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Early-onset colorectal cancer in Lebanon: clinical presentation, molecular features and outcomes in a 618-patient cohort

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Abstract

Background

The incidence of early-onset colorectal cancer (EOCRC), diagnosed before age 50, is rising in many countries, but data from the Middle East and North Africa remain scarce. We compared the clinical presentation, pathological and molecular characteristics, and outcomes of EOCRC and later-onset colorectal cancer (LOCRC) in a Lebanese cohort.

Methods

This retrospective single-center study included all consecutive patients with colorectal adenocarcinoma diagnosed at a tertiary referral center in Beirut, Lebanon, between January 2017 and July 2026. Characteristics were compared between age groups with correction for multiple testing, associations with EOCRC were explored by multivariable logistic regression, and overall survival by Kaplan–Meier and Cox models.

Results

Of 618 patients, 92 (14.9%) had EOCRC, 35.9% of whom were aged 45–49 years; none was detected by screening colonoscopy. Compared with LOCRC, patients with EOCRC more often had a predisposing condition (inflammatory bowel disease or hereditary syndrome: 10.2% vs 2.3%; q = 0.013), a family history of colorectal cancer (29.7% vs 12.3%; q = 0.020) and mucinous or signet-ring histology (19.2% vs 8.1%; q = 0.014). Deficient mismatch repair (dMMR) was more frequent in EOCRC (29.0% vs 11.3%; q = 0.001), with a higher proportion of loss patterns suggestive of Lynch syndrome (45.0% vs 19.1% of dMMR tumors; p = 0.038). In exploratory multivariable analysis, six characteristics remained associated with EOCRC: a predisposing condition (OR 3.55; 95% CI 1.28–9.90), dMMR (OR 4.42; 2.15–9.11), rectal bleeding (OR 2.21; 1.29–3.79), mucinous or signet-ring histology (OR 2.71; 1.28–5.74), left-colon location (OR 1.78; 1.05–3.01) and metastatic disease at diagnosis (OR 1.97; 1.12–3.48). After adjustment for sex and stage, overall survival did not differ significantly between age groups (HR 1.50; 95% CI 0.87–2.59).

Conclusions

In this Lebanese cohort, approximately one in seven patients with colorectal cancer was diagnosed before age 50, more than one third of them at 45–49 years. EOCRC was associated with predisposing conditions, dMMR, mucinous or signet-ring histology and rectal bleeding, whereas stage-adjusted survival did not differ significantly. These findings support universal tumor MMR testing with hereditary

cancer evaluation, prompt investigation of rectal bleeding in young adults and evaluation of earlier screening in Lebanon.

Background

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death worldwide [1]. While its incidence has declined among older adults in several high-income countries, partly because of screening and the removal of precursor lesions, it has increased among adults younger than 50 years [2, 3]. In a recent analysis of population-based registries from 50 countries and territories, the incidence of early-onset colorectal cancer (EOCRC) increased in 27 of them [2]. In the United States, the proportion of CRC diagnosed before age 55 nearly doubled, from 11% in 1995 to 20% in 2019 [3]. In 20 European countries, incidence in adults aged 20–49 years increased between 1990 and 2016, most steeply in those aged 20–29 years (7.9% per year since 2004) [4].

Compared with later-onset disease, EOCRC more frequently involves the distal colon and rectum, presents with rectal bleeding or abdominal pain, and is diagnosed at an advanced stage [3, 5–7]. Hereditary predisposition also plays a larger role in EOCRC: 16% to 20% of patients carry a pathogenic germline variant, most often in a Lynch syndrome gene [8, 9]. About one in ten has a mismatch repair-deficient (dMMR) tumor, and most of these tumors are related to Lynch syndrome [8]. However, a large comprehensive series suggests that, beyond location and symptoms, EOCRC is clinically and genomically similar to average-onset disease [10]. The prognostic impact of young age also remains debated: population-based and trial data have shown similar or even better survival in younger patients [11, 12].

Data from the Middle East and North Africa (MENA) region remain scarce. Series from Arab countries report that about 25% to 46% of CRC occur in young adults (before age 45 or 50, depending on the series), a higher proportion than in Western countries, partly reflecting younger populations [13–15]. Most MENA countries lack an organized screening program, and about one third of patients with CRC are diagnosed with distant metastases [16, 17]. In Lebanon, CRC is the fourth most common cancer, with an estimated 1,644 new cases in 2024 [18], and the national cancer registry reported higher age-specific incidence rates at 40–49 years than in the United States [19]. Yet data on the clinicopathological and molecular features of EOCRC in Lebanon remain limited, although they are needed to guide hereditary cancer evaluation, the recognition of warning symptoms and screening policies.

We aimed to compare the clinical, pathological and molecular characteristics of EOCRC and later-onset colorectal cancer (LOCRC) in a Lebanese tertiary-care cohort, and to explore differences in stage at diagnosis, treatment and survival.

Methods

Ethical approval

The study was approved by the Ethics Committee of Hôtel-Dieu de France, Saint Joseph University of Beirut, on December 17, 2025 (reference CEHDF-2858), and was conducted in accordance with the Declaration of Helsinki. As this was a retrospective review of anonymized medical records, the need for informed consent was waived by the Ethics Committee of Hôtel-Dieu de France.

Study design and population

We conducted a retrospective single-center cohort study at a tertiary referral center in Beirut, Lebanon. We included all consecutive patients with histologically confirmed adenocarcinoma of the colon or rectum, including intramucosal carcinoma (pTis, stage 0), diagnosed between January 2017 and July 2026. Other histological types (neuroendocrine neoplasms, lymphomas and squamous cell carcinomas of the anal canal) and appendiceal tumors were not included. No formal sample size calculation was performed. The main comparisons and the survival analysis were repeated after excluding pTis. Patients were identified and their clinical and pathological data extracted from electronic health records and pathology reports into a standardized, anonymized database. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [20].

