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ORIGINAL RESEARCH

Prognostic Impact of Cetuximab-Related Hypomagnesemia and Hypokalemia in RAS/RAF Wild-Type Colorectal Cancer: A Multicenter Study

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Purpose: The prognostic value of cetuximab-related electrolyte disturbances in metastatic colorectal cancer (CRC) remains unclear. The available reports on the prognostic effect of hypomagnesemia are controversial, while there are no comprehensive analyses regarding hypokalemia. This study aimed to evaluate the impact of hypomagnesemia and hypokalemia on treatment outcomes in patients with RAS/RAF wild-type metastatic CRC receiving first-line cetuximab-based therapy.

Patients and Methods: We retrospectively analysed 305 patients treated across seven oncology centers between March 2013 and December 2024. Patients with baseline renal insufficiency or pre-existing electrolyte disturbance were excluded. Serum magnesium and potassium levels were assessed from the initiation of cetuximab until one month after its discontinuation.

Results: There was one patient with missing magnesium levels and one patient with missing potassium levels. Three-hundred and four patients were available for the final analyses (n=304). Hypomagnesemia and hypokalemia occurred in 29.9% and 20.7% of the patients, respectively. Neither hypomagnesemia nor hypokalemia was significantly associated with progression-free survival (PFS) (11.9 vs 11.7 months for each; p=0.528 and p=0.327) or overall survival (OS) (25.3 vs 27.9 months; p=0.705 and 22.0 vs 28.8 months; p=0.824, respectively). Hypokalemia was correlated with a higher disease control rate (96.8% vs 87.1%, p= 0.028). In multivariate analyses, only metastatic burden (≥2 sites) independently associated with inferior outcomes for both PFS (HR 1.61, 95% CI 1.25–2.08, p< 0.001) and OS (HR 1.77, 95% CI 1.31–2.39, p< 0.001).

Conclusion: Hypomagnesemia and hypokalemia did not significantly impact survival outcomes despite previous studies indicating otherwise. Moreover, hypokalemia was linked to improved disease control. These results provide incremental evidence regarding the clinical relevance of electrolyte disturbances, particularly hypokalemia, and highlight the need for prospective studies to clarify their prognostic and predictive significance.

Keywords: colorectal cancer, cetuximab, hypomagnesemia, hypokalemia

Introduction

Colorectal cancer (CRC) is the third most prevalent malignancy globally and the second leading cause of cancer-related death.[1] The contemporary therapeutic algorithm for metastatic CRC is shaped by molecular profiling, including RAS, BRAF, and mismatch repair (MMR) status, as well as tumor sidedness and individualized treatment objectives.[2] The backbone of systemic therapy is formed by doublet regimens combining fluoropyrimidine (FP) with oxaliplatin or irinotecan, or by triplet regimens incorporating all three agents, whereas FP monotherapy remains an option in certain

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circumstances.[3] Beyond conventional chemotherapy combinations, targeted therapies driven by genomic alterations, reflecting the principles of precision medicine, are continually advancing in the management of metastatic CRC.[2] Findings from the FIRE-3, CRYSTAL, and OPUS trials established the efficacy of first-line cetuximab in combination with chemotherapy in patients with RAS wild-type metastatic CRC.[4,5] Nevertheless, beyond its proven efficacy, cetuximab is accompanied by notable toxicities. The dose-limiting acneiform rash, observed in up to 77% of patients, as well as chemotherapy-combination–related electrolyte disturbances such as hypomagnesemia (35%) and hypokalemia (37%), have been consistently documented.[4] Electrolyte disturbances such as hypomagnesemia and hypokalemia are clinically relevant toxicities in colorectal cancer patients receiving anti-EGFR–based therapies, as they have been associated with treatment interruptions, dose modifications, and increased healthcare utilization, including unplanned hospitalizations and prolonged length of stay.[6,7]

Cetuximab-induced hypomagnesemia is primarily attributed to renal magnesium wasting, driven by dysfunction of transient receptor potential melastatin 6 (TRPM6) channels, which normally mediate magnesium reabsorption at the nephron level.[8,9] Proposed mechanisms implicate impaired function of renal outer-medullary potassium (ROM-K) channels secondary to hypomagnesemia; however, hypokalemia has also been observed in the absence of concomitant hypomagnesemia.[10,11] While acneiform rash remains the adverse event most consistently correlated with cetuximab efficacy and supported by the strongest clinical evidence, the potential predictive value of hypomagnesemia for treatment outcomes has likewise been explored.[12,13] Several of these investigations were performed in subsequent treatment lines, in which the clinical use of cetuximab in CRC is usually limited in routine practice.[14] In the first-line setting, meta-analytic evidence has indicated a potential predictive role of hypomagnesemia for cetuximab efficacy, yet findings from individual trials have been inconsistent and often contradictory.[15] The inconsistent results reported across prior studies evaluating hypomagnesemia may be explained by substantial heterogeneity in study design, including differences in treatment lines, timing of electrolyte measurements, and the possible confounding effects of platinum-based chemotherapy. Moreover, with the exception of a few small case series, the predictive significance of hypokalemia for treatment efficacy has not yet been systematically explored.[16]

Elucidating the potential predictive role of hypokalemia in cetuximab efficacy, together with clarifying the prognostic relevance of hypomagnesemia, may provide valuable insights for optimizing treatment strategies and improving clinical outcomes. Accordingly, the present study aimed to evaluate the predictive significance of hypomagnesemia and hypokalemia on treatment efficacy and survival among patients with RAS/RAF wild-type metastatic CRC treated with first-line chemotherapy in combination with cetuximab.

