survival (29). Further-

more, low platelet count correlates with increased all-cause mortality (30). In previous studies, lymphopenia was associated with increased infection-related deaths (31).

Patients treated with 5-Fu and capecitabine ChemT had significantly lower iron levels. Previous studies have shown that iron deficiency prevalence ranges between 29-56% in patients admitted for acute coronary syndrome. Furthermore, iron deficiency has been associated with a 50% increased risk of non-fatal AMI and CVD death after extensive adjustments including anaemia (32).

In conclusion, the changes observed in blood composition parameters due to long-term effects of 5-FU and capecitabine could be the cause of higher cardiovascular morbidity and mortality after 5 years or long-term, in CRC ChemT patients. Significantly higher presence of CAD could be caused by the adjuvant ChemT effect on arterial endothelium, resulting in long-term obstructive and non-obstructive CAD, AMI, heart failure and death.

ACKNOWLEDGEMENTS

We would like to thank Miss Fenn Cullen and Dr Megan Young for their assistance in proof-reading the manuscript.

FUNDING

DA acknowledges Wellcome Trust Career Re-Entry Fellowship (221604/Z/20/Z) and Barts Charity Grant G-002145.

TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

REFERENCES

1. Argiles G, Tabernero J, Labianca R, Hochhauser D, Salazar R, Iveson T, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(10):1291-305.
2. Nors J, Iversen LH, Erichsen R, Gotschalck KA, Andersen CL. Incidence of Recurrence and Time to Recurrence in Stage I to III Colorectal Cancer: A Nationwide Danish Cohort Study. JAMA Oncol. 2024;10(1):54-62.
3. Gravalos C, Garcia-Escobar I, Garcia-Alfonso P, Cassinello J, Malon D, Carrato A. Adjuvant chemotherapy for stages II, III and IV of colon cancer. Clin Transl Oncol. 2009;11(8):526-33.
4. Wong CK, Ho I, Choo A, Lau R, Ma TF, Chiu ACH, et al. Cardiovascular safety of 5-fluorouracil and capecitabine in colorectal cancer patients: real-world evidence. Cardio-oncology. 2025;11(1):3.
5. Twelves C, Scheithauer W, McKendrick J, Seitz JF, Van Hazel G, Wong A, et al. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. Ann Oncol. 2012;23(5):1190-7.
6. Feng Y, Jin H, Guo K, Wasan HS, Ruan S, Chen C. Causes of Death After Colorectal Cancer Diagnosis: A Population-Based Study. Front Oncol. 2021;11:647179.
7. Zhang S, Wang Y, Zhang P, Ai L, T. L. Cardiovascular Outcomes in the Patients With Colorectal Cancer: A Multi-Registry-Based Cohort Study of 197,699 Cases in the Real World. Front Cardiovas Med. 2022;16(9):851833.
8. Brown JC, Caan BJ, Prado CM, Weltzien E, Xiao J, Cespedes Feliciano EM, et al. Body Composition and Cardiovascular Events in Patients With Colorectal Cancer: A Population-Based Retrospective Cohort Study. JAMA Oncol. 2019;5(7):967-72.
9. Sorrentino MF, Kim J, Foderaro AE, Truesdell AG. 5-fluorouracil induced cardiotoxicity: review of the literature. Cardiol J. 2012;19(5):453-8.
10. Lee SF, Yip PL, Vellayappan BA, Chee CE, Wong LC, Wan EY, et al. Incident Cardiovascular Diseases Among Survivors of High-Risk Stage II-III Colorectal Cancer: A Cluster-Wide Cohort Study. J Natl Compr Canc Netw. 2022;20(10):1125-33 e10.
11. Yuan C, Parekh H, Allegra C, George TJ, Starr JS. 5-FU induced cardiotoxicity: case series and review of the literature. Cardiooncology. 2019;5:13.
12. Tsibiribi P, Bui-Xuan C, Bui-Xuan B, Lombard-Bohas C, Duperret S, Belkhiria M, et al. Cardiac lesions induced by 5-fluorouracil in the rabbit. Hum Exp Toxicol. 2006;25(6):305-9.
13. Shiga T, Hiraide M. Cardiotoxicities of 5-Fluorouracil and Other Fluoropyrimidines. Curr Treat Options Oncol. 2020;21(4):27.
14. Savarese G, von Haehling S, Butler J, Cleland JGF, Ponikowski P, Anker SD. Iron deficiency and cardiovascular disease. Eur Heart J. 2023;44(1):14-27.
15. Liu Z, Zhu Y, Zhang L, Wu M, Huang H, Peng K, et al. Red blood cell count and risk of adverse outcomes in patients with mildly reduced left ventricular ejection fraction. Clin Cardiol. 2023;46(10):1276-84.
16. Zhang Z, Gao S, Dong M, Luo J, Xu C, Wen W, et al. Relationship between Red Blood Cell Indices (MCV, MCH, and MCHC) and Major Adverse Cardiovascular Events in Anemic and Nonanemic Patients with Acute Coronary Syndrome. Dis Markers. 2022;2022:2193343.
17. Li D, Zhang Q, Ruan Z, Zhang Y, Liu X, Zhang G, et al. The relationship between mean corpuscular hemoglobin concentration and mortality in hypertensive individuals: A population-based cohort study. PLoS One. 2024;19(5):e0301903.
18. Baerlocher GM, Beer JH, Owen GR, Meiselman HJ, Reinhart WH. The anti-neoplastic drug 5-fluorouracil produces echinocytosis and affects blood rheology. Br J Haematol. 1997;99(2):426-32.
19. Chong JH, Ghosh AK. Coronary Artery Vasospasm Induced by 5-fluorouracil: Proposed Mechanisms, Existing Management Options and Future Directions. Interv Cardiol. 2019;14(2):89-94.
20. Bajraktari G, Rexhaj Z, Elezi S, Zhubi-Bakija F, Bajraktari A, Bytyci I, et al. Radial Access for Coronary Angiography Carries Fewer Complications Compared with Femoral Access: A Meta-Analysis of Randomized Controlled Trials. J Clin Med. 2021;10(10).

