Basic cardiovascular risk assessment in naïve patients with colon cancer

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Abstract. Cardiovascular assessment of oncological patients suggests that cancer can lead to subclinical damage of the heart. The aim of the present study was to analyze the value of baseline cardiovascular biomarkers in patients with newly diagnosed colon cancer prior to treatment. Additionally, another aim was to establish baseline cut-off alert values for this low-intensity neoplastic damage. A total of 51 patients with newly diagnosed colon cancer, without history of cardiac disease, were enrolled in a prospective, cross-sectional study. All patients underwent clinical, biochemical and basic echocardiographic evaluation before starting treatment. Patients were assessed for myocardial damage using high-sensitivity troponin T (hs-TnT), creatine kinase-MB (CK-MB) and N-terminal-pro B-type natriuretic peptide (NT-proBNP). A group of 28 healthy controls was included for comparison. Cardiac ultrasound revealed similar left ventricular (LV) ejection fraction but enlarged LV chambers compared with the control group (LV at end systole, 29.50 vs. 26.00 mm; LV at end diastole, 44.50 vs. 38.00 mm; P<0.001 in both cases). The levels of cardiovascular biomarkers of myocardial damage were higher in the patients than in the control group (CK-MB, 17.00 vs. 11.00 IU/l, P<0.001; hs-TnT, 8.20 vs. 3.00 ng/l, P<0.001; NT-proBNP, 155.40 vs. 48.50 pg/ml, P=0.001). In multivariate analysis, CK-MB and hs-TnT retained statistical significance (P=0.004 and P=0.045, respectively). Moreover, it was demonstrated that new cut-offs for hs-TnT (8.00 ng/l) and NT-proBNP (220.00 pg/ml) can identify cardiac damage in patients ≥65 years old. Thus, the present study confirmed the hypothesis that a basic cardiovascular assessment of treatment-naïve patients with colon cancer can identify important pre-treatment myocardial impact. Adapted cut-off values should be set for cardiovascular biomarkers in the cancer population, different from those currently accepted for acute coronary syndromes or heart failure.

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Introduction

Cardiovascular disease and cancer are two of the most important contributors of morbidity and mortality in the European Union and worldwide (1). Although the heart may be affected by cancer therapy, it has been suggested that cancer itself is responsible for a subclinical degree of cardiovascular damage in certain patients (2).

High levels of troponin typically indicate acute coronary syndrome (ACS). Lower (relative to ACS), but above-normal levels of troponin, may point to another diagnosis, such as heart failure, myocarditis, pulmonary embolism, sepsis or kidney failure (3). This biochemical abnormality has also been associated with left ventricular hypertrophy (LVH) (4) and is more common in the elderly (5,6). Similarly, N-terminal-pro B-type natriuretic peptide (NT-proBNP) is a widely recognized biomarker of heart failure, although slightly abnormal values have also been associated with increased age and body mass index (BMI) (7,8). Moreover, other clinical conditions are associated with significantly increased levels of NT-proBNP (8,9).

Previous studies have reported elevated levels of hs-TnT (10-15) and NT-proBNP in patients with cancer (2,14). Although there is no evidence of cardiac involvement, these abnormalities are important because they could indicate a subsequent risk for cardiac complications during cancer treatment.

A recent statement of multiple medical societies involved in Cardio-Oncology proposed a baseline proforma assessment, including cardiovascular biomarkers, hs-TnT and NT-proBNP, as easy-to-use tools for oncologists to stratify cardiovascular risk in patients with cancer, prior to the start of treatment (16).

The aim of the present study was to investigate the hypothesis that in patients with newly diagnosed colon cancer, before the start of any cancer treatment, myocardial involvement may already be present. Moreover, regarding cardiovascular biomarkers, another aim of the current study was to establish cut-off values for this hypothetical low-intensity injury.

