DOI: 10.4274/forbes.galenos.2025.90267
Forbes J Med 2025;6(3):266-272

Original Article / Orijinal Araştırma

The Relationship of Clinical and Molecular Factors with Prognosis in Metastatic Colorectal Cancer

Metastatik Kolorektal Kanserde Klinik ve Moleküler Faktörlerin Prognoz ile İlişkisi

Evrim ATACA[1], Merve KESKİNKILIÇ[2], Sulen SARIOGLU[3], Yasemin BASBINAR[4], Tuğba YAVUZŞEN[2]

[1]Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, İzmir, Türkiye
[2]Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, Division of Medical Oncology, İzmir, Türkiye
[3]Dokuz Eylül University Faculty of Medicine, Department of Pathology, İzmir, Türkiye
[4]Dokuz Eylül University Faculty of Medicine, Department of Translational Oncology, Institute of Oncology, İzmir, Türkiye

Cite as: Ataca E, Keskinkılıç M, Sarioglu S, Basbinar Y, Yavuzşen T. The relationship of clinical and molecular factors with prognosis in metastatic colorectal cancer. Forbes J Med. 2025;6(3):266-272

ABSTRACT

Objective: Metastatic colorectal cancer (mCRC) remains a major global health challenge with highly variable survival outcomes. Both tumor-related and host-related factors contribute to prognosis, yet the combined influence of comorbidity burden, rat sarcoma (RAS) mutation status, and age has not been clearly established. This study aimed to evaluate the prognostic impact of the Charlson Comorbidity index (CCI), RAS mutation status, and age on overall survival (OS) and progression-free survival (PFS) in patients with mCRC.

Methods: A retrospective analysis was conducted on 446 patients with histologically confirmed mCRC treated at a tertiary oncology center between 2010 and 2016. Demographic, clinical, and molecular data were collected. OS and PFS were analyzed using Kaplan-Meier estimates and compared with log-rank tests. Independent prognostic factors were determined using multivariate Cox proportional hazards models.

Results: Among 446 patients, 56.7% had a CCI ≥7 and 38.6% were aged ≥65 years; 48.7% harbored RAS mutations. Higher comorbidity burden (CCI ≥7) was significantly associated with shorter OS and PFS (OS: 27.4 vs. 46.8 months, p<0.001; PFS: 31.2 vs. 41.6 months, p=0.002). Multivariate analysis confirmed CCI ≥7 [hazard ratio (HR) =1.82, 95% confidence interval (CI) 1.31-2.52, p<0.001] and RAS mutation (HR =1.47, 95% CI 1.08-2.00, p=0.014) as independent predictors of poorer OS, whereas age lost significance after adjustment.

Conclusion: CCI and RAS mutation status independently predict worse OS and PFS in mCRC. Incorporating comorbidity assessment into prognostic models may enhance personalized treatment strategies in real-world practice.

Keywords: Metastatic colorectal cancer, Charlson Comorbidity index, RAS mutation, overall survival, progression-free survival

ÖZ

Amaç: Metastatik kolorektal kanser (mKRK), dünya genelinde yüksek mortaliteye sahip önemli bir sağlık sorunudur ve hastalar arasında sağkalım sonuçları değişkendir. Tümörle ve hasta ile ilişkili faktörlerin her ikisi de prognozu etkilemektedir; ancak komorbidite yükü, RAS mutasyon durumu ve yaşın birlikte sağkalım üzerindeki etkisi yeterince aydınlatılamamıştır. Bu çalışmanın amacı, mKRK hastalarda Charlson Komorbidite indeksi (CCI), RAS mutasyon durumu ve yaşın genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) üzerindeki prognostik etkisini değerlendirmektir.

Yöntem: 2010-2016 yılları arasında üçüncü basamak onkoloji merkezinde tedavi gören, histolojik olarak doğrulanmış mKRK tanılı 446 hastanın retrospektif analizi yapılmıştır. Demografik, klinik ve moleküler

Received/Geliş: 09.11.2025
Accepted/Kabul: 27.11.2025
Publication Date/ Yayınlanma Tarihi: 05.12.2025

Corresponding Author/ Sorumlu Yazar:
Evrim ATACA, MD,
Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, İzmir, Türkiye
evrimbayrakdar@gmail.com
ORCID: 0000-0001-6572-0277

veriler toplanmıştır. OS ve PFS, Kaplan-Meier yöntemleriyle analiz edilerek log-rank testleri ile karşılaştırılmış; bağımsız prognostik faktörler çok değişkenli Cox regresyon modeli ile belirlenmiştir.