21. Mrotzek SM, Lena A, Hadzibegovic S, Ludwig R, Al-Rashid F, Mahabadi AA, et al. Assessment of coronary artery disease during hospitalization for cancer treatment. Clin Res Cardiol. 2021;110(2):200-10.
22. Zhang S, Wang Y, Zhang P, Ai L, Liu T. Cardiovascular Outcomes in the Patients With Colorectal Cancer: A Multi-Registry-Based Cohort Study of 197,699 Cases in the Real World. Front Cardiovasc Med. 2022;9:851833.
23. Kanduri J, More LA, Godishala A, Asnani A. Fluoropyrimidine-Associated Cardiotoxicity. Cardiol Clin. 2019;37(4):399-405.
24. Kumar S, Gupta RK, Samal N. 5-fluorouracil induced cardiotoxicity in albino rats. Mater Med Pol. 1995;27(2):63-6.
25. Kinhult S, Albertsson M, Eskilsson J, Cwikiel M. Effects of probucol on endothelial damage by 5-fluorouracil. Acta Oncol. 2003;42(4):304-8.
26. Dyhl-Polk A, Vaage-Nilsen M, Schou M, Vistisen KK, Lund CM, Kumler T, et al. Incidence and risk markers of 5-fluorouracil and capecitabine cardiotoxicity in patients with colorectal cancer. Acta Oncol. 2020;59(4):475-83.
27. von Tempelhoff GF, Schelkunov O, Demirhan A, Tsikouras P, Rath W, Velten E, et al. Correlation between blood rheological properties and red blood cell indices(MCH, MCV, MCHC) in healthy women. Clin Hemorheol Microcirc. 2016;62(1):45-54.
28. Choi D, Waksman O, Shaik A, Mar P, Chen Q, Cho DJ, et al. Association of Blood Viscosity With Mortality Among Patients Hospitalized With COVID-19. J Am Coll Cardiol. 2022;80(4):316-28.
29. Gresele P, Guglielmini G, Del Pinto M, Calabro P, Pignatelli P, Patti G, et al. Low platelet count at admission has an adverse impact on outcome in patients with acute coronary syndromes: from the START Antiplatelet registry. Sci Rep. 2024;14(1):14516.
30. Bonaccio M, Di Castelnuovo A, Costanzo S, De Curtis A, Donati MB, Cerletti C, et al. Age-sex-specific ranges of platelet count and all-cause mortality: prospective findings from the MOLI-SANI study. Blood. 2016;127(12):1614-6.
31. Warny M, Helby J, Nordestgaard BG, Birgens H, Bojesen SE. Lymphopenia and risk of infection and infection-related death in 98,344 individuals from a prospective Danish population-based study. PLoS Med. 2018;15(11):e1002685.
32. Reinhold J, Papadopoulou C, Baral R, Vassiliou VS. Iron deficiency for prognosis in acute coronary syndrome - A systematic review and meta-analysis. Int J Cardiol. 2021;328:46-54.