

Covid-19 and Its Impact on Colorectal Cancer Diagnosis in Romania: A Single-Centered 5-year Retrospective Cohort Study

Octavian Adrian Maghiar^{1,2†}, Mircea Șandor^{2†}, Mădălina-Andrada Blaj³, Marius Belean³, Andrei Ardelean^{3,4}, Violeta Turcuș^{4,5}, Teodor Andrei Maghiar^{1,2*}, Adina Pop-Moldovan^{6,4*}, Endre Mathe^{4,7*}, Alin Bodog², Carmen Neamțu^{3,4}, Cristina-Adriana Dehelean^{8,9}, Ovidiu Laurean Pop², Bogdan Dan Totolici^{3,4}, Andreea-Adriana Neamțu^{4,9,10}

¹Doctoral School of Biomedical Sciences, University of Oradea, Romania

²Faculty of Medicine and Pharmacy, University of Oradea, Romania

³1st Department of Surgery, Clinical County Emergency Hospital of Arad, Romania

⁴Faculty of Medicine, Vasile Goldis Western University of Arad, Romania

⁵National Institute for Economic Research Costin C. Kiritescu of the Romanian Academy

⁶Department of Cardiology, Clinical County Emergency Hospital of Arad, Romania

⁷Institute of Nutrition, University of Debrecen, Hungary

⁸Faculty of Pharmacy, Victor Babeș University of Medicine and Pharmacy from Timișoara, Romania

⁹Research Center for Pharmacologic-Toxicological Evaluations, Victor Babeș University of Medicine and Pharmacy from Timișoara, Romania

¹⁰Department of Pathology, Clinical County Emergency Hospital of Arad, Romania

*Corresponding author:

Teodor Andrei Maghiar, M.D.

Universității Street, Oradea, Romania

E-mail: teodormaghiar@yahoo.com

Adina Pop-Moldovan, M.D.

2-4 Andrenyi Karoli Street, Arad, RO

E-mail: ppmoldvn68@yahoo.com

Endre Mathe, M.D.

138 Böszörményi Street, Debrecen

Hungary

E-mail: endre.mathe@agr.unideb.hu

[†]Octavian Adrian Maghiar and Mircea

Șandor contributed equally to this

work and are both considered first

author.

Rezumat

Covid-19 și impactul său asupra diagnosticării cancerului colorectal: o analiză retrospectivă pe 5 ani într-un spital universitar din România

Introducere: Cancerul colorectal, al treilea ca incidență și al doilea ca mortalitate în rândul cancerelor din întreaga lume, reprezintă cea mai frecventă tumoră malignă a tractului digestiv. În România, acesta este cel mai frecvent diagnosticat tip de cancer (afectând aproximativ 0,06% din populație/an). În timpul pandemiei COVID-19, legislația de prevenție a transmisiei virale a SARS-CoV-2 ce a afectat accesul la serviciile de asistență medicală în ambulatoriu, alături de teama de infecție SARS-CoV-2 a pacienților, au avut consecințe asupra diagnosticului și tratamentului tuturor celorlalte patologii.

Metode: Studiul retrospectiv de cohortă pe o perioadă de 5 ani a fost realizat într-un spital clinic județean de urgență din Arad, România, și a inclus 1329 de pacienți nou diagnosticați cu cancer colorectal.

Rezultate: Vârsta la diagnostic a scăzut în perioada inițială a pandemiei COVID-19 până la 68,50 [95% CI (67,90–69,11)] ani, cu cel mai mare procent (7,41%) de pacienți cu cancer colorectal cu debut precoce, o creștere constantă post-pandemică a procentului

Received: 12.08.2023

Accepted: 10.10.2023

de pacienți de sex masculin (de la 52,71% în 2019 la 62,20% în 2022) și a pacienților din mediul urban (de la 54,18% în 2018 la 70,10% în 2022), a pacienților internați prin prezentare în regim de urgență (atingând valoarea maximă de 83,95% în 2020) și care necesită o perioadă mai lungă de spitalizare (10,03 [IC 95% (8,76-11,30)] zile în 2020 scăzând post-pandemic până la 8,37 [IC 95% (7,44-9,30)] zile în 2022). Cel mai frecvent diagnostic de cancer colorectal al pacienților din populația de referință este neoplasmul malign al rectului (cod C20.0 conform ICD-10), în timp ce cele mai frecvente complicații au fost maladia aderențială peritumorală, ocluzia și perforația, întâlnite la pacienții cu comorbidități precum hipertensiune arterială, cardiomiopatie ischemică, diabet zaharat, obezitate și steatohepatită non-alcoolică.

Concluzii: Particularitățile regionale ar trebui analizate pentru a viza cu predilecție populația expusă riscului de dezvoltare a cancerului colorectal și pentru a direcționa cât mai corespunzător resursele necesare în populația de referință, în special în perioadele de criză, similare pandemiei COVID-19.

Cuvinte cheie: cancer colorectal, prezentare la spital, pandemia COVID-19, diagnostic secundar, complicații

Abstract

Background: Colorectal cancer, 3rd in incidence and 2nd in mortality among cancers worldwide, represents the most common malignant tumor of the digestive tract. In Romania, it is the most frequently diagnosed type of cancer (approximately 0.06% of the population/year). During the COVID-19 pandemic the legislation preventing the SARS-CoV-2 viral transmission impairing access to outpatient healthcare services combined with patients' fear of SARS-CoV-2 infection had consequences on the diagnosis and treatment of all other pathologies.

Methods: A 5-year retrospective cohort study was conducted in a tertiary hospital in Arad, Romania, and included 1329 newly diagnosed colorectal cancer patients. For statistical analysis, Fisher's exact test was used for categorical data and the unpaired *t* test with Welch's correction for continuous data.

Results: The age on diagnosis decreased during the early COVID-19 pandemic to 68.50 (95% CI [67.90–69.11]) years, with the highest percentage (7.41%) of early onset colorectal cancer patients, a steady post-pandemic increase in the percentage of male (52.71% in 2019 to 62.20% in 2022) and urban (54.18% in 2018 to 70.10% in 2022) patients, admitted to the hospital due to an emergency presentation (peaking at 83.95% in 2020) and requiring a longer hospitalization period (10.03 [95% CI (8.76-11.30)] days in 2020 to 8.37 [95% CI (7.44-9.30)] days in 2022). The most common colo-rectal cancer diagnosis of patients in our reference population was malignant neoplasm of the rectum (ICD-10 code C20.0), while the most common complications were peritumoral adherence-related disorder, occlusion, and perforation, encountered in patients with comorbidities such as arterial hypertension, ischemic cardiomyopathy, diabetes mellitus, obesity, and non-alcoholic steatohepatitis.

Conclusions: Regional particularities should be analyzed to better target the population at risk and to better direct the necessary healthcare resources towards the reference population, especially during crisis periods similar to the COVID-19 pandemic.

Key words: colorectal cancer, hospital presentation, COVID-19 pandemic, secondary diagnosis, complications

Introduction

Colorectal cancer, 3rd in incidence and 2nd in mortality among cancers worldwide (1) and 2nd in both categories in the European Union in 2020 (2), represents the most common malignancy of the digestive tract. In Romania, with a percentage of 13.1% of all types of cancer, colorectal cancer is the most frequently diagnosed type of cancer (approximately 0.06% of the population/year) (3,4).

