Sys Rev Pharm 2020;11(11):1115-1120
A multifaceted review journal in the field of pharmacy

Acute Coronary Syndrome in Patients with Oncological Diseases

N.A. Shanazarov[1], N.K. Seidalin*[1], A.F. Khalirahmanov[2,3], G.D. Gatiyatullina[2], S.V. Zinchenko[3], K. F. Idrisova[3].

[1]Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan 1 E-495 b.2, Nur-Sultan, Kazakhstan
[2]Health care unit Federal State Budgetary Educational Institution of Higher Education «Volga Federal University», Kazan city, Kazakhstan
[3]Federal State Autonomous Educational Institution of Higher Education «Kazan (Volga) Federal University», Kazan city, Kazakhstan

Corresponding Author: N. K. Seidalin **E-mail**: nkseidalin@mail.ru

ABSTRACT
Cardiovascular diseases (CVD) and malignant neoplasms (MN) are the main reasons of 70 % of death because of diseases in the developed countries. Success in treating MN has led to increased life expectancy of patients and accordingly increased the number of comorbide patients. It also should be noted that a great number of patients with malignant neoplasms or oncopathology have cardiovascular disease in their anamnesis, and as it was discovered, this disease is the main reason of death in patients recovered from oncological disease. The rate of the risks for the patient according to characteristics of the diseases and treatment, and close connection with oncologists are vitally necessary to determine the optimal strategies of treatment in this population. According to the above mentioned, the actuality of treatment cardiovascular pathology and prevention cardiotoxicity connected to chemotherapy of MN have become obvious.

Keywords: Acute coronary syndrome, oncology, cardiovascular diseases.

Correspondence:
N.K. Seidalin
Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan 1 E-495 b.2, Nur-Sultan, Kazakhstan
E-mail: nkseidalin@mail.ru

INTRODUCTION

Cardiovascular diseases (CVD) and malignant neoplasms (MN) are the main reasons of 70 % of death because of diseases in the developed countries [1]. Success in treating MN has led to increased life expectancy of patients and accordingly increased the number of comorbide patients. [2]. It also should be noted that a great number of patients with malignant neoplasms or oncopathology have cardiovascular disease in their anamnesis, and as it was discovered, this disease is the main reason of death in patients recovered from oncological disease. [3]. The rate of the risks for the patient according to characteristics of the diseases and treatment, and close connection with oncologists are vitally necessary to determine the optimal strategies of treatment in this population. According to the above mentioned, the actuality of treatment cardiovascular pathology and prevention cardiotoxicity connected to chemotherapy of MN have become obvious. [2].

Different stages of malignant neoplasms can be revealed in 15 % of patients with acute coronary syndrome (ACS) that is a serious therapeutic problem. [4]. According to the data, the frequency of ACS in patients with the firstly diagnosed cancer is especially high during the first 6 months, since the moment of the diagnosing, and also at the last stages of the disease.[5] In spite of high prevalence of MN, these patients were excluded from all the controlled examinations, which were used to determine the best tactics for treating ACS.[6] Besides, oncological diseases are absent in all the modern scales of the risk stratification, used to determine the risk of ischemic disease and bleeding, in spite of the fact that occurrence of MN has much more serious consequences than accompanied diseases, included into these rates. Taking into account saying above, in the modern literature there is restricted information about clinical outcomes of the hospital treatment of acute myocardial infarction (AMI) in patients with MN, as the researches in the modern literature don't make any difference between current and previous oncological disease, type of onco process and occurrence of metastasises [7,8].

When ACS occurs in patients with MN a number of problems arise, such as accepting of therapeutic decision (including usage of antiaggregants in case of thrombocytopenia), indications for invasive revascularization, bleedings, and necessity of cancer treating. It should be noted that specific risk factor of developing ACS is thrombocytopenia (TP) that is a frequent complication of chemotherapy and radiation therapy. Level of cardiotoxicity of chemotherapeutic medicines is still unknown properly. The main reasons for developing ACS in patients with MN are developing of acute endothelial dysfunction, spasm of coronary arteries [9], direct affection of cardiomyocytes and also hypercoagulation [10]. Severity of TP depends on the duration of held chemotherapy, type and dose of the used medicine [11, 12]. Such processes as DIC – syndrome (disseminated intravascular coagulation) and thrombotic microangiopathy complicate severity of TP. [11]. Risk of bleeding complication in oncological patients increases when increasing the rate of TP (decreasing of number of thrombocytes in blood). To understand the concept of vascular thrombosis in cancer patients for arterial and venous thrombosis, it is important to keep in mind the Virchow triad, blood clotting system, and fibrinolysis [13]. Cancer cells express tissue factor, and subsequently attract factors VII / VIIa to the cell surface, which leads to a powerful activation of the coagulation cascade, thrombin production, and platelet activation [13], which are mainly mediated by stimulation of their surface receptors (for example, PAR-1 and PAR-4 receptors, P2Y12 receptor, and thromboxane receptor) in response to various ligands.

