



Fruquintinib in metastatic colorectal cancer: a multicenter real-world analysis on efficacy, safety, and predictive and prognostic factors

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Background: Randomized trials have shown a survival benefit for fruquintinib over placebo in patients with metastatic colorectal cancer (mCRC) that progressed after standard therapies, but real-world prognostic analyses have been seldom reported. We evaluated survival, safety outcomes, and predictive and prognostic factors in patients treated with fruquintinib in a real-life setting.

Methods: We conducted a multi-center study by collecting relevant data on patients with advanced colorectal cancer (CRC) who received fruquintinib, focusing on progression-free survival (PFS), overall survival (OS), and L3 skeletal muscle index (SMI), including safety follow-up.

Results: From January 2020 to January 2022, a total of 140 patients were selected and included in this study. The cut-off date was 30 July 2022. The median follow-up time was 18.3 months (range, 6–29.3 months) and the median age of included cases was 63 years (range, 32–81 years). The median PFS and OS for the 140 patients was 6.3 and 12.6 months, respectively. The median PFS and OS for the 76 patients who were included in SMI analysis was 6.0 and 12.0 months, respectively. Multivariate analysis suggested brain metastasis [hazard ratio (HR) [95% confidence interval (CI)]: 2.779 (1.162–6.646), $P=0.02$], decrease in SMI of $>5\%$ [HR (95% CI): 9.732 (2.201–43.028), $P=0.003$], and baseline carcinoembryonic antigen (CEA) level [HR (95% CI): 4.061 (1.391–11.858), $P=0.01$] as independent predictors of OS. The most common treatment-related adverse events (TRAEs) were hypertension (24, 17.1%), fatigue (21, 15%), and hand-foot syndrome (20, 14.3%); 9 (13.6%) and 15 (10.7%) patients had dose reduction and treatment discontinuation due to TRAEs respectively.

Conclusions: The real-world efficacy and safety of fruquintinib in advanced CRC patients are numerically

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superior to that in the previous phase III studies. SMI, brain metastasis and CEA could serve as potential markers for patient selection.

Keywords: Fruquintinib; skeletal muscle index (SMI); real world; predictive factor; prognostic factor

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Introduction

Colorectal cancer (CRC) is one of the most common cancers, ranking second for cancer-related deaths worldwide (1). It is estimated that over 1.2 million new CRC cases are diagnosed annually and the disease-related mortality is about 33% (2). Although CRC ranks second in terms of incidence among the Chinese population, there is a trend of increasing incidence, with about 517,100 new cases per year in China (3).

Treatment of metastatic CRC (mCRC) is based on cytotoxic drugs and targeted agents. Currently, the standard first- and second-line treatment for mCRC is oxaliplatin, irinotecan, and fluoropyrimidine-based chemotherapy in combination with bevacizumab or cetuximab [*KRAS* wild-type, epidermal growth factor receptor (EGFR)-expressing] (2). The third-line treatment options in China include regorafenib, fruquintinib, and trifluridine/tipiracil (TAS-102).

Fruquintinib is a highly selective and orally administered

tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor receptors (VEGFRs), which inhibits VEGFR phosphorylation, endothelial cell proliferation, and tubule formation (4). Fruquintinib was approved in China for patients with metastatic CRC who had failed at least two prior systemic anti-neoplastic therapies, including fluorouracil, oxaliplatin, and irinotecan, with or without prior use of anti-VEGF or anti-EGFR therapy (5). The FRESCO and FRESCO-2 study, which are pivotal Phase III clinical trials, demonstrated that fruquintinib was well tolerated with consistent efficacy in mCRC patients in both China and worldwide (6). In the FRESCO study, median overall survival (mOS) was significantly prolonged with fruquintinib compared with placebo [9.3 months, 95% confidence interval (CI): 8.2–10.5 *vs.* 6.6 months, 95% CI: 5.9–8.1]; hazard ratio (HR) for death, 0.65 (95% CI: 0.51–0.83; $P < 0.001$). Median progression-free survival (mPFS) was also significantly increased with fruquintinib (3.7 months, 95% CI: 3.7–4.6 *vs.* 1.8 months, 95% CI: 1.8–1.8 months); HR for progression or death, 0.26 (95% CI: 0.21–0.34; $P < 0.001$) (7). In the FRESCO-2 study, the mOS was 7.4 months in the fruquintinib group ($n=461$) *vs.* 4.8 months in the placebo group ($n=230$) (HR 0.66; 95% CI: 0.55–0.80; $P < 0.001$). mPFS was 3.7 months in the fruquintinib group *vs.* 1.8 months in the placebo group (HR 0.32; 95% CI: 0.27–0.39; $P < 0.001$) (8).