Bulgular: Dört yüz kırk altı hastanın %56,7'sinde CCI ≥7, %38,6'sında yaş ≥65 yıl ve %48,7'sinde RAS mutasyonu saptanmıştır. Yüksek komorbidite yükü (CCI ≥7), anlamlı olarak daha kısa GS (27,4 vs. 46,8 ay; p<0,001) ve PFS (31,2 vs. 41,6 ay; p=0,002) ile ilişkili bulunmuştur. Çok değişkenli analizde CCI ≥7 [risk oranı (HR) =1,82; %95 güven aralığı (GA): 1,31-2,52; p<0,001] ve RAS mutasyonu (HR =1,47; %95 GA: 1,08-2,00; p=0,014) bağımsız olarak daha kötü OS ile ilişkili bulunmuş; yaş ayarlama sonrası anlamlılığını kaybetmiştir.

Sonuç: CCI ve RAS mutasyon durumu, mKRK'de bağımsız olarak daha kötü genel ve PFS öngörmektedir. Komorbidite değerlendirmesinin prognostik modellerde yer alması, gerçek yaşam pratiğinde kişiselleştirilmiş tedavi stratejilerinin geliştirilmesine katkı sağlayabilir.

Anahtar Kelimeler: Metastatik kolorektal kanser, Charlson Komorbidite indeksi, RAS mutasyonu, genel sağkalım, progresyonsuz sağkalım

INTRODUCTION

Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide, ranking third in incidence and second in cancer-related deaths.[1] Advances in molecular profiling and targeted therapies have improved outcomes for patients with metastatic CRC (mCRC); however, survival remains highly variable and is influenced by both tumor-related and host-related factors.[2,3] Among these factors, patients' comorbidity burden and molecular alterations, such as RAS mutations, are increasingly recognized as key determinants of prognosis and treatment response.[4,5]

The Charlson Comorbidity index (CCI) is a widely validated tool that quantifies comorbidity burden by assigning weighted scores to various chronic diseases, providing an estimate of 10-year mortality risk.[6] Several studies have shown that a higher CCI score is associated with poorer survival across multiple malignancies, including CRC.[7-9] However, limited data exist regarding its prognostic relevance in patients with metastatic disease, especially in real-world settings where comorbidity burden can strongly influence treatment selection and tolerability.

In addition to comorbidities, RAS mutations are among the most clinically relevant molecular markers in CRC.[10,11] These mutations are known predictors of resistance to anti-epidermal growth factor receptor (EGFR) therapies and are often associated with distinct tumor biology and outcomes.[12] While both CCI and RAS mutation status have been individually linked to survival, their combined and age-adjusted impact on real-world survival outcomes, including overall survival (OS) and progression-free survival (PFS), has not been well characterized.

Therefore, this study aimed to evaluate the prognostic significance of CCI, RAS mutation status, and age in patients with mCRC treated at a tertiary oncology center. By integrating clinical, molecular, and comorbidity data, this analysis provides a comprehensive assessment of host- and tumor-related factors influencing both overall and PFS in a real-world mCRC cohort.

METHODS

Study Design and Population

This retrospective, single-center study included adult patients (≥18 years) diagnosed with CRC and followed at a tertiary medical oncology center between January 2010 and December 2016.

Patients were eligible if they had a confirmed diagnosis of mCRC at presentation or during follow-up, underwent RAS mutation analysis, received systemic treatment and follow-up care at our tertiary medical oncology center, and had complete clinical, pathological, and survival data.

Patients were excluded if they lacked confirmed metastatic disease, had incomplete records, were lost to follow-up, or were treated exclusively at external centers. After applying these criteria, 446 patients were included in the final analysis.