Tumor cells can produce these ligands, including ADP and thromboxane A2, in addition to thrombin and tissue factor. While in the bloodstream, a circulating tumor cell (CTC) interacts with other cells, such as platelets, using tumor-induced platelet aggregation (TCIPA). This type of platelet aggregation has recently been increasingly recognized and

considered a "loop of platelets and cancer", which is explained by the bidirectional (amplifying) connection between platelets and tumor cells [14]

Activated platelets support tumor growth, metastasis, and angiogenesis [15]. Angiogenesis is associated with vascular endothelial growth factor (VEGF). The tumor-derived VEGF-A triggers the release of von Willebrand factor from endothelial cells [16]. Thus, it is the process of hypercoagulation that is primarily influenced by the malignancy itself, while the vascular wall is the second element and is an integral part in addition to the release of von Willebrand factor, thereby contributing to platelet activation and aggregation [17]. Stasis, in turn, is determined by the initial conditions of a particular patient. The above pathogenesis is a clear indicator that CHD can be diagnosed already at the time of setting the cancer process, as it happens in about 20% of patients over 75 years of age. However, CHD can be asymptomatic and can only be detected during treatment of neoplasm [18].

In addition, current recommendations for ACS are based on studies that exclude patients with ACS due to cancer, so they are not easy to include in randomized clinical testing. And the question of why some patients with the same malignancies, undergoing the same radiation and chemotherapy with similar polypathia, develop ACS remains open.

In his systematic review and meta-analysis of Roule *et al* we evaluated the impact of malignancy on early and late mortality from all causes and because of ACS, including ST-segment elevation myocardial infarction (STEMI) and / or percutaneous coronary intervention (PCI). The results of this analysis demonstrate that patients with cancer and ACS have an increased rate of bleeding, hospital and one-year cardiac mortality. All-cause mortality, measured in hospital and one year later, was also significantly higher in cancer patients, as was all-cause mortality in cancer patients who had undergone PCI. In contrast to short-term results, long-term cardiac mortality rates did not differ significantly between the groups. The results of this study highlight three important points. First, patients suffering from oncopathology belong to the elderly, with many co-existing diseases, that is important for the prognosis of ACS, regardless of the malignant status. Second, cancer patients have higher heart mortality rates measured in the in-patient clinic and in the hospital. Third, cancer patients represent an extremely heterogeneous population, which requires an individual approach and managing in the hospital [19]. Recently, in a large Danish population cohort study they evaluated the risks of myocardial infarction, ischemic stroke (IS), venous thromboembolism (VTE), and bleeding (requiring hospital treatment) in patients with hematopoietic malignancy. The absolute 10-year risk of any thromboembolic events or bleeding was 19%, and the percentages of myocardial infarction, ischemic stroke, VTE, and bleeding were 3.3%, 3.5%, 5.2%, and 8.5%, respectively. It should be noted that the risk of thromboembolic events exceeded the risk of bleeding in all patients, with the exception of patients with acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL) or myelodysplastic syndrome (MDS).

In general, patients with hematopoietic malignancy were at increased risk of acute myocardial infarction (AMI) (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.25–1.49), ischemic stroke (RR 1.22, 95% CI 1.12–1.33) , VTE (RR 3.37, 95% CI 3.13–3.64) , and bleeding (RR 2.39, 95% CI 2.26–2.53) relative to the general population. In a Danish study, the 10-year incidence rate for thromboembolic complications in chronic lymphocytic leukemia(CLL) was 7.94% (compared to 6.07 in the comparison cohort) with an RR of 2.18 (1.80–2.63), while the corresponding values for AMI and ischemic stroke were 7.68 and 6.20% (RR of 1.31 (1.09–1.57) and 0.95 (0.78–1.15), respectively) [20].