Materials and Methods

Study Population

Patients diagnosed with metastatic colorectal adenocarcinoma between March 2013 and December 2024 at seven oncology centers were retrospectively reviewed. The inclusion criteria were as follows: (i) confirmed diagnosis of metastatic colorectal adenocarcinoma, (ii) wild-type status for *KRAS, NRAS*, and *BRAF* gene analyses, and (iii) receipt of first-line systemic chemotherapy combined with cetuximab as the biological agent. The exclusion criteria were as follows: (i) age under 18 years, (ii) undergoing renal replacement therapy and/or being diagnosed with chronic kidney disease with a baseline GFR <45 mL/min/1.73 m^2, (iii) having baseline (before initiation of cetuximab) hypomagnesemia and/or hypokalemia, and (iv) unavailability of complete clinical data. Comorbidities were recorded from medical charts. Concomitant medications known to affect magnesium and/or potassium homeostasis (eg, diuretics, renin–angiotensin–aldosterone system inhibitors) could not be reliably captured in a standardized manner across centers due to the retrospective design; therefore, these medications were not used as exclusion criteria and were not included as covariates in the primary analyses. All patients included in the study received the best available treatment in accordance with the contemporary clinical guidelines relevant to their treatment. Cetuximab was administered at a dose of 500 mg/m^2 every two weeks.

This study was conducted in accordance with the principles of the latest version of the Declaration of Helsinki. Ethical approval for this study was obtained from the Ethics Committee of Antalya Training and Research Hospital on

June 19, 2025 (Approval No: 2025–207). The requirement for informed consent was waived by the committee due to the retrospective design and the use of anonymized patient data.

Data Collection and Study Design

Clinical data were retrospectively collected from patient follow-up records and the hospital information management system. Demographic and clinical variables included age, sex, comorbidities, Eastern Cooperative Oncology Group Performance Status (ECOG PS), smoking history, metastatic status (de novo vs metachronous metastasis), metastatic sites (only liver or presence of extrahepatic metastasis), metastatic burden as the number of metastatic sites (liver, lung, bone, non-regional lymph nodes, adrenal glands, skin, etc)., primary tumor location, and systemic therapies administered. The pathological and laboratory parameters included were MMR analysis, *KRAS, NRAS*, and *BRAF* alterations, serum magnesium (mEq/L), serum potassium (mEq/L), and glomerular filtration rate (GFR) (mL/min/1.73 m²).

Staging of patients treated before 2017 was performed according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition, whereas patients treated in 2017 and thereafter were staged using the AJCC Cancer Staging Manual, 8th Edition. Treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Serum magnesium and potassium levels were assessed from the initiation of cetuximab until one month after its discontinuation. During the cetuximab treatment, as a part of routine clinical practice, blood tests including magnesium and potassium are performed before each treatment cycle. Moreover, these tests were obtained as per clinician preference and there was no center based correlation regarding the electolite measurement intervals. Hypomagnesemia and hypokalemia are defined as s binary treatment-emergent adverse events (ever vs never). In patients who developed hypomagnesemia and/or hypokalemia during this period, these adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5). Missing data were handled using a complete-case approach. *RAS* and *RAF* analyses were performed using polymerase chain reaction (PCR), and mismatch repair (MMR) status was assessed using immunohistochemistry (IHC).

The objective response rate (ORR) was defined as the proportion of patients who achieved either a complete response (CR) or partial response (PR) to cetuximab-containing treatment regimens according to the RECIST v1.1 criteria. The disease control rate (DCR) was defined as the proportion of patients whose best response to cetuximab-containing regimens was at least stable disease (SD). Progression-free survival (PFS) was calculated from the date of cetuximab initiation to the date of documented disease progression or death from any cause, whichever occurred first. Overall survival (OS) was calculated from the date of cetuximab initiation to death from any cause or to the date of the last follow-up for patients who were alive.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as counts and percentages, and continuous variables were presented as medians with interquartile ranges (IQR). The associations between hypomagnesemia, hypokalemia, and clinicopathological features were examined using the chi-square test. PFS and OS according to magnesium and potassium status were estimated using the Kaplan–Meier method, and survival distributions were compared using the Log rank test. Univariate and multivariate Cox proportional hazards regression models were applied to determine the prognostic relevance of clinical variables. The results were expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant.