Definitions

Early-onset colorectal cancer (EOCRC) was defined as age < 50 years at diagnosis and later-onset colorectal cancer (LOCRC) as age ≥ 50 years. EOCRC was further divided into three age bands: < 40, 40–44 and 45–49 years. Tumor location was classified as right colon (cecum to transverse colon), left colon (descending colon, sigmoid colon and rectosigmoid junction) or rectum. Mucinous and signet-ring cell adenocarcinomas, defined by a mucinous or signet-ring cell component of more than 50%, were grouped as mucinous or signet-ring histology. Stage at diagnosis was assigned according to the American Joint Committee on Cancer (AJCC) 8th edition. It corresponded to the pathological stage in patients who underwent upfront resection and to the pretreatment clinical stage in patients who received neoadjuvant chemotherapy or radiotherapy or did not undergo resection; the post-treatment ypTNM stage was not used. Patients with synchronous distant metastases on initial staging were classified as stage IV.

Mismatch-repair (MMR) status was assessed by immunohistochemistry for MLH1, MSH2, MSH6 and PMS2; loss of at least one protein defined deficient MMR (dMMR), and retained expression of all four proteins defined proficient MMR (pMMR). Among dMMR tumors, loss of MLH1 (with or without PMS2) was distinguished from other patterns (loss of MSH2 with or without MSH6, isolated MSH6 or isolated PMS2), which are more suggestive of Lynch syndrome. KRAS, NRAS and BRAF status was recorded when tested in routine care. A predisposing condition was defined as inflammatory bowel disease (IBD) or a known hereditary syndrome (Lynch syndrome, familial adenomatous polyposis, MUTYH-associated polyposis, Peutz–Jeghers syndrome or juvenile polyposis). Family history was defined as colorectal cancer in a first- or second-degree relative.

Mode of detection was recorded as a single, mutually exclusive category corresponding to the circumstance that led to diagnosis: screening colonoscopy, polyp surveillance colonoscopy, symptoms,

emergency presentation (obstruction or perforation), incidental finding on imaging, positive fecal immunochemical test (FIT) or work-up of anemia or iron deficiency. The symptom-to-diagnosis interval was the time between the first symptom and the histological diagnosis. Overall survival (OS) was defined as the time from diagnosis to death from any cause; patients alive at last contact were censored at that date.

Statistical analysis

Categorical variables are reported as n (%) and continuous variables as median [interquartile range, IQR]; percentages were calculated among patients with available data. EOCRC and LOCRC were compared with the χ^2 test, Fisher's exact test or a Monte Carlo exact test for sparse tables, and with the Mann–Whitney U test for continuous variables. False discovery rate-adjusted q-values were calculated with the Benjamini–Hochberg procedure [21] across all 102 comparisons between age groups (Additional file 1: Table S1). Subgroup analyses (MMR loss patterns among dMMR tumors, tumor location by MMR status and analyses restricted to patients with metastatic disease) were considered exploratory and are reported with nominal p-values.

Characteristics associated with EOCRC rather than LOCRC were explored by multivariable logistic regression. Thirteen binary candidate variables were prespecified on clinical grounds among those available for at least 75% of patients: sex, obesity, current or former smoking, a predisposing condition, rectal bleeding, abdominal pain, anemia, weight loss, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, left-colon location (versus right colon or rectum), mucinous or signet-ring histology, dMMR and metastatic disease at diagnosis. Missing data, which ranged from 0% to 21.5% (MMR status), were handled by multiple imputation by chained equations with logistic regression imputation models (20 datasets, 10 iterations), and estimates were combined with Rubin's rules [22]. In the main model, all 13 candidates were entered simultaneously. As a sensitivity analysis, backward selection based on pooled Wald tests (removal at $p \geq 0.05$) was performed, with sex retained as a prespecified adjustment variable. The discrimination of the selected model was summarized by the area under the receiver operating characteristic (ROC) curve (AUC), corrected for optimism by bootstrap (200 resamples, repeating imputation and selection in each), and the stability of each variable by the proportion of resamples in which it was selected. Further sensitivity analyses included a complete-case analysis of the selected model, without imputation, and a reduced model including only sex and the characteristics associated with EOCRC in the main model. Technical details are provided in Additional file 1: Table S2.

OS was estimated with the Kaplan–Meier method and compared with the log-rank test; median follow-up was estimated with the reverse Kaplan–Meier method. The date of diagnosis was the time origin in all survival analyses. Patients without documented follow-up after diagnosis were excluded from all survival analyses and compared with included patients. Hazard ratios (HR) were estimated with Cox models adjusted for sex and stage in patients with known stage and in stage 0–III disease, and in stage IV disease both without and with adjustment for sex, performance status and number of metastatic sites.

The proportional hazards assumption was checked with scaled Schoenfeld residuals, and a model stratified by stage was fitted as a sensitivity analysis. Additional survival sensitivity analyses are reported in Additional file 1: Table S3.

All tests were two-sided with a significance level of 0.05. Analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria) using RStudio version 2026.01.2 (Posit Software, Boston, MA, USA), with the mice package for multiple imputation, pROC for ROC analysis and survival for time-to-event analyses. The completed STROBE checklist is provided in Additional file 2.

Use of generative artificial intelligence

Generative AI tools (Claude, Anthropic; ChatGPT, OpenAI) assisted with language editing and the literature search, which was completed and verified by the authors in PubMed. The authors reviewed and edited all content, verified all data, analyses and references, and take full responsibility for the content of the publication.

Results

Study population and clinical presentation

Of the 618 patients included (median age 66 years [IQR 56–75]; 56.1% men), 92 (14.9%; 95% CI 12.2–17.9) had EOCRC (Figure 1). Their median age was 42 years [IQR 38–45], compared with 69 years [62–77] in LOCRC (Additional file 1: Figure S1). Among patients with EOCRC, 32 (34.8%) were younger than 40 years, 27 (29.3%) were aged 40–44 years and 33 (35.9%) were aged 45–49 years. Patients came from all Lebanese governorates, mainly Mount Lebanon (40.0%) and Beirut (28.2%), without difference between age groups (p = 0.30; Additional file 1: Table S1). Excluding the 30 patients with pTis (4 EOCRC and 26 LOCRC) had little effect on the proportion of EOCRC (15.0%) or the main comparisons (Additional file 1: Tables S3 and S4).