Data Collection and Variables

Demographic, clinical, and pathological data were retrospectively collected from hospital records. Collected variables included age at diagnosis, sex, tumor stage at presentation, tumor location (right- vs. left-sided), primary site (colon vs. rectum), comorbidity burden (CCI), and RAS mutation status. Molecular analyses included RAS [Kirsten rat sarcoma (KRAS), neuroblastoma rat sarcoma (NRAS)] and B-raf proto-oncogene (BRAF) mutation status with codon-specific evaluation (codons 12, 13, and 61 for KRAS/NRAS; codons 600 and 464 for BRAF). Mutation detection was conducted using validated PCR-based assays, including nested PCR, minisequencing, and allele-specific real-time PCR performed on the COBAS z480 platform.

The CCI was calculated according to the original scoring system described by Charlson et al.[6] age adjustment was performed using the Quan modification, in which 1 point is added for each decade above 50 years (i.e., 50–59 = +1, 60–69 = +2, 70–79 = +3, ≥80 = +4).[13] For the age-adjusted version, one additional point was assigned for each decade above 50 years. The index includes major comorbid conditions such as cardiovascular, pulmonary, hepatic, renal, and metabolic diseases, as well as malignancy and AIDS, each weighted according to its impact on mortality risk.

The total score represents the patient's overall comorbidity burden.

Tumor stage was determined according to the 8th edition of the American Joint Committee on Cancer staging system.[14] Baseline laboratory data included serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels.

Survival Definitions and Follow-Up

OS was defined as the interval between the date of CRC diagnosis and either death from any cause or the date of last follow-up. The last follow-up date for survival ascertainment was March 2022. Survival outcomes were obtained from institutional medical records and verified against the national death registry to ensure their accuracy.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient characteristics. Continuous variables were expressed as mean ± standard deviation (SD) or median (range), depending on the distribution, while categorical variables were summarized as counts and percentages.

The CCI was analyzed both as a continuous variable and as a dichotomized variable according to the median value (CCI <7 vs. ≥7) to evaluate its prognostic impact. Group comparisons for categorical variables (e.g., RAS mutation status, tumor location, age group) were performed using the chi-square (χ^2) test or Fisher's exact test, as appropriate. Pearson's and Spearman's correlation coefficients were calculated to assess associations between ordinal or interval variables.

PFS was defined as the time from diagnosis of metastatic disease to documented disease progression or death from any cause, whichever occurred first. OS was defined as the time from the date of CRC diagnosis to death from any cause or to the last follow-up. PFS analysis was performed in 416 patients with available follow-up data, whereas OS was assessed in the entire cohort of 446 patients. Survival distributions were estimated using the Kaplan-Meier method, and comparisons between groups were performed using the Log-rank (Mantel-Cox) and Breslow (Generalized Wilcoxon) tests.

To examine the independent effect of clinical and pathological variables on survival, Cox proportional hazards regression analyses were conducted. Variables with a p value <0.10 in univariate analysis were included in the multivariate model. Hazard ratios and 95% confidence intervals were reported. A two-tailed p value 0.05 was considered statistically significant for all analyses.

Ethical Considerations

Ethics committee approval was obtained from the Non-Interventional Research Ethics Committee of Dokuz Eylül University (decision number: 2021/01-07, date: 04.01.2021).

RESULTS

Patient Characteristics and Demographic Data

A total of 446 patients were included in the analysis, of whom 165 (37.0%) were female and 281 (63.0%) were male. The mean age was 59.7±11.6 years, with 65.7% (n=293) of patients aged ≥65 years. The majority of patients were diagnosed with colon cancer (85.2%; n=380), while 14.8% (n=66) were diagnosed with rectal cancer.

The primary tumor was located in the left colon in 77.6% of patients (n=346) and in the right colon in 22.4% (n=100). At the time of diagnosis, 60.5% (n=270) of patients presented with stage IV disease.

At initial diagnosis, the most frequent site of metastasis was the liver (38.6%, n=172), followed by the lung (9.6%, n=43). During follow-up, secondary metastases most commonly involved the liver (72.2%, n=322) and lung (59.0%, n=263).