Results

Clinicopathological Characteristics of the Study Population

After the initial screening, 330 patients were included in the study. Thirteen were excluded due to insufficient clinical data, six due to a GFR lower than 45 mL/min/1.73 m^2, five due to *KRAS* mutations, and one due to a *BRAF* mutation. Consequently, the final analysis was conducted on 305 eligible patients (n = 305). MMR status was missing for 73 patients (23.9%). Serum magnesium values during follow-up were unavailable for one patient, and potassium values

during follow-up were missing for another patient. Consequently, analyses of magnesium and potassium levels were conducted in 304 patients (n =304). During follow-up, 91 patients (29.9%) developed hypomagnesemia. According to the CTCAE v5.0 guide, hypomagnesemia adverse events occurred as grade 1 or 2 in 27.6% and grade 3–4 in 2.3%. Hypokalemia was observed in 63 patients (20.7%), with 16.1% being grade 1 or 2 and 4.6% grade 3 or 4. (Figure 1) No deaths were attributed to hypomagnesemia or hypokalemia.

When the patients were stratified according to hypomagnesemia and hypokalemia status, the clinicopathological characteristics were homogeneously distributed across the groups. However, among the 63 patients with hypokalemia, 36 (57.1%) also experienced hypomagnesemia, whereas 27 (42.9%) had hypokalemia despite maintaining normomagnesemia ($p < 0.001$). (Table 1).

Efficacy and Survival Analyses

The median follow-up duration was 39.8 months (95% confidence interval [CI]: 33.3–46.3). The median duration of cetuximab exposure was 10.3 months (95% CI: 9.2–11.3). At the time of data collection, cetuximab was discontinued in 269 patients (88.2%). The reasons for discontinuation were disease progression in 67.2% of patients, drug holiday in 10.8%, toxicity in 5.2%, and other less frequent causes in 4.9% of patients. Among the 305 patients included in the study, 176 (57.7%) died during follow-up.

No significant differences were observed in the ORR and DCR analyses between patients with hypomagnesemia and those with normomagnesemia. Patients with hypokalemia demonstrated comparable ORR rates to normokalemic patients, while the DCR was significantly higher in the hypokalemia group (96.8% vs 87.1%, p=0.028). (Figure 2).

In PFS analyses, the median PFS did not differ significantly between patients with or without hypomagnesemia [11.9 months (95% CI: 9.8–13.9) vs 11.7 months (95% CI: 10.3–13.1); log-rank, p=0.528] or between those with or without hypokalemia [11.9 months (95% CI: 10.3–13.4) vs 11.7 months (95% CI: 10.4–13.1); log-rank, p=0.327]. (Figure 3) In the univariate analyses, metastatic sites and metastatic burden were identified as significant covariates. In the multivariate analyses, the effect of extrahepatic metastasis on PFS lost its significance, whereas the presence of ≥2 metastatic sites remained an independent predictor of progression risk [HR: 1.61 (95% CI: 1.25–2.08), p<0.001]. (Table 2).

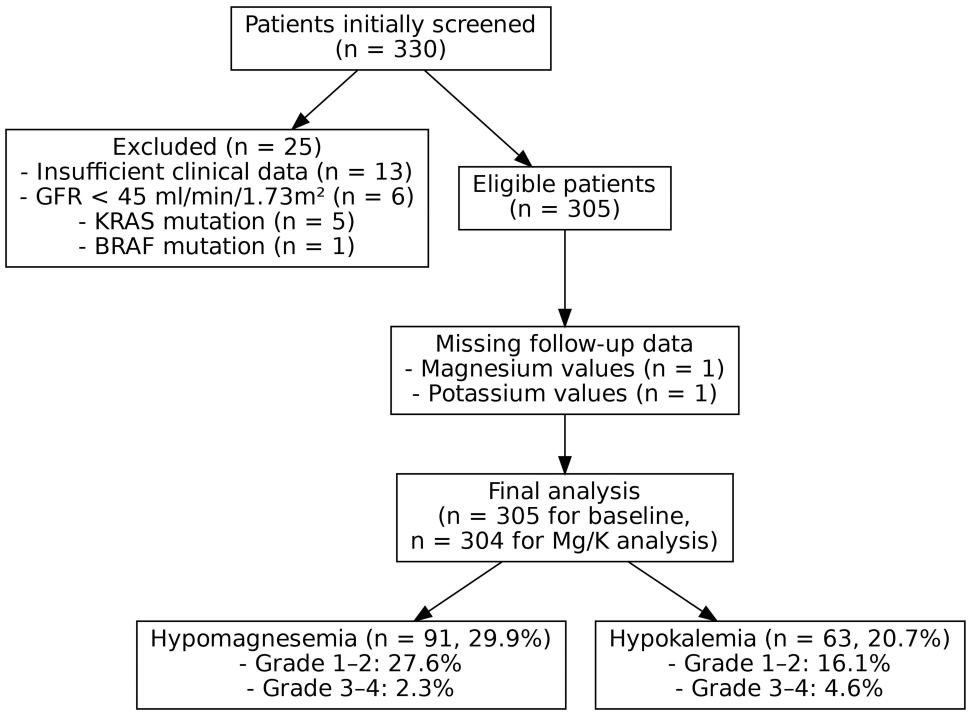

Figure 1 Consort flow diagram.