The sex distribution was similar in both groups (43.5% vs 43.9% women; Table 1). A predisposing condition was more frequent in EOCRC (10.2% vs 2.3%; q = 0.013), including IBD in 5 patients and a known hereditary syndrome in 4 (Lynch syndrome in 2 and familial adenomatous polyposis in 2). A family history of colorectal cancer in a first- or second-degree relative was also more frequent in EOCRC (29.7% vs 12.3% of patients with documented family history; q = 0.020). As expected with age, diabetes (4.5% vs 25.2%), hypertension (7.9% vs 59.9%) and dyslipidemia (3.4% vs 43.5%) were much less frequent in EOCRC (all q < 0.001; Additional file 1: Table S1), whereas body mass index, obesity and smoking did not differ between groups.

Symptoms led to the diagnosis in most patients of both groups (67.5% vs 66.9%). No EOCRC was detected by screening colonoscopy, compared with 12 LOCRC (2.5%); a positive FIT led to the diagnosis in 3 EOCRC (3.8%) and 20 LOCRC (4.1%), and polyp surveillance in 4 (5.0%) and 9 (1.9%), respectively. Emergency presentation occurred in 15.0% of EOCRC and 9.5% of LOCRC, and the overall mode of

detection did not differ between groups (p = 0.20). Rectal bleeding was more frequent in EOCRC (43.9% vs 31.5%; p = 0.029). Abdominal pain was reported by 45.1% of EOCRC and 37.9% of LOCRC, and anemia by 30.5% and 40.0%, respectively. The median symptom-to-diagnosis interval was 1 month in both groups (p = 0.23).

Histological and molecular profile

Mucinous or signet-ring histology was twice as frequent in EOCRC (19.2% vs 8.1%; q = 0.014; Table 2). Left-colon location was numerically more frequent in EOCRC (40.9% vs 31.7%) and right-colon location less frequent (31.8% vs 40.1%), with a similar proportion of rectal cancers (27.3% vs 28.1%; p = 0.20). Stage III–IV disease (59/86, 68.6% vs 257/448, 57.4% of staged patients; p = 0.052) and synchronous metastases (34/90, 37.8% vs 146/511, 28.6% of patients with known metastatic status; p = 0.079) were also numerically more frequent in EOCRC. More lymph nodes were examined in resected EOCRC (median 28 vs 21; q = 0.021), and lymphovascular invasion was less frequent (44.2% vs 61.5%; p = 0.018; q = 0.059).

MMR status was available for a similar proportion of patients in both groups (75.0% vs 79.1%; p = 0.38). dMMR was found in 20 of 69 EOCRC (29.0%) and 47 of 416 LOCRC (11.3%; q = 0.001), with a similar frequency in the three EOCRC age bands (25.0%, 33.3% and 30.0% in patients aged < 40, 40–44 and 45–49 years; Figure 2). A loss pattern other than MLH1 was more frequent in dMMR EOCRC than in dMMR LOCRC (9 of 20, 45.0% vs 9 of 47, 19.1%; p = 0.038) and included loss of MSH2 with or without MSH6 in 7 EOCRC (35.0%). BRAF was tested in only 10 of 49 MLH1-deficient tumors and was mutated in none of 3 EOCRC and 4 of 7 LOCRC. In EOCRC, dMMR tumors were mainly right-sided (12 of 20, 60.0%), whereas the left colon was the most frequent location of pMMR tumors (23 of 48, 47.9%; p = 0.006). The same association between dMMR and right-sided location was observed in LOCRC (82.2% of dMMR tumors were right-sided; p < 0.001), without interaction between age group and MMR status (p = 0.55). Overall, more than half of right-sided EOCRC with known MMR status were dMMR (12 of 22, 54.5%), compared with 22.7% of right-sided LOCRC.

RAS and BRAF were tested in a minority of patients, mostly with metastatic disease, and more often in EOCRC than in LOCRC (KRAS 32.6% vs 21.3%, p = 0.017; BRAF 25.0% vs 14.6%, p = 0.013), which limits the comparability of mutation frequencies. When tested, KRAS mutations were found in 30.0% of EOCRC and 38.4% of LOCRC (p = 0.40), NRAS mutations in none and 7.8% (p = 0.33), and BRAF mutations in 4.3% and 14.3% (p = 0.29).

Exploratory multivariable analysis

In the main model including all 13 candidate variables, six characteristics were associated with EOCRC rather than LOCRC (Figure 3): a predisposing condition (odds ratio [OR] 3.55; 95% CI 1.28–9.90), dMMR (OR 4.42; 2.15–9.11), rectal bleeding at presentation (OR 2.21; 1.29–3.79), mucinous or signet-ring histology (OR 2.71; 1.28–5.74), left-colon location (OR 1.78; 1.05–3.01) and metastatic disease at diagnosis (OR 1.97; 1.12–3.48). These six associations persisted in a model restricted to these

characteristics and sex, and after backward selection, which additionally retained anemia with an inverse association (OR 0.55; 0.31–0.96). In bootstrap resamples, dMMR (96%) and rectal bleeding (87%) were the most consistently selected variables, followed by a predisposing condition (74%), metastatic disease (71%), mucinous or signet-ring histology (70%) and left-colon location (62%), whereas anemia was selected in only 51% of resamples. The selected model had an apparent AUC of 0.73 and an optimism-corrected AUC of 0.68. When the analysis was restricted to the 431 patients without missing data for the selected variables (complete-case analysis), the associations with a predisposing condition (OR 2.19; 0.53–8.15), left-colon location (OR 1.76; 0.92–3.38) and metastatic disease (OR 1.79; 0.87–3.59) were weaker and no longer statistically significant, whereas those with dMMR, rectal bleeding and mucinous or signet-ring histology remained significant (Additional file 1: Table S2).

Metastatic disease and survival

Among the 180 patients with synchronous metastases (34 EOCRC and 146 LOCRC), the liver was the most frequent site in both groups (82.4% vs 77.4%; Table 3), whereas lung metastases were less frequent in EOCRC (11.8% vs 28.1%; p = 0.048). Primary tumor resection (67.6% vs 69.4%) and metastasectomy (29.4% vs 23.7%) were performed at similar rates. In unadjusted exploratory comparisons of treatments received at any time during follow-up, patients with metastatic EOCRC more often received two or more lines of systemic therapy, anti-VEGF and anti-EGFR agents and immunotherapy (Table 3).