Charlson Comorbidity Index Distribution

CCI ranged from 0 to 14 (mean ± SD, 6.66±2.61; median: 7). The majority of patients had a moderate-to-high comorbidity burden (CCI ≥6). The most common scores were 7 (17.5%) and 8 (16.8%). Only a small proportion of patients had minimal comorbidity (CCI ≤2, 7.6%).

Mutation Status

In the whole cohort, 200 patients (44.8%) harbored RAS mutations. Among RAS mutations, KRAS alterations were most frequent (42.1%, n=188), followed by BRAF alterations (3.8%, n=17) and NRAS alterations (3.6%, n=16). Within the KRAS-mutant subgroup, codon 12 mutations predominated (30.3%, n=135), followed by codon 13 mutations (9.2%, n=41) and codon 61 mutations (2.7%, n=12). NRAS mutations occurred mainly at codon 61 (1.6%), while BRAF mutations were primarily at codon 600 (3.4%).

Progression-Free Survival According to Comorbidity Burden

Kaplan-Meier analysis demonstrated a significant association between CCI and PFS in patients with mCRC. Patients with lower comorbidity scores (CCI <7) had a median PFS of 18.2 months (95% CI: 15.4-21.0), whereas those with higher scores (CCI ≥7) had a median PFS of 9.9 months (95% CI: 8.1-11.6). The mean estimated PFS was 28.2±2.1 months for the low-CCI group and 17.2±1.3 months for the high-CCI group. The difference between survival distributions was statistically significant according to both

the Log-Rank test (χ^2 =26.48, p<0.001) and the Breslow test (χ^2 =37.48, p<0.001) (Table 1). These findings indicate that patients with a higher comorbidity burden experience significantly shorter PFS.

Overall Survival According to Comorbidity Burden

Kaplan-Meier analysis revealed that CCI was significantly associated with OS in patients with mCRC. Patients with CCI <7 had a median OS of 52.9 months (95% CI: 46.2-59.6), whereas those with CCI ≥7 had a markedly shorter median OS of 27.8 months (95% CI: 23.9-31.7) (Figure 1). The mean estimated OS was 64.7±3.4 months for patients with low CCI and 41.9±31.1 months for those with high CCI (The mean OS estimate in the high-CCI group was affected by censoring, resulting in a large standard error).

The difference in OS between the two groups was statistically significant according to both the Log-Rank test (χ^2 =25.51, p<0.001) and the Breslow test (χ^2 =41.91, p<0.001). Censoring rates were 24.9% in the CCI <7 group and 15.0% in the CCI ≥7 group (Table 2). These findings indicate that a higher comorbidity burden is associated with substantially poorer OS.

Association Between RAS Mutation Status and Comorbidity Burden

A significant association was observed between RAS mutation status and CCI group (Table 3). Among patients with RAS wild-type (RAS WT) tumors, 50.8% had CCI <7, whereas 49.2% had CCI ≥7.

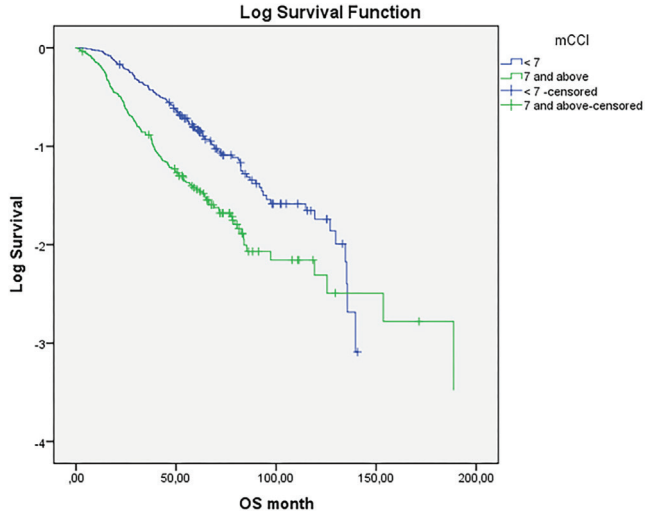

Figure 1. Kaplan-Meier curves for overall survival (OS) according to Charlson Comorbidity index (CCI) group