Table 1 Clinicopathological Characteristics of the Study Population

	Normo-Mg (n=213)	Hypo-Mg (n=91)	P value	Normo-K (n=241)	Hypo-K (n=63)	P value
	n (%)	n (%)		n (%)	n (%)	
Age *Med (IQR)*	59.0 (50.5–67.5)	66.7 (59.6–72.4)		62.2 (52.2–70.0)	60.7 (51.7–68.8)	
Sex			0.326			0.654
Female	65 (30.5)	33 (36.3)		77 (32.0)	22 (34.9)	
Male	148 (69.5)	58 (63.7)		164 (68.0)	41 (65.1)	
ECOG PS			0.251			0.673
0 or 1	198 (93.0)	81 (89.0)		222 (92.1)	57 (90.5)	
2	15 (7.0)	10 (11.0)		19 (7.9)	6 (9.5)	
Smoking History			0.345			0.187
Non-Smoker	134 (62.9)	52 (57.1)		152 (63.1)	34 (54.0)	
Smoker	79 (37.1)	39 (42.9)		89 (36.9)	29 (46.0)	
MMR Status			0.870			0.775
Proficient	149 (70.0)	65 (71.4)		170 (70.5)	43 (68.3)	
Deficient	12 (5.6)	6 (6.6)		15 (6.2)	3 (4.8)	
Unknown	52 (24.4)	20 (22.0)		56 (23.2)	17 (27.0)	
Primary Tumor Location			0.685			0.291
Right Colon	17 (9.0)	10 (11.0)		24 (10.0)	3 (4.8)	
Left Colon	111 (52.1)	47 (51.6)		120 (49.8)	37 (58.7)	
Rectum	85 (39.9)	34 (37.4)		97 (40.2)	23 (36.5)	
Metastasis Status			0.129			0.316
De-Novo	150 (70.4)	56 (61.5)		160 (66.4)	46 (63.0)	
Metachronous	63 (29.6)	35 (38.5)		81 (33.6)	17 (27.0)	
Metastatic Sites			0.834			0.836
Only Liver Met.	87 (40.8)	36 (39.6)		96 (39.8)	26 (41.3)	
Extrahepatic Met.	126 (59.2)	55 (60.4)		145 (60.2)	37 (58.7)	
Metastasis Burden (Number of Metastatis Sites)			0.725			0.437
1	110 (51.6)	49 (53.8)		128 (53.1)	30 (47.6)	
≥2	103 (48.4)	42 (46.2)		113 (46.9)	33 (52.4)	
Chemotherapy Regimen			0.279			0.855
Oxaliplatin Doublet	171 (80.3)	68 (74.4)		190 (78.8)	49 (77.8)	
Irinotecan Doublet	42 (19.7)	23 (25.6)		51 (21.2)	14 (22.2)	
Hypokalemia			**<0.001**			
No	185 (87.3)	35 (60.4)				
Yes	27 (12.7)	36 (39.6)				

Notes: Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: ECOG PS, Eastern Cooperative Oncology Study Group Performance Status; K, Potassium; Mg, Magnesium; MMR, Mismatch repair.