Survival analyses included 512 patients (79 EOCRC and 433 LOCRC); 106 patients without follow-up after diagnosis were excluded (Figure 1): 80 were seen only at diagnosis and 26 had missing follow-up data. Excluded patients were older (median 73.5 vs 65 years) and less often had stage IV disease (17.4% vs 36.8%), whereas the proportion of EOCRC was similar (12.3% vs 15.4%; p = 0.40). Median follow-up was 20 months (36 months in EOCRC and 18 months in LOCRC), and 73 deaths occurred. Three-year OS was 74.6% (95% CI 60.5–84.3) in EOCRC and 85.6% (80.2–89.6) in LOCRC (log-rank p = 0.082; Figure 4). After adjustment for sex and stage (448 patients with known stage, 68 deaths), EOCRC was not significantly associated with mortality (HR 1.50; 95% CI 0.87–2.59; p = 0.15). The proportional hazards assumption was not rejected globally (p = 0.39), for age group (p = 0.35) or for stage (p = 0.27), and a stage-stratified model yielded a similar estimate (HR 1.43; 0.82–2.49). Survival did not differ in stage 0–III disease (adjusted HR 0.92; 0.27–3.18). In stage IV disease, 3-year OS was 42.5% in EOCRC and 68.0% in LOCRC, with only 7 and 40 patients at risk at 36 months; this difference was not statistically significant (unadjusted HR 1.78; 0.97–3.26; p = 0.062) and was further attenuated after adjustment for sex, performance status and number of metastatic sites (Additional file 1: Table S3).

Discussion

In this Lebanese cohort, approximately one in seven patients with colorectal cancer was diagnosed before age 50, more than one third of them at 45–49 years. Younger patients more frequently had a predisposing condition or a family history of colorectal cancer, and their tumors were more often dMMR

or of mucinous or signet-ring histology. Rectal bleeding, left-colon location and metastatic disease at diagnosis were also associated with younger age in exploratory multivariable analysis, although the associations with left-colon location and metastatic disease were less robust in sensitivity analyses. These are features associated with younger age at diagnosis rather than risk factors for developing colorectal cancer. Almost half of dMMR EOCRC showed a loss pattern other than MLH1, which warrants further evaluation for Lynch syndrome. These findings highlight the importance of recognizing possible hereditary predisposition, investigating rectal bleeding in young adults and evaluating earlier screening.

EOCRC in Lebanon and the region

The proportion of EOCRC in our cohort (14.9%) is close to that reported in the United States National Cancer Database (13.3%) [11], but lower than in the Lebanese national registry for 2005–2016 (22.6%) [19] and in hospital series from Oman (32.6%), Qatar (24.8% at age 45 or younger) and the United Arab Emirates (46%) [13–15]. Differences in case definition (the national registry included all malignant tumors coded C18–C21, including appendiceal and anal canal tumors [19]), population age structure, referral patterns and registry coverage probably explain much of this gap. In the absence of an organized screening program in Lebanon [16], no EOCRC in our cohort was detected by screening colonoscopy, and among all patients with a documented mode of detection, only 6.2% were diagnosed by screening colonoscopy or a positive FIT and 2.3% during polyp surveillance. These findings are consistent with a Lebanese multicenter series from 2005–2010, in which screening accounted for only 3% of CRC diagnoses [23]. In line with this low rate of screen detection, the 30.0% of patients with synchronous metastases in our cohort lies within the 26%–45% range of stage IV disease reported by MENA population-based registries [17].

Of patients with EOCRC, 35.9% were aged 45–49 years, an age group eligible for average-risk screening in the United States [24], and the Lebanese national registry has reported high incidence rates at ages 40–49 years [19]. Whether screening from age 45 would offer similar benefits in Lebanon needs to be assessed in population-based studies [16]. Patients with hereditary predisposition or other high-risk conditions require earlier surveillance.

Mismatch-repair deficiency and hereditary predisposition

The frequency of dMMR in EOCRC (20 of 69, 29.0%) was more than twice that observed in LOCRC and similar across the three EOCRC age bands. This proportion is higher than in other series of EOCRC, including 10.7% in an Ohio multicenter study of 450 patients [8], 19% among Jordanian patients aged 45 years or younger [25] and 7.8% in an Omani cohort [14]. The higher frequency of dMMR in EOCRC than in later-onset disease is, however, consistent with previous reports of more frequent high microsatellite instability in younger patients [26]. Only two young patients had a documented diagnosis of Lynch syndrome, which can account for only a small part of this excess. Nevertheless, part of the dMMR excess may be hereditary. A family history of colorectal cancer was more than twice as frequent in EOCRC (29.7% vs 12.3%), and 45% of dMMR EOCRC had a loss pattern other than MLH1, most often MSH2 with or without MSH6. Combined loss of MLH1 and PMS2 is frequently due to sporadic MLH1

promoter hypermethylation, often with a BRAF V600E mutation, particularly in older patients, whereas loss of MSH2/MSH6 or isolated loss of MSH6 or PMS2 warrants evaluation for Lynch syndrome [27]. Consistent with this, BRAF mutations were found only in older patients with MLH1-deficient tumors in our cohort, although few were tested; in other Lebanese series, BRAF mutations were reported in 7.0–7.5% of tested CRC [28,29]. Immunohistochemistry alone, however, cannot establish a diagnosis of Lynch syndrome, and without systematic germline testing we could not determine whether hereditary predisposition was under-recognized. These findings support universal tumor MMR testing of all colorectal cancers, followed by the recommended diagnostic algorithm, including MLH1 promoter methylation or BRAF testing for MLH1/PMS2-deficient tumors, and germline testing when indicated [27].