Materials and methods

Study design and setting. The present prospective, cross-sectional study was conducted between February 2016 and May 2019 in the Clinical Municipal Hospital of Cluj-Napoca (Romania) and included patients with newly diagnosed colon cancer before starting any cancer treatment. The patients were enrolled during hospitalization in internal medicine or gastroenterology departments. Detailed patient history was recorded, and patients were excluded if any previous heart disease or electrocardiogram abnormalities were identified. Age, sex and common risk factors, such as hypertension, diabetes mellitus and smoking status were recorded. To define the baseline levels for each variable, a control group consisting of volunteer medical staff was also similarly analyzed. Patients were diagnosed with colon cancer if they met the criteria for this diagnosis according to the European Society for Medical Oncology guidelines for diagnosis of colorectal cancer (17). Patients <18 years, those with more than one oncological disease and those who underwent any oncological treatment were excluded. Written informed consent was obtained from all participants before their inclusion in the study. The Ethics Committee of The Clinical Municipal Hospital of Cluj-Napoca approved the study.

Anthropometric data. Height, weight and waist circumference (WC) were recorded. BMI was calculated based on height and weight (kg/m^2). The assessment of metabolic syndrome (MetS) was performed according to the Joint Interim Statement of The International Diabetes Federation Task Force on Epidemiology and Prevention 2009 (18). MetS entails the presence of any three of the following five features: i) Elevated WC (≥94 cm for males and ≥80 cm for females) and triglyceride levels (>150 mg/dl); ii) reduced high-density lipoprotein (HDL)-cholesterol (<40 mg/dl in males and <50 mg/dl in females); iii) raised blood pressure (systolic pressure ≥130 mmHg; or diastolic pressure ≥85 mmHg); iv) raised fasting plasma glucose (≥100 mg/dl); and v) previously diagnosed type-2 diabetes.

Laboratory. Venous blood samples were obtained and analyzed in the Clinical Municipal Hospital of Cluj-Napoca, according to our local laboratory standard procedures. In addition to routine measurements [risk factors and MetS evaluation, such as fasting blood sugar, cholesterol, HDL-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides], high-sensitivity C-reactive protein (hs-CRP) and cardiovascular biomarker levels [hs-TnT, creatine kinase-MB (CK-MB) and NT-proBNP] were determined. hs-TnT and NT-proBNP levels were measured using the Elecsys TnT-hs (cat. no. 05092728190) and the Elecsys NT-proBNP (cat. no. 04842464190) kits, respectively, on the Cobas platform (Roche Diagnostics). Normal values for these parameters in our laboratory are 14 ng/l for ACS and 125 pg/ml for heart failure.

Ultrasonography. All patients included in the present study were evaluated using echocardiograms with the ProSound Alpha 7 (Hitachi Aloka Medical Ltd.) ultrasound system and a phased-array transducer (1-15 MHz range). The examinations were performed during the same hospital stay by two qualified physicians.

For the cardiac examinations, the patients were placed in left lateral decubitus. The left atrium (LA), end-diastolic interventricular septum, end-diastolic posterior-wall left ventricle (LV), as well as the LV end-systolic diameter (LVESD) and LV end-diastolic diameter (LVEDD) were measured (in mm) in the parasternal long axis incidence. LV ejection fraction (LVEF) was calculated using LVESD and LVEDD measurements using the Teicholz formula (Volume=$7D^3/(2.4 + D$, where D represents LV diameter) (19). The data regarding the diastolic function were not uniform considering the data collection by two different examiners and were therefore not subsequently analyzed.

Cardiovascular risk stratification. Baseline proforma cardiovascular risk assessment was carried out using the current recommendations for the treatment of patients with colon cancer (16), which included the following: History of prior cardiovascular disease, cardiovascular biomarkers, demographic and cardiovascular risk factors, previous cardiotoxic cancer treatment and lifestyle risk factors. Each class of risk included several variables identified as contributing to cardiovascular risk for patients receiving the specific cancer therapy according to the evidence available and expert opinion. Once completed, a risk level was calculated, and the patients were classified as being at low, medium, high or very high cardiovascular risk (16).