Colorectal cancer develops slowly, following the initial transformation of normal colorectal epithelium into an adenomatous polyp (5). The slow progression through the adenoma-carcinoma sequence enables for detection and removal of tumors through colonoscopy (gold standard of screening), the disease having a more favorable prognosis at an early stage (6). The treatment for colorectal cancer is largely guided by the stage of the disease on diagnosis, emphasizing the importance of a comprehensive

strategy for evaluation, achievable through the involvement of a multidisciplinary medical team. While surgical resection is to date considered the only available curative option (7), there is immense effort put into the development of alternative therapeutic options (8). In addition to curative surgical control of the tumor, it is often necessary to use pre- or post-interventional chemotherapy, immunotherapy and/or radiotherapy to help reduce or stabilize the tumor (9).

Once the World Health Organization declared a Public Health Emergency of International Concern on January 30th 2020 and characterized the COVID-19 outbreak as a pandemic on March 11th 2020, the healthcare systems and general population were impacted worldwide (10). In Romania (*Fig. 1*), based on the regional situation and the international context, the State of Emergency was declared on March 16th 2020 and lasted until May 14th 2020 and was followed by a State of Alert starting

Pre-pandemic period	
December 2019	- The first cases of novel coronavirus (SARS-CoV-2) detected in China
January 30 th 2020	- World Health Organization declares a Public Health Emergency of International Concern
March 11 th 2020	- World Health Organization characterizes the Covid-19 outbreak as a pandemic
Pandemic period	
May 16 th 2020	- State of Emergency declared in Romania for 30 days through the Presidential Decree No. 195/2020 ● interdiction to hospitalize patients that do not constitute a medical emergency in public hospitals ● no outpatient visits for medical consultations in public hospitals
April 14 th 2020	- State of Emergency declared in Romania for 30 days through the Presidential Decree No. 240/2020 ● interdiction to hospitalize patients that do not constitute a medical emergency in public hospitals ● no outpatient visits for medical consultations in public hospitals
May 15 th 2020	- State of Alert declared in Romania for 30 days through the Decision of the National Committee for Emergency Situations and approved by the Parliament ● short term intermittent interdiction to hospitalize patients that do not constitute a medical emergency in public hospitals depending on the epidemiological status of the region ● short term intermittent restrictions of outpatient visits for medical consultations in public hospitals depending on the epidemiological status of the region
State of Alert prolonged	
May 9 th 2022	- State of Alert lifted after the expiration of the Government Decision No. 171/03.02.2022
Return to normal period	
Ongoing	- No restrictions applicable to the healthcare system in Romania related to Covid-19
May 5 th 2023	- World Health Organization Emergency Committee on Covid-19 recommended and the Director-General agreed that Covid-19 no longer fits the definition of a Public Health Emergency of International Concern

Figure 1. Brief summary of relevant dates and measures applied in the healthcare system in Romania during the Covid-19 pandemic (10-16)

from May 15th 2020 to March 9th 2022 (11-16). For the duration of the State of Emergency, public hospitals were not allowed to hospitalize patients not constituting a medical emergency, while for the duration of the State of Alert, depending on the regional epidemiologic context the ambulatory consultations were restricted and hospitalization was occasionally limited to medical emergencies (*Fig. 1*). Thereafter, no directives affected the regular functioning of the healthcare system in Romania due to the COVID-19 pandemic. On May 5th 2023, World Health Organization Emergency Committee on COVID-19 recommended and the Director-General agreed that the disease no longer fits the definition of a Public Health Emergency of International Concern (10).

Additionally, the pandemic has created a certain level of fear of exposure to the SARS-CoV-2 virus in the population, rendering hospitals as unsafe and patients delaying their presentation for as long as possible (17). This tendency was observed in colorectal cancer patients, who are 90% over 50 years old, population at an increased risk for severe symptoms and complications in the unfortunate event of contracting the viral infection, thus influencing patient presentation, and therefore medical and surgical management (18).

This retrospective 5-year analysis aims to examine the regional colorectal cancer patient characteristics and the effects of the COVID-19 pandemic on the presentation and management of patients with this type of cancer, to contribute to the understanding of the context we are currently experiencing.

Materials and Methods

The retrospective cohort study was performed in a tertiary care hospital in the western part of Romania, at the Clinical County Emergency Hospital of Arad, Romania with a reference population of 410143 individuals (Arad County population according to the National Census 2021) (19).

All newly diagnosed colorectal cancer (ICD-10 codes: C18-C20) patients who presented to

the Clinical County Emergency Hospital of Arad in the period March 15th 2018 – March 15th 2023 were included in the study. The newly diagnosed colorectal cancer patients were divided into 5 cohorts, according to the time of their first hospital visit:

- Pre-pandemic cohorts:
 - o March 15th 2018 – March 15th 2019 (denoted further in text as Control 2018);
 - o March 15th 2019 – March 15th 2020 (denoted further in text as Control 2019);
- Pandemic cohort (early COVID-19 pandemic /pre-vaccination period):
 - o March 15th 2020 – March 15th 2021 (denoted further in text as Pandemic 2020);
- Pandemic cohort (late COVID-19 pandemic / post-vaccination period):
 - o March 15th 2021 – March 15th 2022 (denoted further in text as Pandemic 2021);
- Return to normal cohort:
 - o March 15th 2022 – March 15th 2023 (denoted further in text as Control 2022).

For each patient hospital visit at the hospital in the study period the electronic medical record and archived paper-based medical file were analyzed in the elaboration of this retrospective study. Information about the sociodemographic features (age, gender, area of residence), type of hospital admission, ward on which the patient was diagnosed with colorectal cancer, number of days of hospitalization, specific ICD-10 code, associated diagnosis, evolution, complications, and comorbidities were collected. Statistical analysis was conducted using performed using GraphPad Prism Version 9.5.1 (528), January 24, 2023 for macOS (USA).

Patients with a recurrence from a previously treated or diagnosed colorectal cancer were excluded from this retrospective study.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Clinical County Emergency Hospital of Arad, Romania (Protocol No. 56 approved on June 14th 2023). An informed

consent for anonymized, unidentifiable patient data usage for publication was signed by all patients at the time of admission. No personal identifiers are disclosed through the publication of this retrospective cohort study.

Results

In this retrospective cohort study, a total of 6869 electronic medical records and 6760 achieved paper-based medical files pertaining

to 1894 unique patients were screened based on ICD-10 coding C18-C20 (*Fig. 2*). A number of 1329 patients newly diagnosed with colorectal cancer in the study period were included in the analysis. A total of 565 unique patients were excluded from the study for not meeting the inclusion criteria. The distribution into cohorts based on the date of the first colorectal cancer diagnosis is detailed in *Fig. 2*.

Most notably, the number of patients newly diagnosed in the cohort Pandemic 2020 was