Fruquintinib was approved in China by the National Medical Products Administration (NMPA) in 2018, and some retrospective studies have verified its clinical efficacy and safety (9,10). However, the sample size is relatively small or there is only a safety evaluation, and it remains unclear, how to identify the specific patients who are able to achieve significant survival benefits from fruquintinib. The aim of this study was to analyze efficacy, safety, and predictive and prognostic factors of fruquintinib; thus, we could assess its curative effect and create a prognosis prediction model. We present this article in accordance

Highlight box

Key findings

- Fruquintinib showed encouraging antitumor activity and controllable safety in metastatic colorectal cancer. L3 skeletal muscle index (SMI), brain metastasis and carcinoembryonic antigen (CEA) could serve as potential markers for patient selection.

What is known and what is new?

- The real-world efficacy and safety of fruquintinib in advanced colorectal cancer patients are numerically superior to that in the previous phase III studies.
- Multivariate analysis suggested that brain metastasis, decreased L3 SMI $>5\%$, and baseline CEA level as independent predictors of overall survival.

What is the implication, and what should change now?

- Due to the design bias and other limitations, additional trial with large samples is needed.

with the STROBE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-24-559/rc>).

Methods

Patients

This study analyzed mCRC patients who underwent fruquintinib therapy from seven cancer centers in Ningbo, Zhejiang Province. The inclusion criteria were as follows: histologically confirmed mCRC; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; at least one completed course of fruquintinib. Baseline information were recorded, including patient demographics, clinical characteristics, drug dose, prior treatment lines, metastatic sites, and so on. Efficacy and safety data of the enrolled patients were also collected. The patients who met the enrollment criteria to receive fruquintinib, either as a single agent or in combination, with monthly follow-up including adverse reaction recording, and efficacy assessment every 2 months and L3 skeletal muscle index (SMI) recorded until disease progression or intolerable adverse effects.

Image collection and analysis

An experienced radiologist evaluated radiographic sarcopenia in this study. The skeletal muscle area in the third lumbar plane was used as the measurement criterion, including psoas, paraspinous, and abdominal wall muscles. Computed tomography (CT) scans acquired at the baseline were recorded as CT1, and the first follow up CT assessment during therapy was recorded as CT2. All CT examinations were required to have both plain and enhanced scan. L3 SMI is defined as skeletal muscle area (SMA; cm^2) of the skeletal muscle at L3 level/square of the patient's height (m^2) on CT tomography (11,12).

Parameters and statistical analysis

Referring to cut-off values for sarcopenia in the Chinese population, it was defined as males $40.8 \text{ cm}^2/\text{m}^2$ and females $34.9 \text{ cm}^2/\text{m}^2$, and this was used for population analysis in this study (13). Predictive and prognostic value of baseline sarcopenia and subsequent skeletal muscle loss (SML) (at least 5% reduction in SMI compared to baseline) were analyzed. Tumor assessment was performed every 2 cycles according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and adverse effects (AEs) were

classified and graded according to Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. The software SPSS 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis; chi-square test was used for univariate analysis, factors influencing progression-free survival (PFS) and overall survival (OS) after primary screening, followed by Cox regression for multivariate analysis, to find independent factors related to prediction and prognosis. mPFS and mOS were calculated using the Kaplan-Meier method and survival curves were plotted.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ningbo No. 2 Hospital Human Research Ethics Committee (No. PJ-NBEY-KY-2019-146-01) and informed consent was taken from all the patients. All participating hospitals/institutions were informed and agreed with this study.