Statistical analysis. Continuous data are presented either as the median with a 95% confidence interval for skewed variables or as mean ± SD for normally distributed variables. Skewed variables were compared using Mann-Whitney U-test, while Student's t-test was used for comparing normally distributed variables. When >2 variables were compared, Kruskal-Wallis test was used instead (in conjunction with Dunn's test). Normally distributed variables were compared using the independent two-sample t-test. Discrete variables are expressed as n (%). Comparison of the discrete variables was performed using χ^2 test. Variables with $P<0.05$ following univariate analysis (carried out using regression method) were included in the multivariate analysis. For multivariate analysis, a binary logistic regression using the backward logistic regression model was used in order to determine the cardiac markers independently associated with the presence of cancer. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic accuracy of cardiac biomarkers and ultrasound modifications for the subclinical lesions induced by

Table I. Descriptive presentation of the demographic and metabolic features of the patient and control groups.

Variable	Patient group (n=51)	Control group (n=28)	P-value	Normal range
Age, years	63 (59.27-66.26)	33.5 (34.12-46.24)	<0.001	NA
Number of males, n (%)	23 (45.09)	18 (64.28)	0.144	NA
BMI, kg/m^2	23.8 (23.62-25.96)	22.64 (21.52-25.37)	0.088	18.50-24.90
Smoking, n (%)	13 (25.49)	7 (25.00)	0.891	NA
sAP, mmHg	130 (124.35-130.56)	120 (115.14-127.71)	0.004	<120
dAP, mmHg	80 (70.78-75.59)	70 (66.24-74.83)	0.108	<80
Heart rate, bpm	80 (77.25-83.11)	80 (74.70-82.44)	0.472	60-100
Fasting blood glucose, mg/dl	98 (96.20-105.8)	101 (98-111.12)	0.118	70-99
Cholesterol, mg/dl	188.41±37.38	166.11±51.50	0.053	<200
HDL-cholesterol, mg/dl	42 (40.71-48.09)	45 (42.09-54.05)	0.404	>40
LDL-cholesterol, mg/dl	116.51±27.78	101.71±39.94	0.023	<100
Triglycerides, mg/dl	98 (100-141.61)	68 (62.87-93.34)	<0.001	<150
Metabolic syndrome, n (%)	17 (32.72)	7 (25)	0.470	NA
hs-CRP (mg/l)	1.81 (2.16-8.27)	0.09 (0.48-2.24)	<0.001	0.8-1

Mean ± standard deviation (SD) or median and 95% confidence interval (CI) were used for continuous variables, for normal and uneven distributions, respectively. BMI, body mass index; sAP, systolic arterial pressure; dAP, diastolic arterial pressure; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein: NA, not applicable; bpm, beats per minute.

oncological disease. The closest value to the maximum sensitivity and specificity was selected as the optimal cut-off value. Statistical analysis was performed using the SPSS software version 27 (IBM Corp). P<0.05 was considered to indicate a statistically significant difference.

Results

Initially, 78 patients with colon cancer, naïve of any cancer treatment, were included in the analysis. After echocardiography, due to the presence of LVH, which represents a confounding factor, 27 patients were excluded.

The mean age in the final patient group (n=51) was 63.94±11.83 years, with a slight predominance of female sex (54.91%). Most of the patients had normal weight [BMI, 23.80 (23.62-25.96)], normal blood pressure [130 (124.35-130.56)/80 (70.78-75.59) mmHg] and normal fasting plasma glucose [(98 (96.20-105.8) mg/dl], although 32.72% of them met the criteria for MetS. In terms of metabolic risk factors, when comparing the patient group with controls, a significant difference was observed only for systolic arterial blood pressure [130 (124.35-130.56) vs. 120 (115.14-127.71) mmHg; P=0.004], with the values in the normal range. Triglyceride levels were also significantly higher in the study group [98 (100-141.61) vs. 68 (62.87-93.34) mg/dl; P<0.001]. Inflammation was also observed in the patient group, as evidenced by high hs-CRP levels [1.81 (2.16-8.27) vs. 0.09 (0.48-2.24) mg/l; P<0.001]. The other variables measured, namely BMI, smoking, sAP, dAP, heart rate, fasting plasma glucose, cholesterol, HDL-cholesterol, LDL-cholesterol and the presence of metabolic syndrome, were not significantly different between the two groups The general metabolic and demographic data are presented in Table I.