Pathogenesis

The risk of cardiovascular disease varies depending on the type of malignancy and the therapy that the patient has undergone [21]. Despite the fact that malignancy and CVD are two different pathogenetic processes, there is a significant overlap in etiopathogenesis. Common epidemiological risk factors include well-known ones: age, smoking, diabetes, obesity, inflammation, and lipid metabolism disorders [22].

A significant contribution to the development of malignancy and CVD is made by the metabolic syndrome. Metabolic syndrome is characterized by an increase in visceral fat mass, a decrease in peripheral tissue sensitivity to insulin, hyperinsulinemia and, as a result, a violation of carbohydrate, lipid, purine metabolism and arterial hypertension [23]. The effect of metabolic syndrome on CVD is not in doubt. It is a long-established fact that each component of the metabolic syndrome is an independent risk factor for cardiovascular disease, and the combination of these factors increases the frequency and severity of CVD.

Studies of high mortality from malignancy in cases of metabolic syndrome are of greater interest [24]. In a 14-year follow-up of 33,230 men (28% with metabolic syndrome) aged 20 to 88 years without an established cancer diagnosis, it was found that patients with MS had a 56% higher incidence of malignancy. The risk of mortality was 83% higher in individuals with 3 or more components of the metabolic syndrome than in individuals who had none [25]. The risk factors and life expectancy study followed 21,311 men and 15,991 women for an average of 7 years. The results showed that metabolic syndrome significantly increased colorectal cancer mortality (RR 2.96; CI1,05-8,31) for men, RR 2.71; CI 0.59-12.50) for women, RR 2.99; CI 1.27-7.01) together [26].

As for the individual components of MS, according to some research, dyslipidemia, arterial hypertension, insulin resistance, and fatness have a certain role in the development of cancer. For example, low levels of high-density lipoprotein cholesterol (HDL) are reported to be associated with an increased incidence of lung cancer, and people with very low HDL (≤20 mg / DL) have a 6.5-fold increased risk of cancer [27]. It was found that high levels of low-density lipoprotein cholesterol are associated with the development of hematological malignancies (approximately 15 times more) [28]. The most convincing evidence for the Association of metabolic syndrome and cancer is focused on obesity and hyperinsulinemia/insulin resistance [29]. Insulin is the main anabolic hormone that stimulates cell proliferation, and it is assumed that its effect on cancer cell proliferation is associated with the stimulation of insulin-like growth factor 1(IGF-1). Growth hormone is the main stimulator of IGF-1 production in the liver, and insulin stimulates IGF-1 production in the liver by activating growth hormone receptors [30]. Hyperinsulinemia also increases the bioavailability of IGF-1 by reducing hepatic secretion of IGF-binding proteins-1 and 2. the IGF Receptor is overexpressed in breast and colon cancer, and its activation activates the p21 ras / mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol-3 kinase / AKT pathway for cell proliferation [31].

The role of proinflammatory cytokines

After the discovery of the link between TNF-α and insulin resistance, a larger number of cytokines were the focus of attention to identify similar associations, including IL-1β, IL-6, IL-8, IL-10, macrophage inflammatory protein-1, and monocyte chemoattractant protein-1. For example, TNF-α and IL-1β activate the IKKβ / NF-KB and JNK pathways in adipocytes, hepatocytes, and associated macrophages and cause insulin resistance [32]. Inflammation is connected with many types of cancer, including cancer of the stomach, pancreas, esophagus, liver, gallbladder, and colorectal cancer [33,34]. El-Omar and the others shown that the carrier of multiple proinflammatory polymorphisms of the IL-1Bo, TNF-α, and IL-10 receptor antagonist poses a greater risk, with an OR (and 95% CI) of 2.8 (1.6-5.1) for one, 5.4 (2.7). -10.6) for 2, and 27.3 (7.4–99.8) for 3 or 4 high-risk genotypes [35]. The above-mentioned cytokines also lead to cancer cachexia, thereby increasing cancer mortality [36]. In a study by Mantovani *et al*. serum levels of IL-1α, IL-6, and TNFa were significantly higher in cancer patients than in healthy people [37]. Cytokines, reactive oxygen products, and inflammatory pathways (NF-KB) have been found to cause cancer by reducing the function of tumor suppression with an increase in the cell cycle and stimulation of oncogen expression [38].