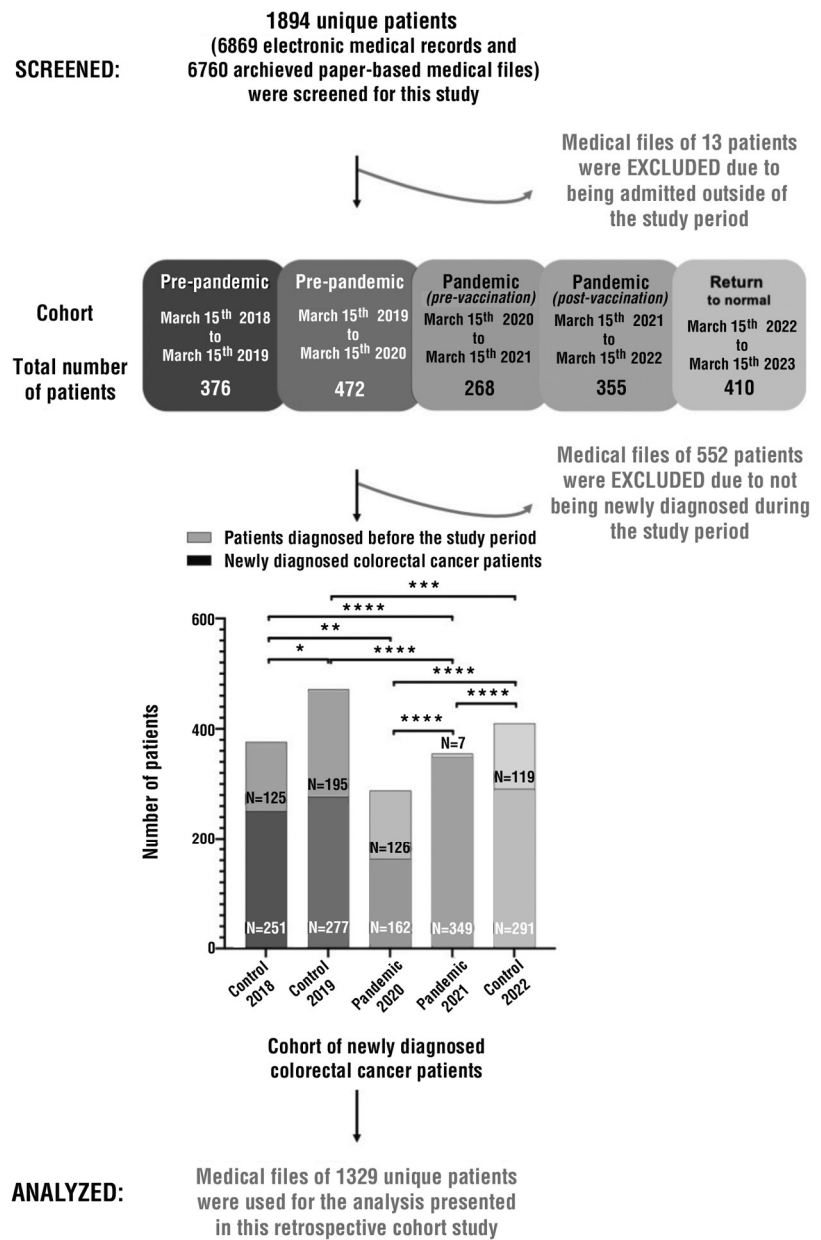


Figure 2. Flow chart of the patients included in/excluded from the retrospective cohort study of colorectal cancer (ICD-10 codes C18-C20) patient presentation conducted at the Clinical County Emergency Hospital of Arad (Romania) from March 15th 2018 to March 15th 2023. The graphical representation of the number of the newly diagnosed colorectal cancer patients (ICD-10 codes C18-C20) was achieved through a stacked bars plot. Statistically significant differences according to Fisher's exact test are marked as follows: * = $P < 0.05$; ** = $P < 0.005$; *** = $P < 0.0005$; **** = $P < 0.0001$.

the lowest (162 patients) and the number of patients admitted for follow-up or complications in the late Covid-19 cohort Pandemic 2021 was drastically reduced – only 7 patients / 356 unique patients admitted that year (*Fig. 2*).

The mean age of all patients included in the study was 68.50 [95% CI (67.90–69.11)] years (*Table 1*). Per study cohort, a slight increase in the age at colorectal cancer diagnosis is observed throughout the non-pandemic periods

Table 1. Summary of patient sociodemographic characteristics (age, gender, residence) presented alongside the type of hospital admission and duration of hospitalization of the diagnostic hospital visit for newly diagnosed colorectal cancer patients in the period March 15th 2018 to March 15th 2023 at the Clinical County Emergency Hospital of Arad, Romania

Patient characteristics	All patients – 5-year study period (N=1329)	Control 2018 (N=251)	Control 2019 (N=277)	Pandemic 2020 (N=162)	Pandemic 2021 (N=348)	Control 2022 (N=291)
Age	Mean age (years) (95% Confidence Interval)					
~ All patients	68.50 (67.90-69.11)	68.65 (67.20-70.09)	68.88 (67.52-70.24)	68.52 (66.64-70.40)	67.47 ^a (66.39-68.56)	69.25 ^a (67.99-70.52)
~ Male	67.98 ^b (67.19-68.77)	67.83 (65.99- 69.68)	67.31 ^c (65.41-69.20)	68.23 (66.03-70.55)	67.39 (66.02-68.76)	69.33 (67.68-70.98)
~ Female	69.24 ^b (68.31-70.16)	70.11 (67.95-72.28)	70.63 ^c (68.72- 72.53)	68.86 (65.65-72.07)	67.59 (65.84-69.34)	69.13 (67.20-71.05)
Early onset colorectal cancer (< 50 years)	Number of patients (percentage)					
~ All patients	72 (5.41%)	13 (5.18%)	16 (5.78%)	12 (7.41%)	16 (4.58%)	15 (5.15%)
~ Male	44 (3.31%)	11 (4.38%)	8 (2.89%)	6 (3.70%)	10 (2.87%)	9 (3.09%)
~ Female	28 (2.11%)	2 (0.79%)	8 (2.89%)	6 (3.70%)	6 (1.72%)	6 (2.06%)
Gender	Number of patients (percentage)					
~ Male	773 (58.16%)	147 (58.57%)	146 ^d (52.71%)	97 (59.88%)	202 (58.05%)	181 ^d (62.20%)
~ Female	556 (41.84%)	104 (41.43%)	131 ^d (47.29%)	65 (40.12%)	146 (41.95%)	110 ^d (37.80%)
Residence	Number of patients (percentage)					
~ Urban	826 (62.15%)	136 ^{e,f} (54.18%)	172 (62.09%)	88 ^{g,h} (54.32%)	226 ^{g,i} (64.94%)	204 ^{i,h} (70.10%)
~ Rural	503 (37.85%)	115 ^{e,f} (45.82%)	105 (37.91%)	74 ^{g,h} (45.68%)	122 ^{g,i} (35.06%)	87 ^{i,h} (29.90%)
Hospital admission	Number of patients (percentage)					
~ Emergency	692 (52.07%)	102 ^j (40.64%)	119 ^{k,l} (42.94%)	136 ^{k,m,n} (83.95%)	192 ^{j,l,m} (55.17%)	143 ⁿ (49.14%)
~ Scheduled	637 (47.93%)	149 ^j (59.36%)	158 ^{k,l} (57.04%)	26 ^{k,m,n} (16.05%)	156 ^{j,l,m} (44.83%)	148 ⁿ (50.86%)
Duration hospitalization	Mean number of days (95% Confidence Interval) (days)					
~ Hospitalization at the initial diagnosis	8.99 (8.58-9.40)	10.37 ^{o,p} (9.51-11.19)	10.00 ^{q,r} (9.09-10.91)	10.03 ^{s,t} (8.76-11.3)	7.22 ^{o,q,s} (6.45-7.99)	8.37 ^{p,r,t} (7.44-9.30)

Note: Statistically significant differences according to the unpaired t-test with Welch's correction are marked as follows:

^a - P = 0.0357 (*); ^b - P = 0.0433 (*); ^c - P = 0.0161 (*).