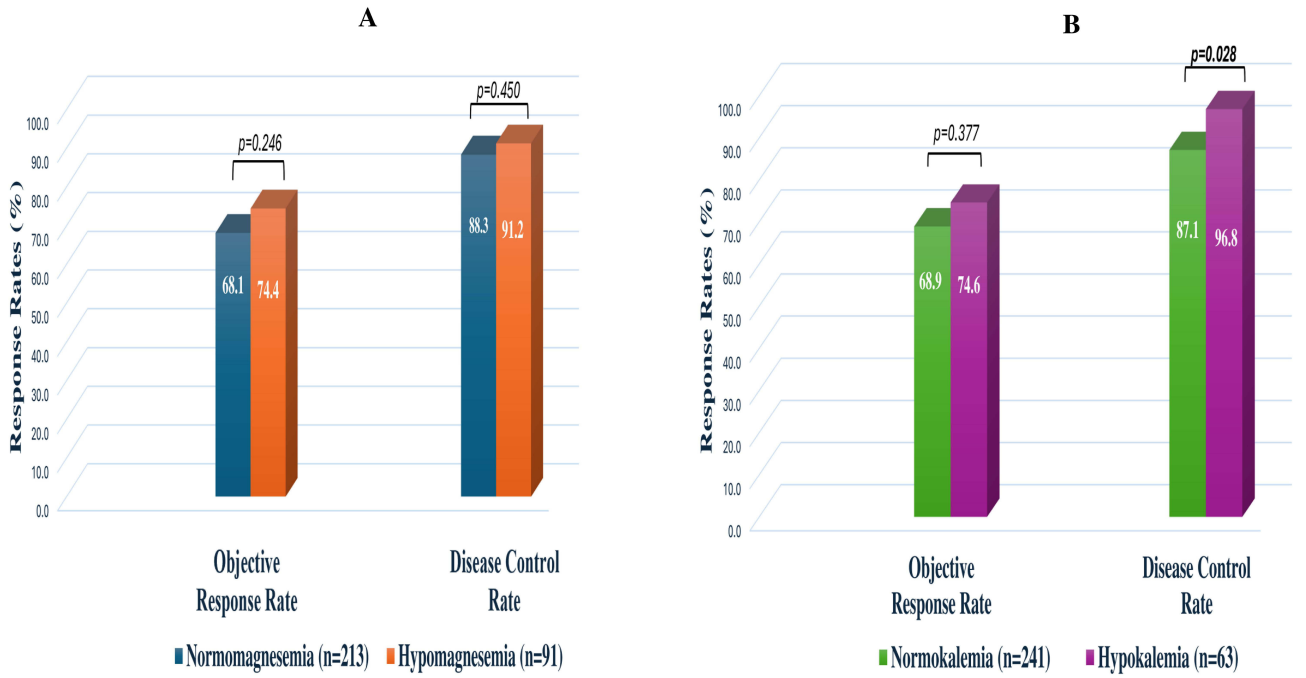

Figure 2 Treatment Response Rates of Patients According to Magnesium and Potassium States. (**A**) Response rate comparison of patients with hypomagnesemia and normomagnesemia. (**B**) Response rate comparison of patients with hypokalemia and normokalemia.

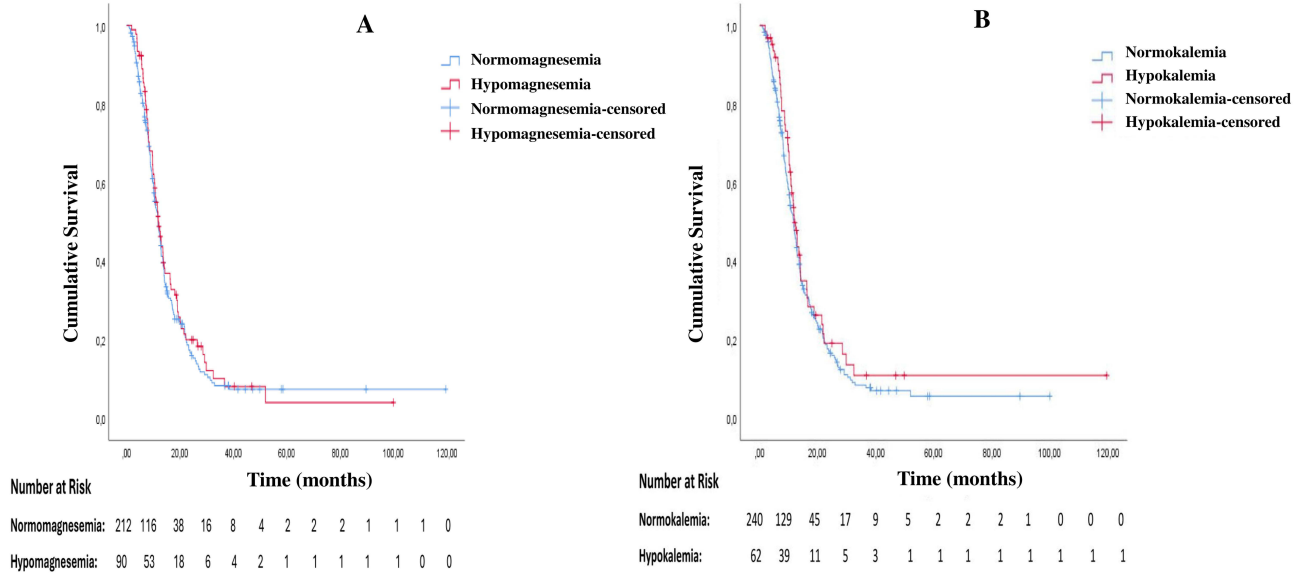

Figure 3 Progression-Free Survival Analyses According to Magnesium and Potassium States (n=304). (**A**) The median PFS was similar for patients with or without hypomagnesemia [11.9 months (95% CI: 9.8–13.9) vs 11.7 months (95% CI: 10.3–13.1); log-rank, p=0.528]. (**B**) The median progression-free survival was similar for patients with or without hypokalemia [11.9 months (95% CI: 10.3–13.4) vs 11.7 months (95% CI: 10.4–13.1); log-rank, p=0.327].