In terms of biochemical analysis, minimal myocardial damage (as evidenced by high values of CK-MB and hs-TnT) was observed in the patient group, with significantly higher values than in healthy subjects, although not indicative of a potential coronary syndrome. Minimal myocardial damage (high values of hs-TnT) and myocardial strain (high values of NT pro-BNP) were observed in the patient group. It should be noted that the myocardial injury did not reach a significant threshold for a possible ACS, while the myocardial strain is compatible with heart failure. Regarding the cardiac morphological modifications detected by ultrasound, larger LV dimensions were observed in the patients in comparison with the control group [(29.50 (28.76-31.84) vs. 26.00 (25.22-27.55) mm; P<0.001]. By contrast, similar LVEF values were observed in both groups [61 (58.59-62.71) vs. 61 (60.31-61.69) mm; P<0.001] (Table II).

In the multivariate analysis (Table III), CK-MB and hs-TNT retained statistical significance (P=0.004 and P=0.045, respectively) for biological variables, while neither NT-proBNP and none of the ultrasound features (LV dimensions and LVEF; data not shown) reached statistical significance.

As the cardiac biomarkers were indicative of minimal myocardial damage, the diagnostic accuracy of hs-TnT, CK-MB and NT-proBNP for the detection of myocardial lesion was then evaluated in the entire patient group (n=78 patients) (Fig. 1). hs-TnT had an area under the ROC curve (AUROC) 0.791. For CK-MB, the AUROC was 0.804, whereas NT-proBNP had the lowest value (0.721).

One of the major aims of the current study was to find and introduce specific cut-offs for hs-TnT that would suggest cardiac microdamage. In this respect, the patients were divided into two age groups: <65 and ≥65 years old. The levels of hs-TnT varied significantly between these two groups [5.36 (5.07-17.89) vs. 16.79 (11.14-22.07) ng/l; P<0.001]. Although

Table II. Comparison of biological and ultrasound variables demonstrating myocardial microlesions in the patient and control groups.

Variable	Patient group (n=51)	Control group (n=28)	P-value
CK-MB, IU/l	17.00 (6.78-82.78)	11.00 (9.94-14.11)	<0.001
hs-TnT, ng/l	8.20 (9.00-17.89)	3.00 (3.29-8.57)	<0.001
NT-proBNP, pg/ml	155.40 (268.71-718.28)	48.50 (37.95-727.03)	0.001
LA, mm	35 (34.35-38.25)	30 (28.91-31.47)	<0.001
IVS, mm	10 (9.72-10.58)	9.50 (9.35-9.95)	0.115
PWLV, mm	10 (9.34-10.06)	9 (8.94-9.45)	0.003
LVs, mm	29.50 (28.76-31.84)	26.00 (25.22-27.55)	<0.001
LVd, mm	44.50 (44.37-47.38)	38.00 (37.13-39.72)	<0.001
LVEF, %	61 (58.59-62.71)	61 (60.31-61.69)	0.938

Mean ± standard deviation (SD) or median and 95% confidence interval (CI) were used for continuous variables, for normal and uneven distributions, respectively. CK-MB, creatine kinase-MB; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal-pro B-type natriuretic peptide; LA, left atrium; IVS, interventricular septum; PWLV, posterior wall of the left ventricle; LVs, left ventricle at end systole; LVd, left ventricle at end diastole; LVEF, left ventricular ejection fraction.

Table III. Multivariate analysis of cardiac biomarkers.