Statistically significant differences in proportion distribution according to Fisher's exact test are marked as follows:

^d - P = 0.0272 (*); ^e - P = 0.0087 (**); ^f - P = 0.0002 (***); ^g - P = 0.0246 (*); ^h - P = 0.0010 (**);
ⁱ - P < 0.0001 (***); ^j - P = 0.0005 (***); ^k - P < 0.0001 (***); ^l - P = 0.0029 (**); ^m - P < 0.0001 (***);
ⁿ - P < 0.0001 (***); ^o - P < 0.0001 (***); ^p - P = 0.0017 (**); ^q - P < 0.0001 (***); ^r - P = 0.0142 (*);
^s - P = 0.0002 (***); ^t - P = 0.0385 (*)

(Control 2018 < Control 2019 < Control 2022). However, during the COVID-19 pandemic, the average age at diagnosis moved against this trend, reaching 68.52 [95% CI (66.64–70.40)] years in the Pandemic 2020 cohort and further decreasing to 67.47 [95% CI (66.39–68.56)] years in the Pandemic 2021 cohort. The only statistically significant difference in between groups was, however, recorded for the late COVID-19 cohort Pandemic 2021 and the Control 2022 cohort, with younger age at diagnosis detected in the former group. Furthermore, our 5-year study assesses that among the reference population of our tertiary care hospital, the average age on diagnosis of colorectal cancer is significantly lower from a statistical point of view for the male population than it is for the female population, with an average of 67.98 [95% CI (67.19–68.77)] for the former, and 69.24 [95% CI (68.31–70.16)] for the latter, respectively. Early onset colorectal cancer is diagnosed in about 5% of the study group, with a slight predominance in male patients and a percentual increase in the Pandemic 2020 cohort despite absolute numerical values not suffering notable changes.

Gender distribution shows a tendency for male patients to be more often diagnosed with colorectal cancer than female patients, in our 5-year study amounting to 58.16%, and 41.84%, respectively (*Table 1*). Among the pre- and post-pandemic cohorts Control 2019 and Control 2022, a statistically significant increase in the number of male patients diagnosed is observed.

According to the demographic analysis, in our 5-year study there were identified 62.15% patients with their residence registered in urban areas and 37.85% in the rural areas. Less than 1% of the patients were reported to have their residence outside the reference jurisdiction of the tertiary hospital. Pre- and post-pandemic statistically significant differences are observed between the Control 2018 and the Control 2022 cohorts. Statistically significant differences between the late COVID-19 period - Pandemic 2021 cohort and the Control 2022 cohort.

The first hospital admission serving as diagnosis visit for colorectal cancer patients

was achieved through either scheduled presentation, when the patients were referred by the family doctor or an external specialist due to suspicion of the pathology based on signs, or emergency presentation in the Emergency Department, due to the presence of clinical symptoms. Both the number and percentage of patients admitted through the Emergency Department prove highly relevant to this retrospective cohort study (*Table 1*). Statistically significant differences were observed among Control and Pandemic cohorts, with most newly diagnosed patients scheduled for their admission based on a referral from a primary care physician in the Control cohorts and the number of Emergency Department admissions peaking in Pandemic 2020 and remaining relatively high in the Pandemic 2021 cohort.

During their first hospital admission, colorectal cancer patients were hospitalized for 8.99 (95% CI [8.58–9.40]) days (*Table 1*). The average number of hospitalization days is observed to show a statistically significantly decrease in the late COVID-19 period – Pandemic 2021 cohort – and the post-pandemic – Control 2022 – cohort.

When diagnosed with colorectal cancer, the patients included in this study were mostly found in Surgery, Gastroenterology, and Oncology wards, specialties trained for the diagnosis (*Table 2*). However, there were instances when patients were diagnosed in wards that are unrelated to colorectal cancer diagnosis, due to their clinical presentation, phenomena increasing in number after the pandemic, slightly observable in the Pandemic 2020 and often noticeable in the Pandemic 2021 and Control 2022 cohorts.

The most frequent comorbidities – above 10% – observed in the 5 cohorts of newly diagnosed colorectal cancer patients are represented by arterial hypertension, ischemic cardiomyopathy, diabetes mellitus, obesity, and non-alcoholic steatohepatitis (*Table 3*). The percentage of patients with comorbidities in the sphere of cardiovascular diseases, such as arterial hypertension, ischemic cardiomyopathy, is however decreasing in the COVID-19

Table 2. Clinical specialties diagnosing new colorectal cancer patients in the period March 15th 2018 to March 15th 2023 at the Clinical County Emergency Hospital of Arad, Romania

Clinical specialty	All patients – 5-year study period (N=1329)	Control cohort 2018 (N=251)	Control cohort 2019 (N=277)	Pandemic cohort 2020 (N=162)	Pandemic cohort 2021 (N=348)	Control cohort 2022 (N=291)
Specialties trained in colorectal cancer diagnosis	Number of patients (percentage)					
General surgery	546 (41.08%)	110 (43.82%)	141 (50.90%)	67 (41.36%)	124 (35.63%)	104 (35.74%)
Medical oncology	334 (22.20%)	43 (17.13%)	78 (28.16%)	37 (22.84%)	114 (32.76%)	62 (21.31%)
Gastroenterology	295 (25.13%)	88 (35.06%)	46 (16.61%)	46 (28.40%)	47 (13.51%)	68 (23.37%)
Internal medicine	30 (2.26%)	4 (1.59%)	6 (2.17%)	2 (1.23%)	7 (2.01%)	11 (3.78%)
TOTAL	1205 (90.67%)	245 ^{a,b} (90.61%)	271 ^{c,d,e} (97.83%)	152 ^{c,f,g} (93.83%)	292 ^{a,d,f} (83.91%)	245 ^{b,e,g} (84.19%)
Other specialties	Number of patients (percentage)					
TOTAL	124 (9.33%)	6 ^{a,b} (2.39%)	6 ^{c,d,e} (2.17%)	10 ^{c,f,g} (6.17%)	56 ^{a,d,f} (16.09%)	46 ^{b,e,g} (15.81%)

Note: Statistically significant differences in proportion distribution according to Fisher's exact test are marked as follows:

^a - P < 0.0001 (***);

^b - P < 0.0001 (***);

^c - P = 0.0121 (*);

^d - P < 0.0001 (***);

^e - P < 0.0001 (***);

^f - P = 0.0012 (*);

^g - P = 0.0004 (***).

pandemic period – Pandemic 2020 and Pandemic 2021 cohorts – despite representing the most common comorbidities of colorectal patients included in this retrospective study. In alignment with these trends, the frequency of diabetes mellitus among the study population also decreases during this period – Pandemic 2020 and Pandemic 2021 cohorts. While not reflected in the percentages, the absolute

number of obese patients remains relatively constant throughout the analyzed cohorts, with an increase in the Control 2019 pre-pandemic cohort. On the other hand, there is an increase observed in the percentage of patients presenting non-alcoholic steatohepatitis that are newly diagnosed with colorectal cancer during the COVID-19 pandemic, in both the Pandemic 2020 and the Pandemic 2021 cohorts.

Table 3. Top 5 most frequent comorbidities for newly diagnosed colorectal cancer patients in the period March 15th 2018 to March 15th 2023 at the Clinical County Emergency Hospital of Arad, Romania

Comorbidity	All patients – 5-year study period (N=1329)	Control 2018 (N=251)	Control 2019 (N=277)	Pandemic 2020 (N=162)	Pandemic 2021 (N=348)	Control 2022 (N=291)
	Number of patients (percentage)					
Arterial hypertension	483 (36.34%)	87 (34.66%)	133 (48.01%)	49 (30.25%)	98 (28.08%)	116 (39.86%)
Diabetes mellitus	221 (16.63%)	43 (17.13%)	61 (22.02%)	14 (8.64%)	47 (13.47%)	53 (18.21%)
Ischemic cardiomyopathy	185 (13.92%)	55 (21.91%)	46 (16.61%)	8 (4.94%)	46 (13.18%)	30 (10.31%)
Obesity	161 (12.11%)	25 (9.96%)	47 (16.97%)	26 (16.05%)	30 (8.60%)	33 (11.34%)
Non-alcoholic steatohepatitis	134 (10.08%)	19 (7.57%)	26 (9.39%)	27 (16.67%)	54 (15.47%)	8 (2.75%)