The pathological mechanisms of ACS in cancer patients differ significantly from those in the General population. They include not only rupture of the coronary artery plaque, but also increased prothrombotic status, endothelial dysfunction, and vasospasms [39]. Previous studies have observed that ACS occurs mainly in patients with advanced cancer (61% of patients had metastases) and with STEMI as the predominant type of ACS [40]. It should be noted that previous studies have shown that ACS was most common in patients with lung cancer, followed by patients with stomach cancer [41].

In recent years, the term "clonal hematopoiesis with uncertain potential" (CHIP) has been coined to describe people who acquire somatic mutations in bone marrow hematopoietic stem cells [42]. Only in a minority of patients (0.5–1% per year), these cells can lead to the generation of clones of mutated white blood cells that populate the peripheral blood and eventually develop acute leukemia. However, CHIP increases the frequency of cardiovascular events (AMI and AI) by 40% [43]. Genes associated with CHIP are DNMT3A, TET2, ASXL1, PPM1D, JAK2, TP53, SF3B1, and SRSF2, genes that are often involved in the pathogenesis of myelodysplastic syndrome and AML (acute myeloid leukemia). The results of experiments on mice suggest a direct mechanism by which the CHIP mutation can accelerate atherosclerosis [44].

Treatment

Treatment of ACS patient with cancer should be based on a thorough assessment and determination what type of ACS he has, its etiology, and the treatment regimen of the tumor. This makes it possible to apply a more individual approach to treatment and the use of interventional methods of treatment [45].

The importance of conservative therapy and interventional treatment of cancer patients with ACS was highlighted in a large retrospective analysis conducted by Guddati *et al*., which showed that even patients with metastatic disease benefit from this therapy [46]. Each patient with ACS and cancer should be considered for treatment based on approved recommendations, including not only interventional treatment, but also conservative treatment, including aspirin, if it is not contraindicated, for example, in TP. Therefore, when prescribing ASA, it is very important to monitor the level of platelets. Restoration of coronary blood flow in ACS in cancer patients is the main type of strategy. There are no specific protocols for the necessary thrombolytic therapy, but researchers Conti, *et al*. it is assumed that the restoration of blood flow can be performed even with low platelet counts, given the presence of signs of bleeding [47]. According to a study conducted at the Subcarpathian cancer center between 2012 and 2018, it was found that the use of aspirin was associated with a reduced risk of death [48]. No Association with the risk of death was observed for other drugs for the treatment of ACS, including ACEI and ARBS [49]. And it should be noted that invasive treatment and the use of aspirin in the acute phase of ACS are associated with better survival, even taking into account the progression of the tumor process [50]. Nosocomial and 30-day all-cause mortality, as well as documented bleeding-related complications, did not differ between groups of patients with and without ZNO, suggesting a comparable perioperative risk in this study [51].

Patients diagnosed with STEMI at discharge from a single-center examination between 2000 and 2006 showed a low level of catheter revascularization, amounting to only 3.3%, since non-invasive therapy is often preferable for cancer patients. The study included patients who were examined by coronary angiography during inpatient cancer treatment and compared with the control group. The severity of CHD determined by the SYNTAX scale, and the distribution for 1-, 2- , or 3-vascular diseases did not differ significantly in the presence or absence of ZNO. However, the frequency of PCI was lower in cancer patients, especially in patients diagnosed with STEMI [52]. A study was conducted to assess the Association of bleeding after discharge with newly diagnosed cancer after ACS. A single-center study included 3,644 patients with ACS who were discharged with double antiplatelet therapy, who underwent PCI, and were selected to investigate the relationship between post-discharge bleeding and the diagnosis of ZNO. During the average follow - up period of 56.2 months, bleeding was reported in 1,216 patients, and newly diagnosed cancer was reported in 227 patients. Bleeding after discharge was associated with ZNO (HR 3.43, 95% CI 2.62 to 4.50), spontaneous bleeding (HR 4.38, 95% CI 3.31 to 5.79) [53]. The BleeMACS study demonstrated that the presence of cancer in patients undergoing PCI negatively affects the prognosis and is the strongest predictor of death or recurrent heart attack and bleeding after ACS in the 1st year of follow-up. On the other hand, cancer patients who develop ACS and undergo interventional treatment benefit from such therapy and have a better cardiovascular prognosis than those who are not considered for invasive treatment [54]. The presence of a malignant neoplasm, as shown in the Dutch registry of stent thrombosis, is an independent predictor of stent thrombosis [55].