Variable	B	SE	Wald	df	P-value	Exp (B)
CK-MB, IU/l	0.172	0.061	8.105	1	0.004	1.188
NT-proBNP, pg/ml	-0.001	0.001	1.186	1	0.276	0.999
hs-TnT, ng/l	0.100	0.058	2.976	1	0.045	1.105

CK-MB, creatine kinase-MB; NT-proBNP, N-terminal-pro B-type natriuretic peptide; hs-TnT, high-sensitivity troponin T; B, unstandardized regression weight; SE, standard error; Wald, Wald's statistical test; df, degrees of freedom; Exp(B), hazard ratio.

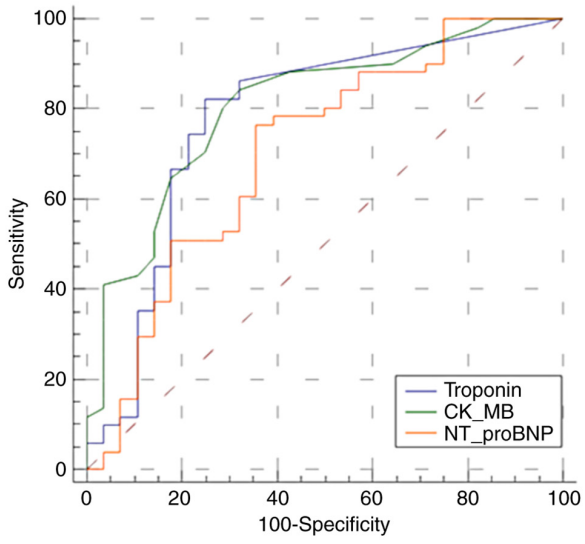

Figure 1. Area under the receiver operating characteristic curves for troponin, CK-MB and NT-proBNP. CK-MB, creatine kinase-MB; NT-proBNP, N-terminal-pro B-type natriuretic peptide. Hs-TnT had an area under the ROC curve 0.791. For CK-MB, the AUROC was 0.804, whereas NT-proBNP had the lowest value of 0.721.

not significantly different from those related to ACS, the levels of NT-proBNP were significantly higher in patients ≥65 years old [75.69 (92.27-313.44) vs. 252.70 (249.23-1162.39) pg/ml; P<0.001]. In addition, the median hs-TnT levels in each age group were then compared with those of the control group. A significant difference was observed both between patients <65 years old and controls and between patients ≥65 years old and controls [5.36 (5.07-17.89) vs. 16.79 (11.14-22.07); P<0.001 and 3.00 (2.88-5.84), respectively; P<0.001] (Table IV).

Moreover, the cut-off hs-TnT value that could identify patients >65 years old with cardiac damage was calculated using Receiver Operating Characteristic (ROC) curve analysis. A cut-off value of 8 ng/l (AUROC, 0.865) and 220.00 pg/ml (AUROC, 0.833) was obtained for hs-TnT and NT-proBNP, respectively.

Using the recently described criteria dividing patients according to their risk of developing cardiac disease after chemotherapy (16), 32 patients in the study group met the criteria for low risk, while the rest were at medium risk. No patient met the criteria for high or very high risk. In the analysis of the low- and medium-risk subgroups, high hs-TnT and NT-proBNP levels were observed in patients at medium risk of developing cardiac disease. The results were as follows when comparing the low-risk with the medium-risk group: i) CK-MB, 17.00 (15.86-22.52) vs. 17.00 (14.46-33.75) IU/l, P=0.49; ii) NT-proBNP, 82.13 (80.61-242.09) vs. 358.30 (334.43-1322.90) pg/ml, P<0.001; and iii) hs-TnT, 5.70 (5.83-8.09) vs. 18.10 (11.21-30.98) ng/l, P<0.001 (Table V).

Table IV. Comparison of cardiac biomarkers between age patient subgroups and controls.