Complications reported for newly diagnosed colorectal cancer patients on the first hospital visit were grouped as local, systemic, and metastases (*Table 4*). The most common among the patients included in the study are systemic complications, with a large number presenting with secondary anemia. Nevertheless, the

percentage of patients presenting with this complication decreases during the COVID-19 period – Pandemic 2020 and Pandemic 2021 cohorts – increasing above the previous values in the post-pandemic period – Control 2022 cohort. Hypokalemia, on the other hand, is detected most often among colorectal cancer

Table 4. Frequency of complications for newly diagnosed colorectal cancer patients in the period March 15th 2018 to March 15th 2023 at the Clinical County Emergency Hospital of Arad, Romania

Complication type	All patients – 5-year study period (N=1329)	Control 2018 (N=251)	Control 2019 (N=277)	Pandemic 2020 (N=162)	Pandemic 2021 (N=348)	Control 2022 (N=291)
Local complications		Number of patients (percentage)				
Peritumoral adhesion-related disorder	203 (15.27%)	29 (11.55%)	50 (18.05%)	39 (24.07%)	42 (12.03%)	43 (14.78%)
Intestinal occlusion	161 (12.11%)	19 (7.57%)	18 (6.50%)	39 (24.07%)	42 (12.03%)	37 (12.71%)
Localized peritonitis	39 (2.93%)	11 (4.38%)	5 (1.81%)	2 (1.23%)	5 (1.43%)	16 (5.50%)
Intestinal perforation	10 (0.75%)	3 (1.20%)	0	2 (1.23%)	2 (0.57%)	3 (1.03%)
Rectovesical fistula	7 (0.53%)	1 (0.40%)	0	0	2 (0.57%)	4 (1.37%)
Rectovaginal fistula	3 (0.23%)	1 (0.40%)	1 (0.36%)	0	0	1 (0.34%)
TOTAL	384 (28.89%)	64 (25.20%)	74 (26.71%)	82 (50.62%)	93 (26.72%)	104 (35.73%)
Systemic complications		Number of patients (percentage)				
Secondary anemia	546 (41.08%)	117 (46.61%)	131 (47.65%)	48 (29.63%)	91 (26.07%)	159 (54.64%)
Hypokalemia	158 (11.89%)	16 (6.37%)	43 (15.52%)	33 (20.37%)	44 (12.61%)	22 (7.56%)
Cachexia	48 (3.61%)	11 (4.38%)	5 (1.81%)	3 (1.85%)	12 (3.44%)	17 (5.84%)
Thrombocytopenia	46 (3.46%)	6 (2.39%)	5 (1.81%)	8 (4.94%)	13 (3.72%)	14 (4.81%)
Sepsis	38 (2.86%)	9 (3.59%)	4 (1.44%)	3 (1.85%)	8 (2.29%)	14 (4.81%)
Hypovolemic shock	7 (0.53%)	1 (0.40%)	1 (0.36%)	2 (1.23%)	3 (0.86%)	0
TOTAL	843 (63.43%)	160 (63.74%)	189 (68.23%)	97 (59.88%)	171 (49.14%)	226 (77.66%)
Metastases		Number of patients (percentage)				
Hepatic metastases	199 (14.97%)	49 (19.52%)	21 (7.58%)	8 (4.94%)	70 (20.06%)	51 (17.53%)
Lymph node metastases	73 (5.49%)	12 (4.78%)	22 (7.94%)	7 (4.32%)	17 (4.87%)	15 (5.15%)
Pulmonary metastases	64 (4.82%)	13 (5.18%)	7 (2.53%)	3 (1.85%)	18 (5.16%)	23 (7.90%)
Carcinomatosis	49 (3.69%)	16 (6.37%)	6 (2.17%)	4 (2.47%)	11 (3.15%)	12 (4.12%)
TOTAL	385 (28.97%)	90 (35.86%)	56 (20.21%)	22 (13.58%)	116 (33.33%)	101 (34.71%)

patients during the COVID-19 period, affecting most the patients diagnosed in the Pandemic 2020 cohort. The most common local complication is represented by peritumoral adhesion-related disorder, followed by intestinal occlusion. The percentage of patients presenting with both the local complications is drastically increased in the Pandemic 2020 cohort, while the values return in the following periods analyzed.

The most common metastatic site on colorectal cancer diagnosis among our patients is the liver, with approximately 15% (5-year analysis) already having developed hepatic metastases of colorectal cancer by the time their primary tumor is diagnosed (*Table 4*).

The specific ICD-10 colorectal cancer diagnosis code of the patients included in the study is generally proportional with the number of cases reported in the respective cohort (*Table 5*). However, it is notable that the only increase is observed for the malignant

neoplasm of hepatic flexure diagnosis (ICD-10 code C18.3), which accounts in the early COVID-19 period Pandemic 2020 cohort for its highest absolute value of 10 cases. It can also be noted that the percentage of malignant neoplasm of rectosigmoid junction diagnosis (ICD-10 code C19.0) is decreasing after the Control 2018 and Control 2019 cohorts. An alarming increase in the percentage of the malignant neoplasms of colon with unspecified localization (ICD-10 code C18.9) is observed in the late COVID-19 period – Pandemic 2021 – cohort and the post-pandemic period, Control 2022 cohort.

Discussion

The COVID-19 pandemic represented a multifaceted global burden. In addition to the SARS-CoV-2 viral infection and its devastating effects on health worldwide, the disease has negatively impacted patients through several

Table 5. Distribution of colorectal cancer specific diagnosis according to the ICD-10 classification for newly diagnosed colorectal cancer patients in the period March 15th 2018 to March 15th 2023 at the Clinical County Emergency Hospital of Arad, Romania

ICD-10 diagnosis code	All patients – 5-year study period (N=1329)	Control 2018 (N=251)	Control 2019 (N=277)	Pandemic 2020 (N=162)	Pandemic 2021 (N=348)	Control 2022 (N=291)
	Number of patients (percentage)					
C18.0 - Malignant neoplasm of cecum	70 (5.27%)	16 (6.37%)	11 (3.97%)	10 (6.17%)	19 (5.46%)	14 (4.81%)
C18.2 - Malignant neoplasm of ascending colon	165 (12.19%)	28 (11.16%)	39 (14.08%)	23 (14.20%)	34 (9.77%)	41 (14.09%)
C18.3 - Malignant neoplasm of hepatic flexure	39 (2.94%)	6 (2.39%)	9 (3.25%)	10 (6.17%)	9 (2.59%)	5 (1.72%)
C18.4 - Malignant neoplasm of transverse colon	75 (5.64%)	14 (5.58%)	17 (6.14%)	7 (4.32%)	14 (4.02%)	23 (7.9%)
C18.5 - Malignant neoplasm of splenic flexure	40 (3.01%)	7 (2.79%)	9 (3.25%)	3 (1.85%)	17 (4.89%)	4 (1.37%)
C18.6 - Malignant neoplasm of descending colon	72 (5.42%)	11 (4.38%)	16 (5.78%)	8 (4.94%)	20 (5.75%)	17 (5.84%)
C18.7 - Malignant neoplasm of sigmoid colon	245 (17.83%)	36 (14.34%)	61 (22.02%)	29 (17.90%)	65 (18.68%)	5 (17.87%)
C18.8 - Malignant neoplasm of overlapping sites of colon	57 (4.29%)	10 (3.98%)	11 (3.97%)	8 (4.94%)	17 (4.89%)	52 (3.78%)
C18.9 - Malignant neoplasm of colon. unspecified	116 (8.73%)	9 (3.59%)	9 (3.25%)	12 (7.41%)	45 (12.93%)	11 (14.09%)
C19.0 - Malignant neoplasm of rectosigmoid junction	156 (11.74%)	48 (19.12%)	27 (9.75%)	21 (12.96%)	29 (8.33%)	41 (10.65%)
C20.0 - Malignant neoplasm of rectum	296 (21.67%)	66 (26.29%)	68 (24.55%)	31 (19.14%)	79 (22.70%)	52 (17.87%)