In cancer patients, previously preference was given to holometallic stents, while data in the General population clearly indicate in favor of drug-coated stents. It is interesting to note that an extensive analysis of data from a National sample of patients for hospital discharge in the United States between 2004 and 2014 showed better results in cancer patients and PCI when treated with drug-coated stents, compared to uncoated stents [56]. Another study documented significantly higher in-hospital mortality in patients with lung cancer who underwent PCI [57].

In the Duke study, the various subgroups of patients that were studied included "pre-PCI ZNO" (any pre-PCI ZNO treatment), "post-PCI ZNO" (patients who received post-PCI ZNO treatment), and "recent cancer process" (1-year pre-PCI ZNO treatment). In this database, most patients received PCI for acute coronary syndrome. The adjusted risk of long-term cardiovascular mortality did not differ significantly in patients with pre-PCI ZNO and in patients without cancer. However, the risk of death from cardiovascular diseases was significantly higher for patients with ZNO after PCI than for the control group [58]. Analysis of data from the Mayo clinic's PCI registry, which included patients with STEMI, revealed that cancer patients had higher community-acquired mortality, but the same cardiac mortality as in the control group. Even after 6.2 years of the average follow-up period, higher mortality in the cancer group was due to non-cardiac causes [59].

CONCLUSION

Patients with current or established cancer who have AMI have more comorbidities compared to patients without cancer. The presence of disorders associated with the pathogenesis of carcinogenesis and changes in the bloodstream necessitates the study and development of a special treatment regimen for cancer patients. Most of these patients are treated conservatively without PCI, and outcomes such as hospital mortality and cardiovascular disease become much higher. In addition, there are significant differences in clinical outcomes noted among different types of neoplasm. The presence of metastases is associated with worse clinical outcomes regardless of the type of cancer. Due to the complete lack of data from randomized trials, physicians are often confronted with numerous clinical and therapeutic mysteries in the treatment of cancer patients with ACS. These patients should be approached from a multidisciplinary perspective, including cardiology and oncology, positioning the current ACS in the context of the expected prognosis and adapting treatment accordingly.

The study was carried out within the framework of the scientific and technical program BR05236375 "Study of the genetic risk of diseases associated with metabolic syndrome in the Kazakh population", commissioned by the " Committee of science of the Ministry of education and science of the Republic of Kazakhstan»