Table 1. Comparison of PFS between comorbidity groups based on median CCI (n=416)

CCI group	Mean PFS (months) ± SE	95% CI (mean)	Median PFS (months) ± SE	95% CI (median)	Events (n)	Log-rank p
<7	28.23±2.06	24.20-32.27	18.20±1.45	15.36-21.05	181	**<0.001**
≥7	17.17±1.28	14.67-19.68	9.87±0.89	8.11-11.62	235	
Overall	21.99±1.18	19.67-24.30	13.77±0.77	12.26-15.27	416	

CCI: Charlson Comorbidity index, OS: Overall survival, PFS: Progression-free survival, CI: Confidence interval, SE: Standard error

Table 2. OS according to CCI group (n=446)

CCI group	Mean OS (months) ± SE	95% CI (mean)	Median OS (months) ± SE	95% CI (median)	Events (n)	Censored (%)	Log-rank p
<7	64.69±3.36	58.11-71.27	52.90±3.40	46.23-59.57	145	24.9 %	**<0.001**
≥7	41.86±31.06	0-1027.3*	27.80±1.98	23.91-31.69	215	15.0 %	
Overall	38.10±2.28	33.63-42.57	—	—	360	19.3 %	

*Wide CI due to right censoring at longest follow-up time.
CCI: Charlson Comorbidity index, OS: Overall survival, PFS: Progression-free survival, CI: Confidence interval, SE: Standard error

Table 3. Association between RAS mutation status and CCI group (n=446)

RAS mutation status	CCI <7 (n, %)	CCI ≥7 (n, %)	Total (n, %)
RAS wild-type	125 (50.8%)	121 (49.2%)	246 (55.2%)
RAS mutant	68 (34.0%)	132 (66.0%)	200 (44.8%)
Total	193 (43.3%)	253 (56.7%)	446 (100%)

Pearson χ^2 =12.70, df =1, p<0.001 , Spearman's p=0.169, p<0.001
CCI: Charlson Comorbidity index, RAS: Rat sarcoma

In contrast, patients with RAS-mutant tumors had a higher comorbidity burden: 66.0% had CCI ≥7. The difference in distribution between RAS mutation groups was statistically significant (χ^2 =12.70, p<0.001). A weak but significant positive correlation was found between RAS mutation status and comorbidity level (Spearman's ρ=0.169, p<0.001), indicating that RAS-mutant patients tended to present with higher CCI scores.

Association Between Comorbidity Burden and Primary Tumor Sidedness

No statistically significant association was found between CCI group and primary tumor sidedness. Among patients with CCI <7, 81.3% had left-sided tumors and 18.7% had right-sided tumors. In those with CCI ≥7, 74.7% had left-sided tumors and 25.3% had right-sided tumors. Although right-sided tumors were numerically more frequent in patients with higher comorbidity burden, this difference did not reach statistical significance (χ^2 =2.78, p=0.096). The weak negative correlation between CCI and tumor sidedness (Spearman's ρ=-0.079, p=0.096) also did not indicate a meaningful relationship.

Progression-Free Survival According to Age Group

The mean age at diagnosis was 61.1±11.8 years. Patients were dichotomized into two age groups: <65 years (n=259) and ≥65 years (n=157). Kaplan-Meier analysis revealed no significant difference in PFS between the two age groups.

The median PFS was 13.9 months (95% CI: 12.1-15.7) for patients aged <65 years and 13.0 months (95% CI: 10.2-15.8) for those aged ≥65 years (Log-rank test: χ^2 =2.60, p=0.107). Similarly, the Breslow (Wilcoxon) test did not indicate a significant difference (p=0.641). These findings suggest that age at diagnosis was not a determining factor for PFS in this cohort.

Overall Survival According to Age Group

When stratified by age, 274 patients (61.4%) were younger than 65 years and 172 patients (38.6%) were 65 years or older. Kaplan-Meier survival analysis demonstrated a significant difference in OS between the two groups (Log-rank χ^2 =7.62, p=0.006; Breslow χ^2 =7.20, p=0.007) (Figure 2). The median OS was 40.7 months (95% CI: 34.6-46.8) in patients aged <65 years, compared with 30.2 months (95% CI: 22.1-38.3) in those aged ≥65 years (Table 4). Although the mean OS estimate was numerically higher in the younger group, this estimate was limited by censoring. These results indicate that older age was associated with shorter OS in this cohort.