mechanisms, posing as a significant risk for indirect morbidity and mortality from other preventable and treatable diseases, as a result of essential healthcare services disruption (20). These mechanisms included restricted access to public healthcare facilities for cases that did not represent an emergency due to the legislation adopted in the hope of limiting the spread of the viral disease (*Fig. 1*) (11-14), shortage of staff in healthcare facilities due to quarantine periods and SARS-CoV-2-related deaths of medical personnel (21), shortage of medicines and personal protective equipment (22), and shortage of hospital beds available due to the high number of critical SARS-CoV-2-infected patients (23). On the other hand, people were shy to visit healthcare facilities, due to fear of SARS-CoV-2 infection (24) and the freedom of circulation and availability of transportation were also impacted for intermittent periods of time, especially during the early COVID-19 pandemic period (11-14).

According to our retrospective cohort study, the number of newly diagnosed patients decreased significantly, with more than one third as compared with pre-pandemic Control 2018 and Control 2019 cohorts, in the early COVID-19 period Pandemic 2020 cohort, and more than doubled in the late COVID-19 period Pandemic 2021 cohort. According to the scientific literature, a delay in the diagnosis of colorectal cancer has reported between 5.4 - 26% during the COVID-19 pandemic (25). According to a modeling study incurring a 3-month delay in diagnosis of colorectal cancer, a reduction in the 10-year net survival of colorectal cancer patients in the United Kingdom is estimated to range from 10.22% to 16.36% among different patient age groups (26). This would represent a setback the progress achieved in increasing survival to the values from 2010, impacting both patient lives and clinical management of colorectal cancer cases.

Nevertheless, the most worrying finding of our retrospective cohort study was incidental and infers the poor outcome of the patients treated in the early COVID-19 period, pandemic 2020 cohort, due to the lack of follow-up/

treatment/re-intervention visits in the 2nd pandemic year. Only 7 (1.93%) out of the 362 unique patients with colorectal cancer from the period March 15th 2021 – March 15th 2022 were diagnosed prior to this period. According to the ESMO guidelines for metastatic colorectal cancer, the follow-up visits after treatment are suggested at every 3 months during the first 2 years (27), however the COVID-19 pandemic revision of the guidelines mark follow-up visits as “low priority” in the epidemiological context.

Considering the advanced age of colorectal cancer diagnosis assessed to be 68.50 [95% CI (67.90–69.11)] years for our reference population, an average that situates itself around the literature quoted values of 70 years (27), it is relevant that it coincides with the population at risk for complications of the SARS-CoV-2 infection (28). Individuals in the 60–69 age group presented a case fatality rate of 3.5% in Italy and 3.6% in China coupled with the extremely common need for hospitalization (29). During the pandemic, the age of colorectal cancer diagnosis decreased to 67.47 [95% CI (66.39–68.56)] years (Pandemic 2021 cohort), trend opposing the one observed in Italy for colorectal cancer diagnosis during this global crisis (30). Fortunately, the age at colorectal cancer diagnosis increases in the post-pandemic period to 69.25 [95% CI (67.99–70.52)] years in the Control 2022 cohort, surpassing the pre-pandemic cohorts. This trend is mainly based on the variations in the average age of female patients, while the age of male patients only briefly fluctuates. The statistically significant difference in age between male [67.98 (95% CI (67.19–68.77)) years] and female {69.24 years [95% CI (68.31–70.16)]} patients is observed in our 5-year retrospective study, results aligned with the scientific literature, and explained by the fact that a large proportion of women are diagnosed with colorectal cancer at advanced age – in Germany, 27.3% of colorectal cancer female patients are diagnosed at > 80 years old (31).

Despite a global increase in the number of early onset colorectal cancer patients (32), in our study the proportion of patients < 50 years

old gravitates around the 5-year average of 5.41%, peaking in the Pandemic 2020 cohort (7.41%), but returns to values similar to the pre-pandemic in the upcoming period.

Particularities of the region are represented by the post-pandemic enlarged gender gap – statistically significant increase of the percentage of males, from 52.71% in the Control 2019 to 62.20% in the Control 2022 cohort – and population living in urban areas - statistically significant increase from 54.18% in the Control 2018 to 70.10% in the Control 2022 cohort. While the data follows the trends worldwide (1), the COVID-19 pandemic seems to have accentuated the disparities in lifestyle and dietary habits (33), putting urban male population at a higher risk than ever before for developing colorectal cancer.

During the COVID-19 pandemic the admission of colorectal cancer patients was done predominantly through the Emergency Room – peaking for the Pandemic 2020 cohort with 83.95% of patients, descending in the upcoming periods to 55.17% in the late COVID-19 period Pandemic 2021 and further reaching 49.14% in the Control 2022 cohort. This coincides with the decreasing trend in the number of hospitalizations of colorectal cancer patients at their first diagnostic visit, decreasing from 10.00 [95% CI (8.76–11.30)] for the Pandemic 2018 to 8.37 [95% CI (7.44–9.30)] days for the Control 2022 cohort. While the internal and international guidelines suggested a reduction of in-hospital stay to a minimum (34-36), colorectal cancer patients presented themselves to the first diagnosis visit in a more advanced stage with local complications such as peritumoral adhesion-related disorder, occlusion, and perforation requiring a longer hospitalization time. Moreover, ever since the COVID-19 period, cohort Pandemic 2020, there is an increasing trend in the percentage of patients incidentally diagnosed with colorectal cancer during their hospitalization for symptoms pertaining to specialties outside the normal sphere of diagnosis. This is continued in the Control 2022 cohort, accounting for 15.81% of the newly diagnosed colorectal cancer patients. One plausible reason behind this

could be the late presentation of patients to the hospital, correlating with also with the increased age of diagnosis observed for the same cohort.

In what concerns complications experienced by colorectal cancer patients, there is a decrease in the frequency of secondary anemia for newly diagnosed colorectal cancer patients during the COVID-19 pandemic period. Anemia at any level should be considered as an important negative prognosis factor for colorectal cancer in the pre-operative stage (36,37). Distant metastases of colorectal cancer – a prognosis for poorer survival (38) – such as hepatic metastases also decrease in frequency during the early COVID-19 pandemic period, but they increase drastically in the following year in the Pandemic 2021 cohort. Increased frequencies of adhesion-related disorder, intestinal occlusion, and hypokalemia are observed in the early COVID-19 period in the Pandemic 2020 cohort. Epidemiological studies report electrolyte imbalances in COVID-19 patients, with studies reporting around 40% of the SARS-CoV-2 hospitalized patients as hypokalemic (39,40). The gradual increase of thrombocytopenia was observed since the beginning of the COVID-19 pandemic. Thrombocytopenia is uncommon in the initial presentation after the SARS-CoV-2 infection, but it reflects disease severity due to the ability of the virus to activate platelets and it also represents a rare side effect of the vaccine (41). With a large percentage of population either undergoing at least one SARS-CoV-2 infection and/or antiviral vaccination (42), the steady increase in thrombocytopenia as secondary diagnosis could be rationalized.