Variable	Patients <65 years (n=21)	Patients ≥65 years (n=30)	Controls (n=28)	P-value[a]	P-value[b]	P-value[c]
CK-MB, IU/l	17.00 (16.27-23.57)	17.00 (13.88-31.27)	11.00 (9.71-12.99)	0.82	<0.001	<0.001
hs-TNT, ng/l	5.36 (5.07-17.89)	16.79 (11.14-22.07)	3.00 (2.88-5.84)	<0.001	<0.001	<0.001
NT-proBNP, pg/ml	75.69 (92.27-313.44)	252.70 (249.23-1,162.39)	44.45 (126.26-603.92)	<0.001	0.002	<0.001

[a]P-value for patients <65 years vs. patients ≥65 years; [b]P-value for patients <65 years old vs. controls; [c]P-value for patients ≥65 years old vs. controls. CK-MB, creatine kinase-MB; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal-pro B-type natriuretic peptide.

Table V. Comparison of cardiac biomarker levels in patients at low or medium risk of developing cardiac disease following cancer treatment.

Variable	Low risk (n=32)	Medium risk (n=21)	P-value
CK-MB, IU/l	17.00 (15.86-22.52)	17.00 (14.46-33.75)	0.49
hs-TnT, ng/l	5.70 (5.83-8.09)	18.10 (11.21-30.98)	<0.001
NT-proBNP, pg/ml	82.13 (80.61-242.09)	358.30 (334.43-1322.90)	<0.001

CK-MB, creatine kinase-MB; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal-pro B-type natriuretic peptide.

Discussion

Cardiovascular disease and cancer share several common pathophysiological mechanisms for disease incidence and progression (14,15,20). Furthermore, the prognosis of patients with cancer is associated with cardiovascular status prior or during cancer therapy. The hypothesis that cancer itself may damage the heart muscle irrespectively of exposure to cancer therapy has been previously studied using different echocardiographic techniques and/or cardiovascular biomarkers (2,21).

Cardiovascular vulnerability due to cancer or treatment regimen differs depending on tumor type and localization (12-14,20). For this reason, the present study only included patients with colon tumors. In the recruited population, due to the inclusion and exclusion criteria, baseline cardiovascular risk assessment (16) identified only low- and moderate-risk patients.

In an echocardiographic study, patients with cancer, whether treated or not, had similarly reduced strain measurements, indicating impaired heart function, compared with healthy individuals (22). Another study used combined speckle tracking echocardiography and hs-TnT for early detection and prediction of future cardiac dysfunction (21). In serial analyses, global longitudinal strain and hs-TnT provided a reliable and non-invasive method for the prediction of cardiac dysfunction in patients receiving anthracycline-based chemotherapy (20).

In the present study, impaired systolic heart function was observed using basic techniques (the Teicholz formula for LVEF). However, patients with colon cancer presented higher left cardiac chamber dimensions compared with healthy individuals, suggesting adaptative remodeling compatible with LV dysfunction. Due to its complex function, LA size is considered an important risk identifier in preclinical cardiovascular disease (23). In addition, in a cohort study (Multi-Ethnic Study of Atherosclerosis) involving asymptomatic adults without cardiovascular disease, LV dilation predicted heart failure during a 12-year follow-up period (24). In a study regarding the association between hs-TnT elevation and metabolic syndrome in a general population sample, the prevalence of MetS was higher in those with detectable and elevated levels of hs-TnT. The number of MetS components and presence of MetS were markedly associated with an increased risk for detectable hs-TnT levels (18,25). In the present study, although LDL-cholesterol and triglyceride levels were significantly different between patients and controls, the incidence of MetS was similar in both groups. Therefore, it may be concluded that lipid levels did not significantly result in detectable differences in hs-TnT levels.

Elevated levels of cardiovascular biomarkers, such as hs-TNT or NT-proBNP are encountered mostly in solid cancer types. Slightly elevated hs-TnT levels are frequent findings among hospitalized patients, mostly unrelated to ACS (1). Heart failure, myocarditis, pulmonary embolism, sepsis or kidney failure are some of the most diagnosed clinical conditions (3,5,6). Age and LVH are also associated with high concentrations of hs-TnT (4-6).