REFERENCES

1. Yeh ET, Chang HM. Oncocardiology-past, present, and future: a review. //JAMA Cardiol. 2016.- 1(9):1066–1072.
2. Chang HM, Okwuosa TM, Scarabelli T, Moudgil R, Yeh ETH. Cardiovascular complications of Cancer therapy: best practices in diagnosis, prevention, and management: part 2. //J AmCollCardiol. - 2017;70(20):2552–65
3. Rassaf T, Totzeck M, Backs J, Bokemeyer C, Hallek M, Hilfiker Kleiner D *et al*. Onco-cardiology: consensus paper of the German cardiac society, the German society for pediatric cardiology and congenital heart defects and the german society for hematology and medical oncology. //Clin Res Cardiol. – 2020.
4. Ward KK, Shah NR, Saenz CC, McHale MT, Alvarez EA, Plaxe SC. Cardiovascular disease is the leading cause of death among endometrial cancer patients. //Gynecol Oncol/ - 2012; 126:176–179.
5. Banasiak W, Zymlinski R, Undas A. Optimal management of cancerpatients with acute coronary syndrome. // Pol Arch Intern Med 2018; 128:244–53.
6. Chen HY, Saczynski JS, McManus DD, *et al*. The impact of cardiac and non-cardiac comorbidities on the short-term outcomes of patients hospitalized with acute myocardial infarction: a population-based perspective. ClinEpidemiol 2013; 5:439–44.
7. Navi BB, Reiner AS, Kamel H, *et al*. Risk of arterial thromboembolism in patients with cancer. J Am Coll Cardiol 2017; 70:926–38; avi BB, Reiner AS, Kamel H, *et al*. Arterial thromboembolic events preceding the diagnosis of cancer in older people. Blood. - 2019; 133:781–9.
8. Malmborg M, Christiansen CB, Schmiegelow MD, Torp-Pedersen C, Gislason G, Schou M.Incidence of new onset cancer in patients with a myocardial infarction- a nationwide cohort study. //BMC Cardiovasc Disord. - 2018;18(1):198
9. Canale ML, Camerini A, Stroppa S, Porta RP, Caravelli P, Mariani M, Balbarini A, Ricci S. A case of acute myocardial infarction during 5-fluorouracil infusion. J Cardiovasc Med (Hagerstown). 2006 Nov;7(11):835-7. doi: 10.2459/01.JCM.0000250874.09273.9b. PMID: 17060812.
10. History of Cancer Confers Worse PCI Outcomes for Acute MI www.medscape.com/ Review article/871624 available 27.11.2016.
11. Liebman HA. Thrombocytopenia in cancer patients. Thromb Res. 2014; 133:63–9.
12. Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. Oncology (Williston Park, N.Y.). 2015 Apr;29(4):282-294.
13. Tuzovic M, Herrmann J, Iliescu C, Marmagkiolis K, Ziaeian B, Yang EH. Arterial Thrombosis in Patients with Cancer. Curr Treat Options Cardiovasc Med. 2018 Apr 7;20(5):40. doi: 10.1007/s11936-018-0635-x. PMID: 29627870.
14. Goubran, H. A., Burnouf, T., Radosevic, M., and El-Ekiaby, M. (2013). The platelet-cancer loop. Eur. J. Intern. Med. 24, 393–400. doi: 10.1016/j.ejim.2013.01.017.
15. Goubran HA, Stakiw J, Radosevic M, Burnouf T. Platelet- cancer interactions. Semin Thromb Hemost. 2014; 40:296–305.
16. Bauer AT, Suckau J, Frank K, Desch A, Goertz L, Wagner AH, Hecker M, Goerge T, Umansky L, Beckhove P, Utikal J, Gorzelanny C, Diaz-Valdes N, Umansky V, Schneider SW. von Willebrand factor fibers promote cancer-associated platelet aggregation in malignant melanoma of mice and humans. Blood. 2015 May 14;125(20):3153-63. doi: 10.1182/blood-2014-08-595686. Epub 2015 Feb 24. PMID: 25977583; PMCID: PMC4432010.
17. Quillard T, Franck G, Mawson T, Folco E, Libby P. Mechanisms of erosion of atherosclerotic plaques.Curr Opin Lipidol. 2017; 28:434–441. doi: 10.1097/MOL.0000000000000440.
18. Wang F, Gulati R, Lennon RJ, *et al*. Cancer History Portends Worse Acute and Long-term Noncardiac (but Not Cardiac) Mortality After Primary Percutaneous Coronary Intervention for Acute ST-Segment Elevation Myocardial Infarction. Mayo Clinic Proceedings. 2016 Dec;91(12):1680-1692. DOI: 10.1016/j.mayocp.2016.06.029.
19. Roule V, Verdier L, Blanchart K, Ardouin P, Lemaitre A, Bignon M, SabatierR,Alexandre J, Beygui F.System aticreviewandmeta analysisoftheprognostic impact

of cancer amog patients with acute coronary syndrome and/orpercutaneous coronary intervention. // BMC Cardiovasc Disord. - 2020; 20(1):38