The most prevalent comorbidities among colorectal cancer patients were in the sphere of cardiovascular diseases, which constitute both risk and negative prognosis factors for the development of colorectal cancer (43,44). In our study, however, there is a decrease during the COVID-19 period observed in the percentage of colorectal cancer patients presenting arterial hypertension and ischemic cardiomyopathy as comorbidities. Yet another risk factor of colorectal cancer, diabetes

mellitus (45), also decreases in frequency in our study cohorts during the COVID-19 period. The only risk-factor of colorectal cancer (46) that increases during the COVID-19 period in our study group is non-alcoholic steatohepatitis. SARS-CoV-2 infection was observed to produce mild-to-moderate liver dysfunction in about one-third of the patients, with prevalence greater in men than women, and in the elderly population (47), which could explain the observed increase in frequency of this comorbidity.

While it remains the leading diagnosis among colorectal cancers, the malignant neoplasm of the rectum starts decreasing in the COVID-19 period, reaching its lowest value in the Pandemic 2020 cohort.

Through this retrospective cohort study, we would like to underline the particularities posed by the newly diagnosed colorectal cancer patients in the reference population of our hospital during the COVID-19 pandemic. Comparing five 1-year cohorts from both the pre- and post-pandemic period allowed for the description of shifting scenarios in patient characteristics in a statistically significant manner. We hope that the high frequency colorectal cancer patient characteristics observed could be addressed by primary prevention campaigns in the reference and global risk groups.

Conclusions

Through this 5-year retrospective cohort analysis conducted on 1329 patients it was observed that the average age at colorectal cancer diagnosis decreased during the early COVID-19 period, with patients showing a higher proportion of early onset (< 50 years) colorectal cancer diagnosis, affecting primarily the male population with a constantly increasing predisposition for those residing in urban areas. Moreover, since the pandemic, there has been a steady increase in the number of colorectal cancer patients diagnosed in wards that do not have a specific focus on the disease, due to patient presentation with complications and comorbidities on

their initial diagnosis visit. A peak of colorectal cancer diagnosis through emergency hospital admission was reached in the early COVID-19 period. The most common colorectal cancer diagnosis of patients in our reference population is malignant neoplasm of the rectum (ICD-10 code C20.0), while the most common complications are peritumoral adherence-related disorder, occlusion, and perforation, encountered in patients presenting with comorbidities such as arterial hypertension, ischemic cardiomyopathy, diabetes mellitus, obesity, and non-alcoholic steatohepatitis.

Supplementary Materials

The supporting information containing the anonymized raw data used in the presented analysis (sociodemographic features – age, gender, area of residence – type of hospital admission, clinical on which the patient was diagnosed with colorectal cancer, number of days of hospitalization, specific ICD-10 code, associated diagnosis, evolution, complications, and comorbidities) and the results pertaining to the statistic tests conducted on the data set can be obtained upon request from the authors.

Acknowledgments

We would like to thank Professor Dr. Adrian Marius Maghiar and Professor Dr. Florin Bodog for fruitful discussions and unconditional support. We would like to thank medical students Melisa Levin Cherim, David Pralea, Ines Dorya Djerroud, David Matei and Alexandru Mihai Avram for their involvement in the research project.

Authors' Contributions

Conceptualization, Octavian Adrian Maghiar, Mircea Șandor, Teodor Andrei Maghiar, Endre Mathe, Carmen Neamțu, Ovidiu Laurean Pop, Bogdan Dan Totolici, Andreea-Adriana Neamțu; Methodology, Octavian Adrian Maghiar, Mircea Șandor, Teodor Andrei Maghiar, Adina Pop-Moldovan, Endre Mathe, Andreea-Adriana Neamțu; Formal Analysis,

Octavian Adrian Maghiar, Violeta Turcuș, Teodor Andrei Maghiar, Alin Bodog, Violeta Turcuș, Cristina-Adriana Dehelean; Investigation, Mircea Șandor, Andrei Ardelean, Carmen Neamțu, Ovidiu Laurean Pop, Bogdan Dan Totolici, Andreea-Adriana Neamțu; Resources, Carmen Neamțu, Ovidiu Laurean Pop, Bogdan Dan Totolici; Data Curation, Mădălina-Andrada Blaj, Marius Belean, Andrei Ardelean, Violeta Turcuș, Teodor Andrei Maghiar, Alin Bodog; Writing – Original Draft Preparation, Octavian Adrian Maghiar, Mircea Șandor, Teodor Andrei Maghiar; Ovidiu Laurean Pop, Andreea-Adriana Neamțu; Writing – Review & Editing, Octavian Adrian Maghiar, Mircea Șandor, Teodor Andrei Maghiar, Adina Pop-Moldovan, Endre Mathe, Carmen Neamțu, Ovidiu Laurean Pop, Bogdan Dan Totolici, Andreea-Adriana Neamțu; Visualization, Mădălina-Andrada Blaj, Marius Belean, Adina Pop-Moldovan, Cristina-Adriana Dehelean; Supervision, Carmen Neamțu, Ovidiu Laurean Pop, Bogdan Dan Totolici, Andreea-Adriana Neamțu; Project Administration, Carmen Neamțu, Bogdan Dan Totolici, Andreea-Adriana Neamțu; Funding Acquisition, Carmen Neamțu, Bogdan Dan Totolici.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

This research received no external funding.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Clinical County Emergency Hospital of Arad, Romania (Protocol Registration Number 56, approved on June 14th, 2023).

Informed Consent Statement

Informed consent was obtained from all sub-

jects involved in the study. An informed consent for anonymized, unidentifiable patient data usage for publication was signed by all patients at the time of their hospitalization. No personal identifiers are disclosed through the publication of this manuscript.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. European Cancer Information System. Colorectal cancer burden in EU-27. European Commission. 2021. Available from: https://ecis.jrc.ec.europa.eu/pdf/Colorectal_cancer_factsheet-Mar_2021.pdf
3. The Global Cancer Observatory. GLOBOCAN 2020. World Health Organization, International Agency for Research on Cancer. 2021
4. The Global Cancer Observatory. Romania - GLOBOCAN 2020. World Health Organization, International Agency for Research on Cancer. 2021
5. Brenner H, Altenhofen L, Stock C, Hoffmeister M. Natural history of colorectal adenomas: Birth cohort analysis among 3.6 million participants of screening colonoscopy. *Cancer Epidemiol Biomarkers Prev*. 2013;22(6):1043-51.
6. Biller LH, Schrag D. Diagnosis and treatment of metastatic colorectal cancer: a review. *Jama*. 2021;325(7):669-685.
7. Brown KGM, Solomon MJ. Progress and future direction in the management of advanced colorectal cancer. *J Brit Surg*. 2018;105(6):615-617.
8. Ganesh K, Stadler ZK, Cercek A, Mendelsohn RB, Shia J, Segal NH, et al. Immunotherapy in colorectal cancer: rationale, challenges and potential. *Nat Rev Gastroenterol Hepatol*. 2019;16(6):361-375.
9. Messersmith W. NCCN Guidelines Updates: Management of Metastatic Colorectal Cancer. *J Natl Compr Canc Netw*. 2019;17(5.5):599-601.
10. World Health Organization. Coronavirus disease (COVID-19) pandemic. 2023. Available from: <https://www.who.int/europe/emergencies/situations/covid-19>
11. Decretul Presedintelui României nr. 195/2020 privind instituirea stării de urgență pe teritoriul României. 2020. Available from: <https://www.onrc.ro/index.php/ro/legislatie/legislatie-covid19>. Romanian
12. Decretul Presedintelui României nr. 240/2020 privind prelungirea stării de urgență pe teritoriul României. 2020. Available from: <https://www.onrc.ro/index.php/ro/legislatie/legislatie-covid19>. Romanian
13. Hotărârea Comitetului Național pentru Situații de Urgență nr. 24 din 14 mai 2020. 2020. Available from: <https://www.onrc.ro/index.php/ro/legislatie/legislatie-covid19>. Romanian
14. Hotărârea Parlamentului României nr. 5/2020. 2020. Available from: <https://www.onrc.ro/index.php/ro/legislatie/legislatie-covid19>. Romanian
15. Hotărârea de Guvern nr. 171 din 03 februarie 2022. 2022. Available from: <https://www.onrc.ro/index.php/ro/legislatie/legislatie-covid19>. Romanian
16. Ministerul Afacerilor Interne. Comunicat de presă 8 martie 2022. 2022. Available from: <https://www.mai.gov.ro/comunicat-de-presa-313/>. Romanian
17. Alshahrani MS, Alfaraj D, AlHumaid J, Alshahrani K, Alsabaie A, Almulhim N, et al. Prevalence, Causes, and Adverse Clinical Impact of Delayed Presentation of Non-COVID-19-Related Emergencies during the COVID-19 Pandemic: Findings from a Multicenter Observational Study. *Int J Environ Res Public Health*. 2022;19(16):9818.
18. Alam W, Bouferra Y, Haibe Y, Mukherji D, Shamseddine A. Management of colorectal cancer in the era of COVID-19: Challenges and suggestions. *Sci Prog*. 2021;104(2):368504211010626.
19. Institutul Național de Statistică. Recensământul Populației și Locuințelor. Romania. 2021. Available from: <https://www.recensamantromania.ro/rezultate-rpl-2021/rezultate-definitive-caracteristici-demografice/>. Romanian
20. Department of Health and Social Care, Office for National Statistics, Government Actuary's Department and Home Office. Direct and Indirect