Several studies have analyzed different cardiovascular biomarkers at baseline before starting cancer therapies. One study on cardiac involvement using myocardial troponins demonstrated frequent subclinical damage in patients with gynecological cancers. Whether using conventional or high-sensitivity assays, a considerable percentage of untreated patients with ovarian cancer presented higher values of TnT I, compared with other surgical patients with non-malignant masses or endometriosis (10). In search for better tools to predict the cardiac complications of anthracycline chemotherapy, a previous study investigated the utility of hs-TnT, NT-proBNP, cardiac TnT and troponin I and CK-MB in patients with

different types of solid and hematological cancer before and during therapy (9). Upregulated baseline hs-TnT levels identified a patient subgroup at high risk of developing cardiac complications following chemotherapy. NT-proBNP levels were indicated to be elevated in previous studies in patients with cancer (8,9). Markedly elevated NT-proBNP may indicate volume overload in the cancer population (8). One possible explanation is that a number of abnormalities, more frequently observed in older patients, seem to be significantly associated with the risk of increased levels of hs-TnT, CK-MB and/or NT-proBNP.

Another study published in 2015 analyzed several circulating cardiovascular hormones along with hs-TnT levels, including NT-proBNP, prior to cancer therapy (2). The study revealed elevated cardiovascular biomarkers in patients with untreated cancer. Furthermore, cardiac biomarker levels increased concomitantly with tumor stage and were strongly associated with all-cause mortality during follow-up. The underlying mechanism remained unclear since no clinical manifestation of a cardiac disease could be confirmed.

Using the recently proposed baseline assessment to stratify cardiovascular risk in cancer patients (16) prior to treatment start, the present study identified groups of patients with low and moderate cardiovascular risk, with significant differences between groups when comparing cardiovascular biomarker levels. In the recruited population with newly diagnosed colon neoplasia prior to any cancer therapy, patients with elevated hs-TnT and NT-proBNP levels were identified, contributing to significantly higher values overall compared with the healthy group. The values remained higher also when the group was divided according to age, compared with the control group. Interestingly, although higher in patients with colon cancer, hs-TnT and NT-proBNP had different behaviors compared to traditional levels of ACS and heart failure, respectively they reported a degree of myocardial strain without myocardial injury. These results are consistent with the hypothesis that hs-TnT and NT-proBNP baseline cut-off values for cardiac involvement in cancer are different than the accepted value for ischemic disease and heart failure, with different thresholds according to age.

The attempted selection in order to obtain a group of patients without cardiovascular disease, subclinical or clinically manifest, led us to a significantly younger age in the control group when compared to the study group. Even when rigorous exclusions of people with subclinical heart disease are performed, different age-related troponin concentrations are real (26,27). In this respect, significant differences between groups could bias our results. For this reason, a comparison between cardiac biomarkers in the control group and age subgroups in the study group was added.

The main limitations of the present study are the cross-sectional design and the limited availability of advanced echocardiographic techniques for LV function analysis. In addition, probably with a limited impact, the differences in the prevalence of certain risk factors for coronary artery disease, such as age, systolic blood pressure and LDL-cholesterol, could have partially resulted in the differences in cardiac biomarker levels and LV size between the two groups.

In conclusion, our study demonstrated the presence of a certain degree of cardiovascular injury in treatment-naïve patients with colon cancer, regardless of age or comorbidities. This was evidenced by enlarged left chambers on echocardiography and elevated levels of cardiovascular biomarkers, compared with healthy subjects. Due to slight differences at baseline, appropriate cut-off values of cardiovascular biomarkers adapted for patients with cancer were proposed, although further studies on a larger population are required to confirm these values.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

LR, LA and EB contributed to the conception, design of the study and writing of the manuscript. AG, CG, LS, VD, SC and VM contributed to the design of the study and writing of the manuscript. LR, LA, DC and EB performed the data analysis and interpretation. DR and AB contributed to the conception, design of the study, and final proofreading. DC and EB confirm the authenticity of all raw data. All authors critically revised the manuscript, approved the final version to be published and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

The present study was approved by The Ethics Committee of The Clinical Municipal Hospital in Cluj-Napoca, Romania. Written informed consent was obtained from all participants before their inclusion in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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