For OS analyses, the median OS was similar between patients with hypomagnesemia and those with normomagnesemia [25.3 months (95% CI: 19.0–31.5) vs 27.9 months (95% CI: 24.4–31.4); log-rank, p=0.705]. Similarly, OS did not differ significantly between patients with hypokalemia and those without [22.0 months (95% CI: 4.5–39.5) vs 28.8 months (95% CI: 25.8–31.8); log-rank, p=0.824]. (Figure 4) In univariate analyses, metastatic sites, number of metastatic

Table 2 Univariate and Multivariate Analyses of Variables for Progression-Free Survival

	Univariate Analysis HR (95% CI)	P value	Multivariate Analysis HR (95% CI)	P value
Age	1.00 (0.99–1.01)	0.688	1.00 (0.99–1.02)	0.540
Sex		0.967		
Female	Reference			
Male	1.01 (0.77–1.31)			
Hypomagnesemia Status		0.529		0.276
No	Reference		Reference	
Yes	1.08 (0.83–1.44)		0.86 (0.65–1.13)	
Hypokalemia Status		0.329		0.477
No	Reference		Reference	
Yes	0.85 (0.62–1.18)		0.88 (0.62–1.25)	
Primary Tumor Location				
Right Colon	Reference		Reference	
Left Colon	1.08 (0.67–1.75)	0.753	1.14 (0.70–1.85)	0.603
Rectum	1.35 (0.83–2.21)	0.229	1.40 (0.85–2.29)	0.187
Metastasis Status		0.066		0.061
De-Novo	Reference		Reference	
Metachronous	1.29 (0.98–1.69)		1.29 (0.99–1.69)	
Metastatic Sites		**0.002**		0.928
Only Liver Met.	Reference		Reference	
Extrahepatic Met.	1.52 (1.17–1.97)		0.98 (0.63–1.52)	
Metastatic Burden (Number of Metastatis Sites)		**<0.001**		**<0.001**
1	Reference		Reference	
≥2	1.63 (1.26–2.10)		1.61 (1.25–2.08)	
Chemotherapy Regimen		0.195		0.471
Oxaliplatin Doublet	Reference		Reference	
Irinotecan Doublet	1.22 (0.90–1.66)		1.13 (0.81–1.58)	

Notes: P values in univariate and multivariate analyses were derived from Cox proportional hazards regression models. Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: CI, Confidence Interval; HR, Hazard ratio.

sites, and chemotherapy regimen type were significant variables; however, in the multivariate model, only metastatic burden retained statistical significance [HR: 1.77 (95% CI: 1.31–2.39), $p<0.001$]. (Table 3).

Discussion

In this study, we demonstrated that the development of hypomagnesemia or hypokalemia in patients with RAS/RAF wild-type metastatic colorectal cancer receiving first-line chemotherapy in combination with cetuximab had no significant impact on PFS or OS. Similarly, hypomagnesemia did not result in significant differences in ORR or DCR. In contrast, patients who developed hypokalemia had a significantly higher DCR. In addition, our analysis identified metastatic burden as the most important prognostic determinant of both PFS and OS.

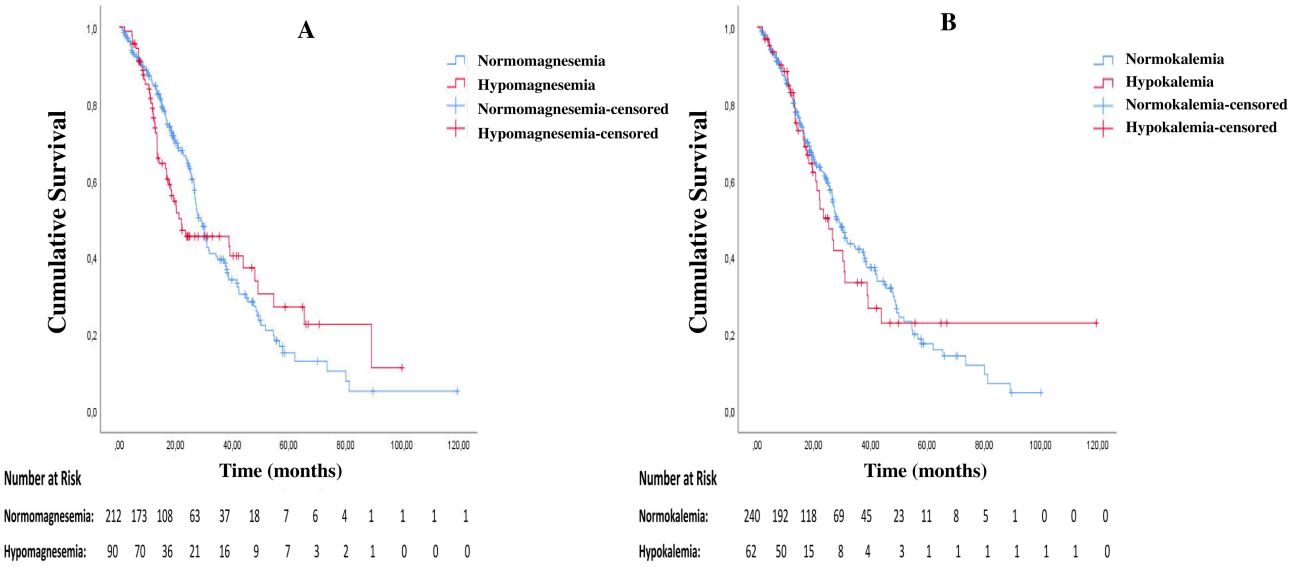

Figure 4 Overall Survival Analyses According to Magnesium and Potassium States. (**A**) The median OS was similar between patients with hypomagnesemia and those with normomagnesemia [25.3 months (95% CI: 19.0–31.5) vs 27.9 months (95% CI: 24.4–31.4); log-rank, p=0.705]. (**B**) The median of overall survival of patients with hypokalemia and normokalemia was similar [22.0 months (95% CI: 4.5–39.5) vs 28.8 months (95% CI: 25.8–31.8); log-rank, p=0.824].