Tumor profiles and clinical presentation

Mucinous or signet-ring histology was twice as frequent in EOCRC, as in regional series from Oman and Qatar [14,15], and signet-ring histology was most frequent in the youngest patients of a large North American series [26]. In EOCRC, dMMR tumors were mostly right-sided, whereas pMMR tumors were most often located in the left colon. More than half of right-sided EOCRC were dMMR, compared with less than one quarter of right-sided LOCRC. A right-sided tumor in a young patient should therefore raise particular suspicion of MMR deficiency. Distal pMMR tumors nevertheless remained the most frequent presentation of EOCRC, as in large Western series [5,10,26]. The rising incidence of EOCRC mainly involves such distal tumors and has been attributed to environmental and lifestyle exposures [5,6]. Rectal bleeding, consistent with this predominance of distal tumors, was more frequent in young patients, in line with claims-based data identifying rectal bleeding, abdominal pain, diarrhea and iron-deficiency anemia as red flags that precede the diagnosis of EOCRC by months [30]. In a matched study of rectal cancer, the median interval from symptom onset to treatment was 217 days in patients younger than 50 years, compared with 29.5 days in older patients, mainly because of delays before the first medical consultation and slower referral [31]; such delays may reflect a tendency to attribute rectal bleeding to benign anorectal disease in young adults. The symptom-to-diagnosis interval did not differ by age in our cohort, whereas a systematic review reported long intervals in younger adults [32]; this interval may have been underestimated by retrospective recording.

Prognosis and clinical implications

Synchronous metastatic disease was numerically more frequent in EOCRC, consistent with American population-based data [3,11]. After adjustment for sex and stage, the risk of death did not differ significantly between age groups, although the confidence interval did not exclude a clinically relevant increase in risk in younger patients; this is consistent with literature suggesting that younger age does not uniformly confer a survival advantage [11,12]. Although patients with metastatic EOCRC more frequently received targeted therapies and immunotherapy, these unadjusted comparisons may reflect differences in molecular characteristics, treatment eligibility and follow-up duration, as well as age-related treatment decisions. In a large US cohort, younger patients with colon cancer received more intensive treatment without corresponding survival gains [33].

Strengths and limitations

This study adds to the limited data on EOCRC from the MENA region, with contemporary clinical, pathological and molecular data from consecutive patients over nearly ten years, MMR status available in more than three quarters of patients and similar testing rates in both age groups. Correction for multiple testing was applied across all 102 comparisons, missing data in the exploratory multivariable analysis were addressed by multiple imputation, and model stability was assessed using bootstrap resampling.

This study also has limitations. First, its retrospective single-center design in a tertiary referral center exposes it to selection bias and may limit generalizability, although patients came from all Lebanese governorates. Second, some variables were frequently missing, particularly family history and RAS and BRAF status. About one quarter of EOCRC lacked MMR results and testing varied by stage, so that the dMMR frequency refers only to tumors with available results; MLH1 promoter methylation was not tested, BRAF status was available for only 12 of 67 dMMR tumors (10 of 49 with MLH1 loss) and germline testing was not systematic, which precluded distinguishing sporadic from hereditary dMMR tumors. Third, survival was a secondary objective, as prognostic factors of CRC have already been examined in other Lebanese cohorts [23,28]; our survival analysis was limited by a short follow-up that differed by age group and by the exclusion of 106 patients without follow-up. Fourth, the multivariable analysis was exploratory, with a limited number of EOCRC cases relative to the number of variables examined. Some associations were less robust in complete-case and bootstrap analyses, and the model should not be interpreted as a validated prediction tool. Finally, the observational design does not allow causal inference, and lifestyle exposures such as diet and physical activity were not recorded.

Conclusion

In this Lebanese cohort, approximately one in seven patients with colorectal cancer was younger than 50 years at diagnosis, and more than one third of them were aged 45–49 years. EOCRC was characterized by a higher frequency of predisposing conditions, dMMR tumors and mucinous or signet-ring histology, and more often presented with rectal bleeding. The high proportion of dMMR tumors, including loss patterns suggestive of Lynch syndrome, reinforces the importance of universal tumor MMR testing and appropriate hereditary cancer evaluation. Rectal bleeding in young adults should prompt endoscopic investigation rather than being attributed to benign anorectal disease. The proportion of patients diagnosed between ages 45 and 49 further supports evaluating the potential role of earlier colorectal cancer screening in Lebanon through population-based studies.

Abbreviations

AJCC, American Joint Committee on Cancer; AUC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; dMMR, deficient mismatch repair;

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EOCRC, early-onset colorectal cancer; FIT, fecal immunochemical test; HR, hazard ratio; IBD, inflammatory bowel disease; IQR, interquartile range; LOCRC, later-onset colorectal cancer; MENA, Middle East and North Africa; MMR, mismatch repair; OR, odds ratio; OS, overall survival; pMMR, proficient mismatch repair; pTis, intramucosal carcinoma; ROC, receiver operating characteristic; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; VEGF, vascular endothelial growth factor.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Hôtel-Dieu de France, Saint Joseph University of Beirut, on December 17, 2025 (reference CEHDF-2858), and was conducted in accordance with the Declaration of Helsinki. Because of the retrospective design and the use of anonymized data, the need for informed consent was waived by the Ethics Committee of Hôtel-Dieu de France.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are not publicly available because of patient confidentiality but are available from the corresponding author on reasonable request, subject to approval by the Ethics Committee of Hôtel-Dieu de France.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PW and JA conceived and designed the study. PW and LA collected the data. PW curated the data and wrote the first draft of the manuscript. AK and CY performed the statistical analysis. LA, EM, KH and RS contributed to the interpretation of the data and critically revised the manuscript. JA supervised the study and critically revised the manuscript. All authors read and approved the final manuscript.

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Not applicable.