20. K. Adelborg, P. Corraini, B. Darvalics, *et al*. Risk of thromboembolic and bleeding outcomes following hematological cancers: a Danish population-based cohort study // J. Thromb. Haemost. – 2016., pp. 1305-1318
21. Brown BW, Brauner C, Minnotte MC; Non cancer deaths in white adult cancer patients. //J NatlCancerInst. – 1993. - 85(12):979–987.
22. Anker MS, Ebner N, Hildebrandt B, Springer J, Sinn M, Riess H *et al* (2016) Resting heart rate is an independent predictor of death in patients with colorectal, pancreatic, and non-small cell lung cancer: results of a prospective cardiovascular long-term study. //Eur J Heart Fail 18(12):1524–1534.
23. Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MM. Influence of tumour stage at breast cancer detection on survival in modern times: population-based study in 173,797 patients. //BMJ. 2015;351:h4901
24. Henley SJ, Ward EM, Scott S, Ma J, Anderson RN, Firth AU *et al* (2020) Annual report to the nation on the status of cancer, part I: national cancer statistics. Cancer 126(10):2225–2249.
25. Al-Kindi SG, Oliveira GH. Prevalence of preexisting car-diovascular disease in patients with different types of cancer: the unmet need for onco-cardiology. //Mayo Clin Proc. 2016. - 91(1):81–83.
26. Giza DE, Marmagkiolis K, Mouhayar E, Durand JB, Iliescu C. Management of CAD in patients with active cancer: the interventional cardiologists' perspective. Curr Cardiol Rep 2017; 19:56.
27. Uppalakal B, Karanayil LS. Incidence of Metabolic Syndrome in Patients Admitted to Medical Wards with ST Elevation Myocardial Infarction. //J Clin Diagn Res. 2017;11(3): OC17-OC20.
28. Battelli MG, Bortolotti M, Polito L, Bolognesi A. Metabolic syndrome and cancer risk: The role of xanthine oxidoreductase. //Redox Biol.- 2019; 21:101070.
29. Uzunlulu M, Telci Caklili O, Oguz A. Association between Metabolic Syndrome and Cancer. Ann Nutr Metab. 2016;68(3):173-179.
30. Totzeck M, Mincu RI, Rassaf T. Cardiovascular adverse events in patients with cancer treated with bevacizumab: a meta-analysis of more than 20 000 patients. //J Am Heart Assoc. 2017. 6:8.
31. Michel L, Rassaf T. Cardio-oncology: need for novel structures. //Eur J Med Res. 2019. - 24(1):1.
32. Rassaf T, Totzeck M Modern concepts in cardio-oncology. //J Thorac Dis. 2018. 10: S4386–S4390.
33. Chang HM, Moudgil R, Scarabelli T, Okwuosa TM, Yeh ETH. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 1. //JAm Coll Cardiol. 2017-70(20):2536–2551.
34. Banasiak W, Zymlinski R, Undas A. Optimal manage-ment of cancer patients with acute coronary syndrome. //Pol Arch Intern Med. 2018. - 128(4):244–253
35. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M *et al*. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. //N Engl J Med. 2003. - 349(2):146–153.
36. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U *et al*. 2018 ESC/EACTS Guidelines on myo-cardial revascularization. //Eur Heart J. 2019. - 40(2):87–165
37. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F *et al*. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment Elevation. Rev Esp Cardiol (Engl Ed). 2015. - 68(12):1125.
38. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ *et al*. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Inter-ventions, and Society of Thoracic Surgeons. //J Am Coll Cardiol. 2014 - 64(18):1929–1949.
39. Genereux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O *et al*. Quantification and impact of untreated coronary artery disease after percutaneous coronary interven-tion: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. //J Am Coll Cardiol. 2012. - 59(24):2165–2174.
40. Michel L, Rassaf T, Totzeck M. Biomarkers for the detection of apparent and subclinical cancer therapy-related cardiotoxicity. //J Thorac Dis. 2018. - 10: S4282–S4295.
41. Mitrugno A, Tassi Yunga S, Sylman JL, *et al*. The role of coagulation and platelets in colon cancer-associated thrombosis. //Am J Physiol Cell Physiol. - 2019;316(2):C264-C273.
42. Carrier M, Blais N, Crowther M, *et al*. Treatment algorithm in cancer-associated thrombosis: Canadian expert consensus. //Curr Oncol. -2018;25(5):329-337
43. Raposeiras-RoubínS, Abu-AssiE, Muñoz-PousaI, etal.Usefulness of Bleeding After Acute Coronary Syndromes for Unmasking Silent Cancer. //Am J Cardiol. 2020;125(12):1801-1808.
44. Landes U, Kornowski R, Bental T, Assali A, Vaknin-Assa H, Lev E, Iakobishvili Z. Long-term outcomes after percutaneous coronary interventions in cancer survivors. Coron Artery Dis 2017; 28:5–10]. Duke [Hess CN, Roe MT, Clare RM, Chiswell K, Kelly J, Tcheng JE, Hagstrom E, James SK, Khouri MG, Hirsch BR, Kong DF, Abernethy AP, Krucoff MW. Relationship between cancer and cardiovascular outcomes following percutaneous coronary intervention. //J Am Heart Assoc 2015;4; e001779
45. Oren O, Herrmann J. Arterial events in cancer patients—the case of acute coronary thrombosis. J Thorac Dis 2018;10: S4367-85.
46. Guddati AK, Joy PS, Kumar G. Analysis of outcomes of percutaneous coronary intervention in metastatic cancer patients with acute coronary syndrome over a 10-year period. // J Cancer Res Clin Oncol 2016; 142:471–9
47. Conti CR. Thrombolytic therapy in thrombocytopenic patients. Clin Cardiol. 1995 Jun;18(6):299-300. doi: 10.1002/clc.4960180603. PMID: 7664502.
48. Styczkiewicz K, Styczkiewicz M, Myćka M, *et al*. Clinical presentation and treatment of acute coronary syndrome as well as 1-year survival of patients