Several biological and methodological factors may explain why neither hypomagnesemia nor hypokalemia was associated with PFS or OS in our cohort. From a biological perspective, cetuximab-induced hypomagnesemia primarily reflects renal magnesium wasting secondary to EGFR inhibition in the distal tubule and may represent a pharmacodynamic on-target effect rather than a surrogate of antitumor efficacy.[6] Methodologically, heterogeneity in the timing and definition of electrolyte disturbances, together with longer treatment exposure and monitoring intensity, may introduce time-dependent or immortal-time bias when these events are analyzed as time-fixed variables. In addition, concomitant chemotherapy and center-specific monitoring practices may influence electrolyte detection in real-world settings. Biologically, hypokalemia often reflects a downstream toxicity of magnesium loss or gastrointestinal disturbances rather than a direct marker of antitumor activity. In a meta-analysis of twenty-five randomized controlled trials, the incidence of cetuximab-associated hypomagnesemia and hypokalemia was reported to be 34.9% and 12.6%, respectively, with grade

Table 3 Univariate and Multivariate Analyses of Variables for Overall Survival

	Univariate Analysis HR (95% CI)	P value	Multivariate Analysis HR (95% CI)	P value
Age	1.02 (1.01–1.03)	**0.007**	1.02 (1.01–1.03)	**0.006**
Sex		0.950		
Female	Reference			
Male	1.01 (0.74–1.38)			
Hypomagnesemia Status No Yes	 Reference 1.04 (0.75–1.44)	0.824	 Reference 0.87 (0.61–1.25)	0.449
Hypokalemia Status		0.705		0.420
No	Reference		Reference	
Yes	1.08 (0.74–1.56)		1.17 (0.80–1.71)	

(*Continued*)

Table 3 (Continued).

	Univariate Analysis HR (95% CI)	P value	Multivariate Analysis HR (95% CI)	P value
Primary Tumor Location				
Right Colon	Reference		Reference	
Left Colon	0.67 (0.40–1.14)	0.139	0.74 (0.44–1.25)	0.256
Rectum	0.94 (0.56–1.60)	0.824	1.00 (0.59–1.71)	0.989
Metastasis Status		0.727		
De-Novo	Reference			
Metachronous	1.06 (0.77–1.45)			
Metastatic Sites		**<0.001**		0.343
Only Liver Met.	Reference		Reference	
Extrahepatic Met.	1.84 (1.34–2.54)		1.28 (0.88–2.12)	
Metastatic Burden (Number of Metastatis Sites)		**<0.001**		**<0.001**
1	Reference		Reference	
≥2	1.83 (1.36–2.47)		1.77 (1.31–2.39)	
Chemotherapy Regimen		**0.037**		0.059
Oxaliplatin Doublet	Reference		Reference	
Irinotecan Doublet	1.46 (1.02–2.09)		1.41 (0.99–2.03)	

Notes: P values in univariate and multivariate analyses were derived from Cox proportional hazards regression models. Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: CI, Confidence Interval; HR, Hazard Ratio.

3–4 events occurring in 4.4% and 6.1% of cases, respectively.[6,17] In our cohort, 57.1% of patients who developed hypokalemia also exhibited hypomagnesemia, supporting this underlying pathophysiological mechanism. As the clinical counterpart of this molecular mechanism and similar to our study results, hypokalemia has been reported to have clinical correlation with both hypomagnesemia and hypocalcemia in patients receiving cetuximab.[18]

In contrast to hypomagnesemia, evidence regarding the clinical relevance of hypokalemia in cetuximab-treated metastatic colorectal cancer remains extremely limited. The available literature is largely restricted to isolated case reports or small case series, primarily describing refractory hypokalemia as a toxicity rather than systematically evaluating its association with treatment response or survival outcomes.[16] To our knowledge, no prior study has comprehensively examined hypokalemia alongside hypomagnesemia within a well-defined, RAS/RAF wild-type metastatic colorectal cancer population treated uniformly with first-line cetuximab-based therapy. This gap underscores the novelty and clinical relevance of the present analysis. Additionally, the observation that hypokalemia was associated with a higher disease control rate without a corresponding improvement in progression-free or overall survival warrants careful interpretation.