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Tables

Table 1. Patient characteristics and clinical presentation by age at diagnosis

Characteristic	EOCRC (n = 92)	LOCRC (n = 526)	p	q
Age, years, median [IQR]	42 [38–45]	69 [62–77]	—	—
Female sex	40 (43.5)	231 (43.9)	0.94	1.00
BMI, kg/m², median [IQR]	25.5 [22.7–29.6]	25.4 [22.4–28.4]	0.47	0.56
BMI ≥ 30 kg/m²	20 (23.8)	82 (17.0)	0.24	0.37
Current or former smoking	32 (36.4)	221 (43.2)	0.49	0.57
Inflammatory bowel disease	5 (5.6)	4 (0.8)	0.005	0.020
Known hereditary syndrome	4 (4.5)	8 (1.5)	0.081	0.19
Predisposing condition (IBD or hereditary syndrome)	9 (10.2)	12 (2.3)	0.001	0.013
Family history of CRC, first or second degree	11/37 (29.7)	35/284 (12.3)	0.004	0.020
Diabetes	4 (4.5)	131 (25.2)	< 0.001	< 0.001
Hypertension	7 (7.9)	312 (59.9)	< 0.001	< 0.001
Aspirin use	2 (2.2)	108 (20.8)	< 0.001	< 0.001
ECOG performance status ≥ 2	4 (4.5)	26 (5.3)	1.00	1.00
Mode of detection (EOCRC N = 80; LOCRC N = 484)			0.20	0.33
Symptoms	54 (67.5)	324 (66.9)		
Emergency (obstruction or perforation)	12 (15.0)	46 (9.5)		
Screening colonoscopy	0 (0.0)	12 (2.5)		
Positive FIT	3 (3.8)	20 (4.1)		
Polyp surveillance	4 (5.0)	9 (1.9)		
Anemia or iron deficiency work-up	6 (7.5)	44 (9.1)		
Incidental finding on imaging	1 (1.2)	29 (6.0)		
Rectal bleeding (hematochezia)	36 (43.9)	153 (31.5)	0.055	0.15
Abdominal pain	37 (45.1)	184 (37.9)	0.22	0.36
Anemia	25 (30.5)	193 (40.0)	0.10	0.21

Characteristic	EOCRC (n = 92)	LOCRC (n = 526)	p	q
Weight loss	13 (16.0)	117 (25.4)	0.068	0.17
Symptom-to-diagnosis interval, months, median [IQR]	1.0 [1.0–3.0]	1.0 [0.4–3.0]	0.23	0.36

Values are n (%) among patients with available data, unless stated otherwise. q-values were calculated with the Benjamini–Hochberg procedure across 102 comparisons. p-value for the whole categorical variable (BMI classes, smoking never/former/current, mode of detection, rectal bleeding none/hematochezia/melena). Among patients with documented family history. Mode of detection is a single, mutually exclusive category. The multivariable model used hematochezia as a binary variable (nominal p = 0.029 for hematochezia vs none or melena). Numbers of patients with missing data for each variable are given in Additional file 1: Table S1.

Table 2. Tumor characteristics, stage, molecular profile and treatment by age at diagnosis

Characteristic	EOCRC (n = 92)	LOCRC (n = 526)	p	q
Tumor location			0.20	0.33
Right colon	28 (31.8)	201 (40.1)		
Left colon	36 (40.9)	159 (31.7)		
Rectum	24 (27.3)	141 (28.1)		
Mucinous or signet-ring cell histology	15/78 (19.2)	39/482 (8.1)	0.002	0.014
Grade □			0.13	0.24
Well differentiated	17 (26.6)	63 (16.3)		
Moderately differentiated	39 (60.9)	274 (71.0)		
Poorly differentiated	8 (12.5)	49 (12.7)		
Stage (AJCC 8th edition)			0.32	0.43
0	4 (4.7)	26 (5.8)		
I	9 (10.5)	47 (10.5)		
II	14 (16.3)	118 (26.3)		
III	25 (29.1)	111 (24.8)		
IV	34 (39.5)	146 (32.6)		
Stage III–IV	59 (68.6)	257 (57.4)	0.052	0.14
Lymph nodes examined, median [IQR] □	28 [17.5–41.5]	21 [14–31]	0.005	0.021
Lymphovascular invasion □	23/52 (44.2)	209/340 (61.5)	0.018	0.059
MMR status tested	69 (75.0)	416 (79.1)	0.38	—
Deficient MMR (dMMR)	20 (29.0)	47 (11.3)	< 0.001	0.001
Loss pattern other than MLH1, among dMMR	9/20 (45.0)	9/47 (19.1)	0.038	—
KRAS mutation, among tested	9/30 (30.0)	43/112 (38.4)	0.40	0.49
NRAS mutation, among tested	0/23 (0.0)	6/77 (7.8)	0.33	0.43
BRAF mutation, among tested	1/23 (4.3)	11/77 (14.3)	0.29	0.41
Surgery	77/92 (83.7)	424/505 (84.0)	0.95	1.00
Neoadjuvant radiotherapy	7/89 (7.9)	66/456 (14.5)	0.094	0.20

Characteristic	EOCRC (n = 92)	LOCRC (n = 526)	p	q
Adjuvant chemotherapy	29/85 (34.1)	114/441 (25.9)	0.12	0.22

Values are n (%) among patients with available data, unless stated otherwise. q-values were calculated across 102 comparisons; — = no q-value (secondary comparison, not part of the 102 comparisons corrected for multiple testing). Stage percentages are among staged patients (86 EOCRC and 448 LOCRC). Treatment percentages are among all patients with available treatment data, irrespective of stage or treatment indication, and are not treatment rates among eligible patients. p-value for the three grades. Among resected tumors.

Table 3. Metastatic disease at diagnosis: sites, treatment and survival by age at diagnosis