Overall Survival by Age Group Stratified According to Charlson Comorbidity Index

When analyses were stratified by CCI level, the impact of age on OS was not statistically significant after adjustment. Among patients with CCI below the median (<7), the median OS was 50.7 months (95% CI: 42.6-58.8) for patients aged <65 years and 58.5 months (95% CI: 39.6-77.3) for those aged ≥65 years. In contrast, among patients with CCI ≥7, the median OS was 30.7 months (95% CI: 21.6-39.8) for younger patients and 24.2 months (95% CI: 19.5-28.9) for older patients. The log-rank test, adjusted for CCI, did not show a significant difference in OS between age groups (χ^2 =2.77, p=0.096; Breslow χ^2 =1.58, p=0.209) (Table 5).

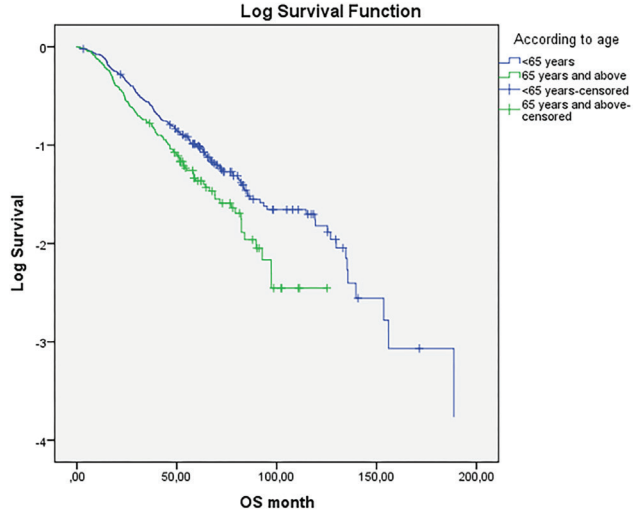

Figure 2. Kaplan-Meier curves for OS according to age group

OS: Overall survival

Table 4. OS according to age group

Age group	n	Events (n)	Censored (%)	Median OS (months)	95% CI	Log-rank p	Breslow p
<65 years	**274**	**218**	**20.4**	**40.7**	**34.6-46.8**	**0.006**	**0.007**
≥65 years	**172**	**142**	**17.4**	**30.2**	**22.1-38.3**		
Overall	**446**	**360**	19.3	38.1	33.6-42.6		

OS: Overall survival, CI: Confidence interval

Table 5. OS by age group, stratified according to CCI								
CCI group	**Age group**	**n**	**Events (n)**	**Censored (%)**	**Median OS (months)**	**95% CI**	**Log-rank p (adjusted)**	**Breslow p**
CCI <7	**<65 years**	**143**	**112**	21.7	50.7	42.6-58.8		
	≥65 years	50	33	34.0	58.5	39.6-77.3		
CCI ≥7	**<65 years**	**131**	**106**	**19.1**	**30.7**	**21.6-39.8**		
	≥65 years	122	109	10.7	24.2	19.5-28.9		
Overall		**446**	**360**	**19.3**	**38.1**	**33.6-42.6**	**0.096**	**0.209**
CCI: Charlson Comorbidity index, OS: Overall survival, CI: Confidence interval								

DISCUSSION

In our single-centre retrospective cohort of 446 patients with mCRC, we found that a higher comorbidity burden, older age, and RAS mutation status were each associated with poorer survival outcomes. Specifically, patients with CCI ≥7 had significantly shorter PFS and OS than those with CCI <7; RAS-mutant patients were more likely to have a high CCI; and older age was strongly associated with worse OS, although the effect on PFS was less pronounced. These findings highlight the importance of integrating host-related factors (age, comorbidities) with tumour molecular features in prognostic modelling of mCRC.