hospitalized due to cancer: A 7-year experience of a nonacademic center. //Medicine (Baltimore). 2020;99(5): e18972.
49. Iliescu CA, Grines CL, Herrmann J, Yang EH, Cilingiroglu M, Charitakis K, Hakeem A, Toutouzas KP, Leesar MA, Marmagkiolis K. SCAI Expert consensus statement: evaluation, management, and special considerations of cardiooncology patients in the cardiac catheterization laboratory (endorsed by the cardiological society of india, and sociedad Latino Americana de Cardiologia intervencionista). //Catheter Cardiovasc Interv 2016;87: E202–E223
50. PottsJE, IliescuCA, LopezMatteiJC, MartinezSC, HolmvangL, LudmanP *et al*. Percutaneous coronary intervention in cancer patients: a report of the prevalence and outcomes in the United States. //Eur Heart J. – 2018. - 40(22):1790–1800.
51. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H *et al*. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. //N Engl J Med. 2009. - 361(24):2342–2352.
52. Potts JE, Iliescu CA, Lopez Mattei JC, Martinez SC, Holmvang L, Ludman P *et al*. Percutaneous coronary intervention in can-cer patients: a report of the prevalence and outcomes in the United States. //Eur Heart J. 2019 - 40(22):1790–1800.
53. Kastrati A, Dibra A, Spaulding C, Laarman GJ, Menichelli M, Valgimigli M *et al*. Meta-analysis of randomized trials on drug-eluting stents vs bare-metal stents in patients with acute myocardial infarction. //Eur Heart J. 2007. - 28(22):2706–2713.
54. IannacconeM, D'AscenzoF, Vadala` P, WiltonSB, NoussanP, ColomboF, RaposeirasRoubı´nS, AbuAssiE, Gonza´lez-JuanateyJR, SimaoHenriquesJP, SaucedoJ, KikkertWJ, Nu~nez-GilI, Ariza-SoleA, SongX-T, AlexopoulosD, LiebetrauC, KawajiT, MorettiC, GarboR, HuczekZ, NieS-P, FujiiT, CorreiaLCL, KawashiriM-A, Garcı´aAcu~naJM, SouthernD, AlfonsoE, TerolB, GarayA, ZhangD, ChenY, XanthopoulouI, OsmanN, Mo¨llmannH, ShiomiH, GiordanaF, KowaraM, FilipiakK, WangX, YanY, FanJ-Y, IkariY, NakahashiT, SakataK, GaitaF, YamagishiM, KalpakO, KedevS. Prevalence and outcome of patients with cancer and acute coronary syndrome undergoing percutaneous coronary intervention: aBleeMACSsubstudy. Eur Heart J. Acute Cardiovasc Care. - 2018; 7:631–638.
55. Van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, Koolen JJ, Brueren BR, Dambrink JH, Hautvast RW, Verheugt FW, TenBerg JM. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J. Am. CollCardiol. - 2009; 53:1399–1409.
56. Aditya Bharadwaj, Jessica Potts, Mohamed O Mohamed, Purvi Parwani, Pooja Swamy, Juan C Lopez-Mattei, Muhammad Rashid, Chun Shing Kwok , David L Fischman, Vassilios S Vassiliou, Philip Freeman , Erin D Michos, Mamas A Mamas. Acute myocardial infarction treatments and outcomes in 6.5 million patients with a current or historical diagnosis of cancer in the USA. //Eur Heart J. - 2020 Jun 14;41(23):2183-2193.
57. Yusuf SW, Daraban N, Abbasi N, *et al*. Treatment and outcomes of acute coronary syndrome in the cancer population. ClinCardiol 2012; 35:443–50.
58. Hess CN, Roe MT, Clare RM, Chiswell K, Kelly J, Tcheng JE, Hagstrom E, James SK, Khouri MG, Hirsch BR, Kong DF, Abernethy AP, Krucoff MW. Relationship between cancer and cardiovascular outcom.es following percutaneous coronary intervention. //J Am Heart Assoc 2015;4; e001779
59. Wang F, Gulati R, Lennon RJ, Lewis BR, Park J, Sandhu GS, Wright RS, Lerman A, Herrmann J. Cancer history portends worse acute and long-term noncardiac (but not cardiac) mortality after primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction. Mayo Clin Proc 2016;91: 1680–1692.