Characteristic	EOCRC (n = 34)	LOCRC (n = 146)	p
Liver	28 (82.4)	113 (77.4)	0.53
Liver only	17 (50.0)	67 (45.9)	0.67
Lung	4 (11.8)	41 (28.1)	0.048
Peritoneum	8 (23.5)	29 (19.9)	0.63
Distant lymph nodes	4 (11.8)	15/144 (10.4)	0.76
Bone	2 (5.9)	11 (7.5)	1.00
Brain	2 (5.9)	0 (0.0)	0.035
Two or more metastatic sites	12 (35.3)	54 (37.0)	0.85
ECOG performance status ≥ 2	3/33 (9.1)	9/125 (7.2)	0.72
Primary tumor resection	23 (67.6)	100/144 (69.4)	0.84
Metastasectomy	10 (29.4)	33/139 (23.7)	0.49
At least one line of systemic therapy	34 (100)	112/123 (91.1)	0.12
Two or more lines of systemic therapy	21 (61.8)	50/123 (40.7)	0.029
Anti-VEGF therapy	25/32 (78.1)	67/122 (54.9)	0.017
Anti-EGFR therapy	20/32 (62.5)	45/121 (37.2)	0.010
Immunotherapy	5/32 (15.6)	5/124 (4.0)	0.031
Deaths, stage IV patients with follow-up	15/32	36/133	—
3-year overall survival, % (95% CI)	42.5 (20.4–63.1)	68.0 (56.4–77.1)	0.059 [a]
HR for death, unadjusted (95% CI)	1.78 (0.97–3.26)	1 (reference)	0.062
HR adjusted for sex	1.67 (0.90–3.09)	1 (reference)	0.10
HR adjusted for sex, ECOG ≥ 2 and number of sites [b]	1.41 (0.74–2.66)	1 (reference)	0.29

Values are n (%) unless stated otherwise; denominators are given when data were missing. Treatments are those received at any time during follow-up, and these comparisons are exploratory; missing treatment information was not counted as absence of treatment. [a] Log-rank test. [b] Complete-case analysis (146 patients, 49 deaths).

Figures

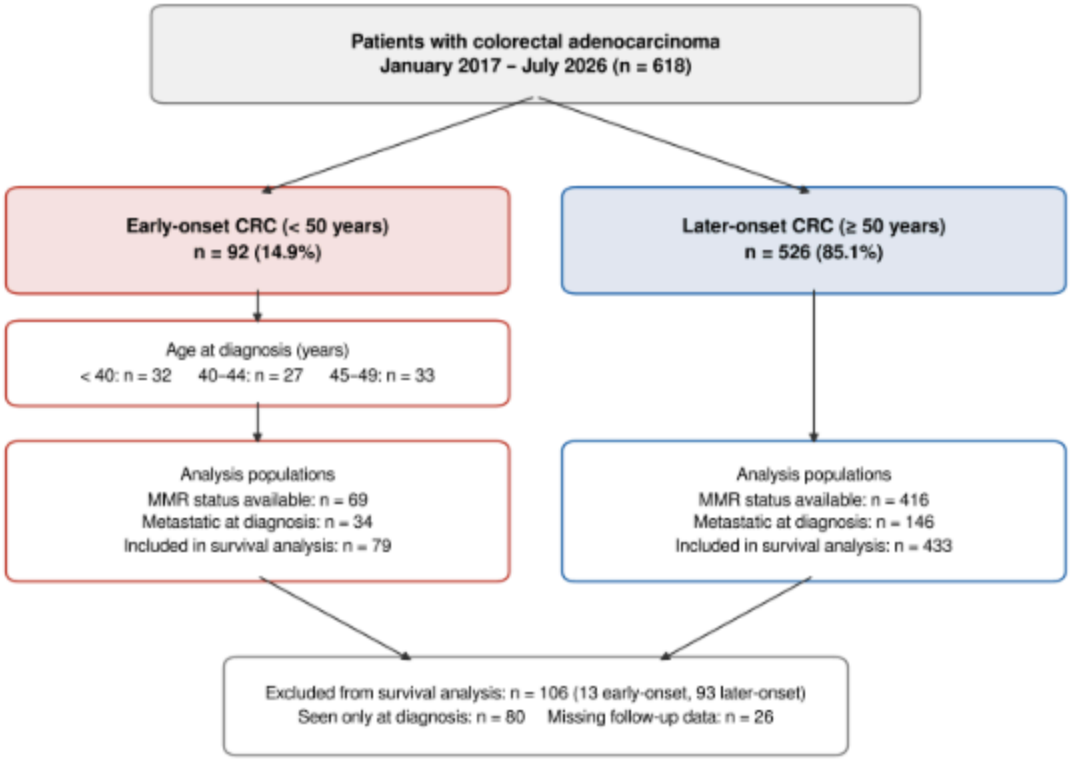


Figure 1

Study flow chart. EOCRC, early-onset colorectal cancer (< 50 years); LOCRC, later-onset colorectal cancer (≥ 50 years); MMR, mismatch repair.

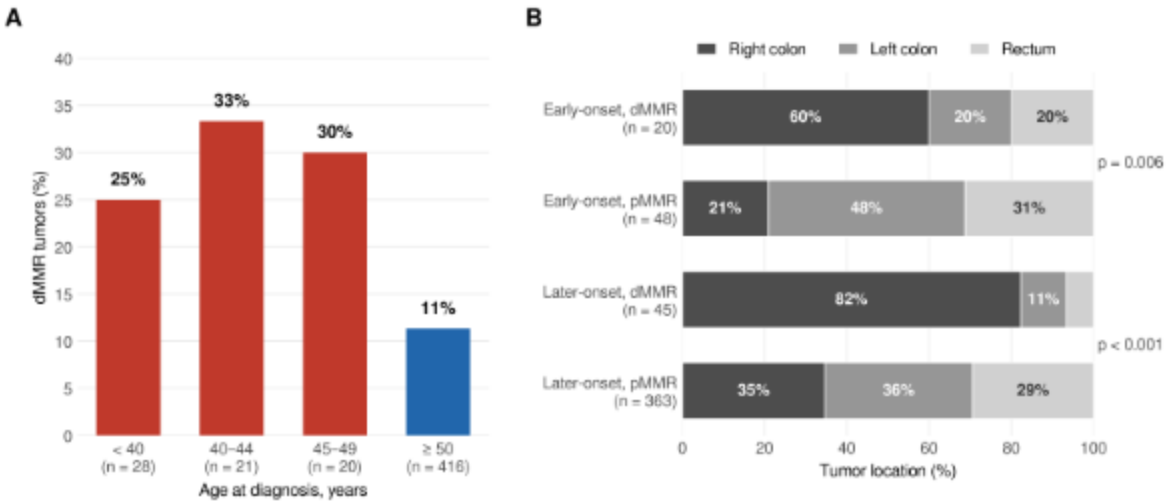


Figure 2

Mismatch-repair deficiency in early-onset colorectal cancer. (A) Proportion of dMMR tumors by age at diagnosis among patients with known MMR status (< 40 years, 7/28; 40–44 years, 7/21; 45–49 years, 6/20; ≥ 50 years, 47/416). (B) Tumor location by MMR status among patients with known MMR status

and tumor location (68 EOCRC and 408 LOCRC); p-values compare location between dMMR and pMMR tumors within each age group (χ^2 test).