The demographic and clinical characteristics observed in this study are consistent with previously reported epidemiologic patterns of CRC, including a predominance of older patients and males, and a higher frequency of left-sided tumors.[1] The high proportion of patients presenting with stage IV disease could be related our selection criteria , while the liver and lung remained the most common sites of metastasis, as documented in prior studies.[1] The overall RAS mutation frequency (44.8%) aligns with large multicenter analyses reporting mutation rates of approximately 40-50% in mCRC.[15]

Our findings reinforce the prognostic importance of comorbidity in mCRC. Patients with higher CCI experienced nearly twofold reductions in both PFS and OS compared with patients with lower comorbidity burden. This is consistent with prior studies demonstrating that comorbidities negatively influence treatment tolerance, clinical decision-making, and long-term outcomes in CRC.[16-18] Population-based analyses have also shown that comorbidity independently predicts cancer-specific mortality regardless of stage or treatment modality.[19]

The mechanisms underlying this association are likely multifactorial. Chronic comorbidities such as cardiovascular, pulmonary, or metabolic disorders can impair physiological reserve, limit the ability to undergo intensive systemic therapies, and exacerbate treatment-related toxicities. Furthermore, comorbidity-associated inflammation and immune dysregulation may promote tumor progression and reduce therapeutic efficacy. Therefore, comorbidity assessment should be an integral component of baseline evaluation and prognostic modeling in patients with mCRC.

An intriguing observation in our study was the positive association between RAS mutation and a higher comorbidity burden. Patients with RAS-mutant tumors were significantly more likely to have a CCI ≥7 compared with RAS WT counterparts. Similar patterns have been reported in population-based datasets, where RAS-mutant mCRC patients demonstrated increased comorbidity and poorer outcomes.[20] The biological basis for this relationship remains speculative, but may involve shared molecular mechanisms linking metabolic dysregulation, inflammation, and RAS-driven carcinogenesis. These findings suggest that host systemic health may influence or reflect tumor biology, emphasizing the need for integrated clinical-molecular risk stratification.

Age alone was not associated with differences in PFS, implying comparable disease control under treatment in both younger and older patients. However, OS was significantly shorter in older patients, likely reflecting the cumulative effects of frailty, comorbidities, and reduced tolerance to systemic therapy, rather than intrinsic tumor aggressiveness.[3,17] Importantly, after adjustment for comorbidity (CCI), the prognostic effect of age on OS was no longer significant, suggesting that comorbidity burden, rather than chronological age, is the dominant determinant of long-term survival. This finding aligns with prior reports that the adverse effect of aging on CRC outcomes is largely mediated through comorbid conditions and functional decline.[21]

Our results highlight the prognostic value of systematically incorporating comorbidity assessment into the management of mCRC. Relying solely on age or tumor stage may underestimate the heterogeneity in treatment tolerance and outcomes among mCRC patients. Because of its simplicity and reproducibility, CCI remains a practical

and informative tool for prognostic stratification and individualized therapy planning, particularly in older or medically complex patients.

Study Limitations

Our study has several limitations. Its retrospective, single-center design may limit external validity. Moreover, treatment heterogeneity (chemotherapy regimens, anti-EGFR use, or treatment lines) was not analyzed in detail and may partly explain survival differences. Nevertheless, our cohort represents a real-world population, enhancing the generalizability of these findings to clinical practice.

CONCLUSION

In summary, this study demonstrates that a higher comorbidity burden, older age, and RAS mutation status are significant determinants of survival in mCRC. CCI provides clinically relevant prognostic information beyond traditional tumor features. Incorporating comorbidities and molecular data into prognostic models may improve risk stratification and guide individualized management strategies for patients with mCRC.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Non-Interventional Research Ethics Committee of Dokuz Eylül University (decision number: 2021/01-07, date: 04.01.2021).

Informed Consent: Retrospective study.

This study was derived from the medical specialty thesis of Evrim Ataca, completed in 2022.