In terms of hypomagnesemia, there are conflicting results regarding its impact on survival and treatment response in patients with RAS wild-type CRC treated with cetuximab.[19] Kimura et al demonstrated that hypomagnesemia was not associated with survival outcomes in patients with RAS wild-type CRC who received first-line chemotherapy in combination with anti-EGFR monoclonal antibodies (cetuximab or panitumumab).[20] Similarly, several retrospective cohort studies with smaller patient populations have also failed to demonstrate any significant impact of hypomagnesemia on survival outcomes.[21,22] Moreover, in a post-hoc analysis of the NCIC CTG/AGITG CO.17 randomized controlled trial, patients treated with cetuximab were stratified into hypomagnesemia and normomagnesemia groups based on their magnesium levels on day 28 of treatment. Interestingly, patients who developed hypomagnesemia demonstrated

significantly decreased overall survival compared with those who remained normomagnesemic.[23] Conversely, a meta-analysis conducted by Hsieh et al evaluated patients with KRAS wild-type mCRC treated with first-line or subsequent-line anti-EGFR monoclonal antibodies (cetuximab or panitumumab). This meta-analysis included five studies comprising 1723 patients and reported an incidence of hypomagnesemia of 33.0%. Notably, hypomagnesemia was associated with improved ORR, PFS, and OS, irrespective of the treatment line.[15] In a retrospective cohort study of 79 patients, Stintzing et al demonstrated that hypomagnesemia was associated with significantly prolonged PFS, particularly in patients who received platinum-based therapy, although no association was observed with OS. They also reported that patients who developed hypomagnesemia achieved a better ORR than those who maintained normomagnesemia, whereas the DCR remained similar. Another important finding of their study was that patients receiving cetuximab in combination with platinum exhibited a more profound decline in serum magnesium levels.[24] The previously reported associations between treatment-related hypomagnesemia and improved survival raise the question of whether these electrolyte disturbances represent a true biological surrogate of treatment efficacy or a coincidental finding driven by confounding factors. Several explanations have been proposed, including longer treatment exposure in responding patients, time-dependent bias, and differential monitoring intensity. The absence of a survival advantage associated with hypomagnesemia or hypokalemia in our cohort, together with the inconsistent findings across prior studies, suggests that these electrolyte abnormalities are more likely treatment-related toxicities rather than reliable biological markers of cetuximab efficacy. Moreover, hypomagnesemia is a well-recognized adverse effect associated with all platinum-based chemotherapy agents (cisplatin, carboplatin, and oxaliplatin).[25] However, in our study, the incidences of both hypomagnesemia and hypokalemia were comparable between patients receiving oxaliplatin-based therapy and those treated with irinotecan-based regimen.

In our cohort, metastatic burden (≥2 metastatic sites) retained independent prognostic significance for both progression-free and overall survival, whereas the presence of extrahepatic metastasis was associated with poor survival outcomes only in univariate analyses. These results are consistent with the large data of Bachet et al They reported the data from 48 randomised trials which included 37560 patients and they found that number of metastatic sites is one of the main determinants of prognosis metastatic CRC.[26]

The principal limitation of this study was its retrospective design. In addition, serum magnesium and potassium levels were not uniformly monitored across the participating centers, which may have introduced variability in the measurement frequency. Although the exclusion of patients with severe baseline renal dysfunction or pre-existing electrolyte disturbances strengthens the validity of our findings, the lack of available data on the use of diuretics or renin–angiotensin–aldosterone system inhibitors constitutes another limitation, as these agents may influence electrolyte homeostasis. Because electrolyte disturbances develop during treatment, analyzing hypomagnesemia and hypokalemia as time-fixed (ever/never) variables may introduce time-dependent or immortal-time bias. Time-dependent cox or landmark analyses could further refine risk estimation but were not feasible due to heterogeneity in monitoring intervals and limited high-grade events. Nevertheless, a key strength of our study was the relatively large multicenter cohort, which provided real-world evidence on patients treated with first-line chemotherapy in combination with cetuximab. Restricting the study to RAS/RAF wild-type patients reduced molecular heterogeneity, thereby enhancing the robustness of our results. Furthermore, the systematic assessment of both hypomagnesemia and hypokalemia, along with their potential interactions with treatment response, represents a novel and valuable contribution to the literature.

Conclusion

In patients with RAS/RAF wild-type metastatic colorectal cancer treated with first-line cetuximab-based chemotherapy, neither hypomagnesemia nor hypokalemia was associated with survival outcomes. Hypokalemia was linked to a higher disease control rate, whereas metastatic burden emerged as the strongest independent predictor of both progression-free and overall survival. These findings suggest that cetuximab-related electrolyte disturbances may not serve as reliable prognostic or predictive biomarkers in this setting. Further large-scale prospective studies are warranted to clarify their clinical relevance.

Abbreviations

CI, Confidence interval; CRC, Colorectal cancer; CTACE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Study Group performance status; EGFR, Epithelial Growth Factor Receptor; HR, Hazard ratio; IQR: Interquartile Range; K, Potassium; Mg, Magnesium; MMR, Mismatch Repair; OS, Overall survival; PFS, Progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Data Sharing Statement

The data generated in this study is available upon a reasonable request from the corresponding author.

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