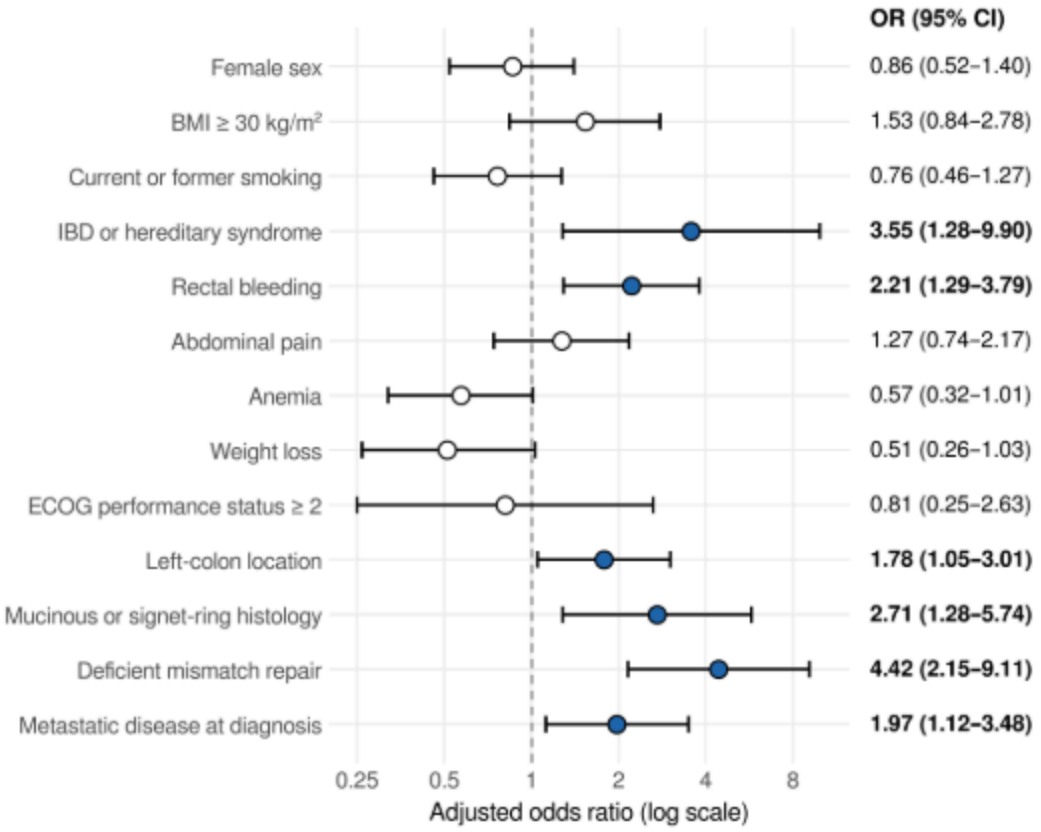


Figure 3

Characteristics associated with early-onset colorectal cancer in exploratory multivariable analysis. Adjusted odds ratios and 95% confidence intervals from the multivariable logistic regression including all 13 candidate variables, after multiple imputation (20 datasets; Rubin's rules). Filled symbols and bold values indicate $p < 0.05$.

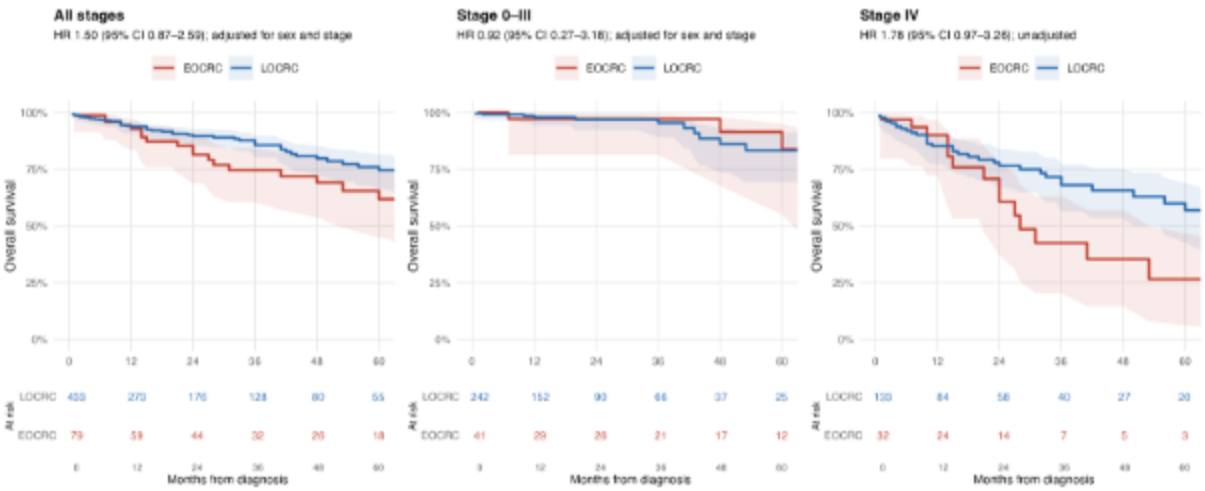


Figure 4

Overall survival by age at diagnosis. Kaplan–Meier curves for all stages, stage 0–III and stage IV, with numbers at risk. Hazard ratios were adjusted for sex and stage (all stages and stage 0–III) or unadjusted (stage IV). The all-stage curves include the 512 patients with follow-up, whereas the stage-adjusted Cox model and the stage-specific panels are restricted to the 448 patients with known stage. Numbers at risk beyond 36 months were small, particularly in stage IV EOCRC, and late estimates should be interpreted with caution.

Supplementary Files

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- Additionalfile1.docx
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