Footnotes

Authorship Contributions

Concept: E.A., M.K., S.S., Y.B., T.Y., Design: E.A., M.K., S.S., Y.B., T.Y., Data Collection or Processing: E.A., M.K., Analysis or Interpretation: E.A., M.K., Literature Search: E.A., M.K., T.Y., Writing: E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. CA Cancer J Clin. 2025;75:10-45.
2. Biller LH, Schrag D. Diagnosis and treatment of metastatic colorectal cancer: a review. JAMA. 2021;325:669-85.
3. McCleary NJ, Zhang S, Ma C, et al. Age and comorbidity association with survival outcomes in metastatic colorectal cancer: CALGB 80405 analysis. J Geriatr Oncol. 2022;13:469-79.
4. Boakye D, Rillmann B, Walter V, Jansen L, Hoffmeister M, Brenner H. Impact of comorbidity and frailty on prognosis in colorectal cancer patients: a systematic review and meta-analysis. Cancer Treat Rev. 2018;64:30-9.
5. Osumi H, Shinozaki E, Suenaga M, et al. RAS mutation is a prognostic biomarker in colorectal cancer patients with metastasectomy. Int J Cancer. 2016;139:803-11.
6. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.
7. Morishima T, Matsumoto Y, Koeda N, et al. Impact of comorbidities on survival in gastric, colorectal, and lung cancer patients. J Epidemiol. 2019;29:110-5.
8. Braithwaite D, Moore DH, Satariano WA, et al. Prognostic impact of comorbidity among long-term breast cancer survivors: results from the LACE study. Cancer Epidemiol Biomarkers Prev. 2012;21:1115-25.
9. Zhang X, Wang X, Wang M, et al. Effect of comorbidity assessed by the Charlson Comorbidity index on the length of stay, costs, and mortality among colorectal cancer patients undergoing colorectal surgery. Curr Med Res Opin. 2023;39:187-95.
10. Winder T, Mündlein A, Rhomberg S, et al. Different types of K-Ras mutations are conversely associated with overall survival in patients with colorectal cancer. Oncol Rep. 2009;21:1283-7.
11. Rimbert J, Tachon G, Junca A, Villalva C, Karayan-Tapon L, Tougeron D. Association between clinicopathological characteristics and RAS mutation in colorectal cancer. Mod Pathol. 2018;31:517-26.
12. Wang X, Wu W, Zheng Z, Chi P. Exploring better strategies for RAS mutation-associated EGFR-targeted resistance in colorectal cancer: from the perspective of cancer community ecology. Front Oncol. 2021;11:754220.
13. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173:676-82.
14. Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67:93-9.
15. Kavgaci G, Akiva I, Ozon YH, et al. Evaluation of KRAS and NRAS mutations in metastatic colorectal cancer: an 8-year study of 10754 patients in Turkey. Mol Oncol. 2025;19:2967-77.
16. Rieker RJ, Hammer E, Eisele R, Schmid E, Högel J. The impact of comorbidity on the overall survival and the cause of death in patients after colorectal cancer resection. Langenbecks Arch Surg. 2002;387:72-6.
17. Tominaga T, Nonaka T, Takeshita H, et al. The Charlson Comorbidity index as an ındependent prognostic factor in older colorectal cancer patients. Indian J Surg. 2018;80:54-60.
18. Cuthbert CA, Hemmelgarn BR, Xu Y, Cheung WY. The effect of comorbidities on outcomes in colorectal cancer survivors: a population-based cohort study. J Cancer Surviv. 2018;12:733-43.
19. Ostenfeld EB, Nørgaard M, Thomsen RW, Iversen LH, Jacobsen JB, Søgaard M. Comorbidity and survival of Danish patients with colon and rectal cancer from 2000-2011: a population-based cohort study. Clin Epidemiol. 2013;5:65-74.
20. Ording AG, Öztürk B, Spindler KG, Sørensen HT, McCusker M, Ehrenstein V. KRAS mutation status, comorbidity, and mortality in patients with metastatic colorectal cancer in Denmark. Acta Oncol. 2018;57:1727-9.
21. Wu CC, Hsu TW, Chang CM, Yu CH, Lee CC. Age-adjusted Charlson comorbidity index scores as predictor of survival in colorectal cancer patients who underwent surgical resection and chemoradiation. Medicine (Baltimore). 2015;94:e431.