- Impacts of COVID-19 on Excess Deaths and Morbidity. United Kingdom. 2020. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/907616/s0650-direct-indirect-impacts-covid-19-excess-deaths-morbidity-sage-48.pdf
21. Nyashanu M, Pfende F, Ekenyong M. Exploring the challenges faced by frontline workers in health and social care amid the COVID-19 pandemic: experiences of frontline workers in the English Midlands region, UK. *J Interprofessional Care*. 2020;34(5):655-661.
 22. Choo EK, Rajkumar SV. Medication shortages during the COVID-19 crisis: what we must do. *Elsevier Mayo Clinic Proceedings*. 2020;95(6):1112-1115.
 23. Massonnaud C, Roux J, Crépey P. COVID-19: Forecasting short term hospital needs in France. *Medrxiv*. 2020.
 24. Einav S, Tankel, J. The unseen pandemic: treatment delays and loss to follow-up due to fear of COVID. *J Anesthesia, Analgesia and Critical Care*. 2022;2(1):5.
 25. Pirozzi BM, Siragusa L, Baldini G, Pellicciaro M, Grande M, Efrati C, et al. Influence of COVID-19 Pandemic on Colorectal Cancer Presentation, Management and Outcome during the COVID-19 Pandemic. *J Clin Med*. 2023;12(4):1425.
 26. Sud T, Broggio J, Loveday S, Gronthoud G, Jhanji N, Williams B, et al. Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: a modelling study. *The Lancet Oncol*. 2020.
 27. Young CJ, Sweeney JL, Hunter, A. Implications of delayed diagnosis in colorectal cancer. *Australian and New Zealand J Surg*. 2000;70(9):635-638.
 28. Vishnevetsky A, Levy M. Rethinking high-risk groups in COVID-19. *Multiple sclerosis and related disorders*. 2020;42.
 29. Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. *Jama*. 2020;323(14):1335-1335.
 30. Mazidimoradi A, Hadavandsiri F, Momenimovahed Z, Salehiniya H. Impact of the COVID-19 Pandemic on Colorectal Cancer Diagnosis and Treatment: a Systematic Review. *J Gastrointest Cancer*. 2023;54(1):171-187.
 31. Schmuck R, Gerken M, Teegen EM, Krebs I, Klinkhammer-Schalke M, Aigner F, et al. Gender comparison of clinical, histopathological, therapeutic and outcome factors in 185,967 colon cancer patients. *Langenbecks Arch Surg*. 2020;405(1):71-80.
 32. Sinicrope FA. Increasing Incidence of Early-Onset Colorectal Cancer. *N Engl J Med*. 2022;386(16):1547-1558.
 33. Kinoshita K, Ozato N, Yamaguchi T, Bushita H, Sudo M, Yamashiro Y, et al. Association of the COVID-19 pandemic with changes in objectively measured sedentary behaviour and adiposity. *Int J Obes (Lond)*. 2023;47(5):375-381.
 34. Pertile D, Gipponi M, Aprile A, Batistotti P, Ferrari CM, Massobrio A, et al. Colorectal Cancer Surgery During the COVID-19 Pandemic: A Single Center Experience. *In Vivo*. 2021;35(2):1299-1305.
 35. Morris EJ, Goldacre R, Spata E, Mafham M, Finan PJ, Shelton J, et al. Impact of the COVID-19 pandemic on the detection and management of colorectal cancer in England: a population-based study. *The Lancet Gastroenterol Hep*. 2021;6(3):199-208.
 36. Curigliano G, Banerjee S, Cervantes A, Garassino MC, Garrido P, Girard N, et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. *Ann Oncol*. 2020;31(10):1320-1335.
 37. Gvirtzman R, Livovsky DM, Tahover E, Goldin E, Koslowsky B. Anemia can predict the prognosis of colorectal cancer in the pre-operative stage: a retrospective analysis. *World J Surg Oncol*. 2021;19(1):341.
 38. Wang J, Li S, Liu Y, Zhang C, Li H, Lai B. Metastatic patterns and survival outcomes in patients with stage IV colon cancer: A population-based analysis. *Cancer Med*. 2020;9(1):361-373.
 39. Chen D, Li X, Song Q, Hu C, Su F, Dai J. Hypokalemia and clinical implications in patients with coronavirus disease 2019 (COVID-19). *MedRxiv*. 2020.
 40. Alfano G, Ferrari A, Fontana F, Perrone R, Mori G, Ascione E. Hypokalemia in patients with COVID-19. *Clinical and experimental nephrology*. 2021;25:401-409.
 41. Iba T, Levy JH. Thrombosis and thrombocytopenia in COVID-19 and after COVID-19 vaccination. *Trends Cardiovasc Med*. 2022;32(5):249-256.
 42. Marcau FC, Purec S, Niculescu G. Study on the Refusal of Vaccination against COVID-19 in Romania. *Vaccines (Basel)*. 2022;10(2):261.
 43. Xuan K, Zhao T, Sun C, Patel AS, Liu H, Chen X, et al. The association between hypertension and colorectal cancer: a meta-analysis of observational studies. *Eur J Cancer Prev*. 2021;30(1):84-96.
 44. Flynn DE, Mao D, Yerkovich ST, Franz R, Iswariah H, Hughes A. The impact of comorbidities on post-operative complications following colorectal cancer surgery. *PLoS One*. 2020;15(12):0243995.
 45. Ahmadi A, Mobasheri M, Hashemi-Nazari SS, Baradaran A, Choobini ZM. Prevalence of hypertension and type 2 diabetes mellitus in patients with colorectal cancer and their median survival time: A cohort study. *J Res Med Sci*. 2014;19(9):850-854.
 46. Tapper EB, Fleming C, Rendon A, Fernandes J, Johansen, P, Augusto M, et al. The burden of non-alcoholic steatohepatitis: A systematic review of epidemiology studies. *Gastro Hep Advances*. 2022;1:1049-1087.
 47. Portincasa P, Krawczyk M, Machill A, Lammert F, Di Ciaula A. Hepatic consequences of COVID-19 infection. Lapping or biting?. *Eur J Int Med*. 2020;77:18-24.