Results

Clinical characteristics of patients

From January 2020 to January 2022, a total of 140 patients were selected and included in this study. The cut-off date was 30 July 2022. The median follow-up time 18.3 months (range, 6–29.3 months) and the median age was 63 years (range, 32–81 years). Most patients had good performance status (ECOG PS 0–1: 85%). The primary tumor site was mainly rectal cancer (51.4%), and metastases sites were as follows: liver metastasis (55.7%), lung metastasis (58.6%), lymph node metastasis (37.1%), brain metastasis (8.9%), and bone metastasis (11.3%). The median initial dose was 3.85 mg and the median relative dose intensity was 80%.

A total of 76 patients with completed CT1 and CT2 results were included in SMI analysis. The median SMI values for CT1 and CT2 were 40.3 (range, 23.1–62) and 39.2 (range, 21.1–53.9), respectively. According to the predefined criteria, 43 (56.6%) patients were identified as sarcopenia at the baseline measurements. During follow-up, SMI remained relatively stable, the majority of patients (74.3%) having decreases in SMI of $\leq 5\%$ (as shown in *Table 1*).

Efficacy

Efficacy evaluation results of the 76 patients are shown in *Table 2*. The clinical partial response (PR) rate was 15.8%

Table 1 Characteristics of enrolled population

Characteristics	No. patients (%)
Age	
<70 years	106 (75.7)
≥70 years	34 (24.3)
Gender	
Male	92 (65.7)
Female	48 (34.3)
PS score	
0 to 1	119 (85.0)
2	21 (15.0)
BMI, kg/m ²	
<18.5	11 (7.9)
≥18.5	129 (92.1)
Liver metastases	
Yes	78 (55.7)
No	62 (44.3)
Lung metastases	
Yes	82 (58.6)
No	58 (41.4)
Lymphatic metastasis	
Yes	52 (37.1)
No	88 (62.9)
Pelvic metastasis	
Yes	32 (22.9)
No	108 (77.1)
Brain metastasis	
Yes	5 (3.6)
No	135 (96.4)
Bone metastasis	
Yes	25 (17.9)
No	115 (82.1)
Peritoneal metastasis	
Yes	14 (10.0)
No	126 (90.0)
Primary tumor site	
Rectum	72 (51.4)
Colon	64 (45.7)
Small intestine	4 (2.9)

Table 1 (continued)**Table 1** (continued)

Characteristics	No. patients (%)
Gene	
KRAS mutant	89 (65.4)
KRAS wild type	47 (34.6)
SMI baseline	
Male ≥40.8, female ≥34.9	33 (43.3)
Male <40.8, female <34.9	43 (56.5)
SMI change	
Decrease ≤5%	55 (74.3)
Decrease >5%	19 (25.7)
CEA	
≤5 ng/L	56 (40.0)
>5 ng/L	84 (60.0)
CA19-9	
≤34 U/mL	49 (52.1)
>34 U/mL	45 (47.9)
Therapeutic drug	
<3 rd line	21 (22.6)
≥3 rd line	72 (77.4)
Dose administered	
2 mg	2 (1.4)
3 mg	64 (45.7)
4 mg	27 (19.3)
5 mg	47 (33.6)

During the data statistics, it was found that some baselines were missing, resulting in a non-uniform total number of cases. PS, performance status; BMI, body mass index; SMI, skeletal muscle mass index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 2 Efficacy evaluation results for 76 patients who underwent CT follow-up (L3 cross-sectional measurement)

Tumor response criteria by RECIST v.1.1	No. patients (%)
CR	0
PR	12 (15.8)
SD	57 (75.0)
PD	7 (9.2)
DCR	69 (90.8)

CT, computed tomography; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate.

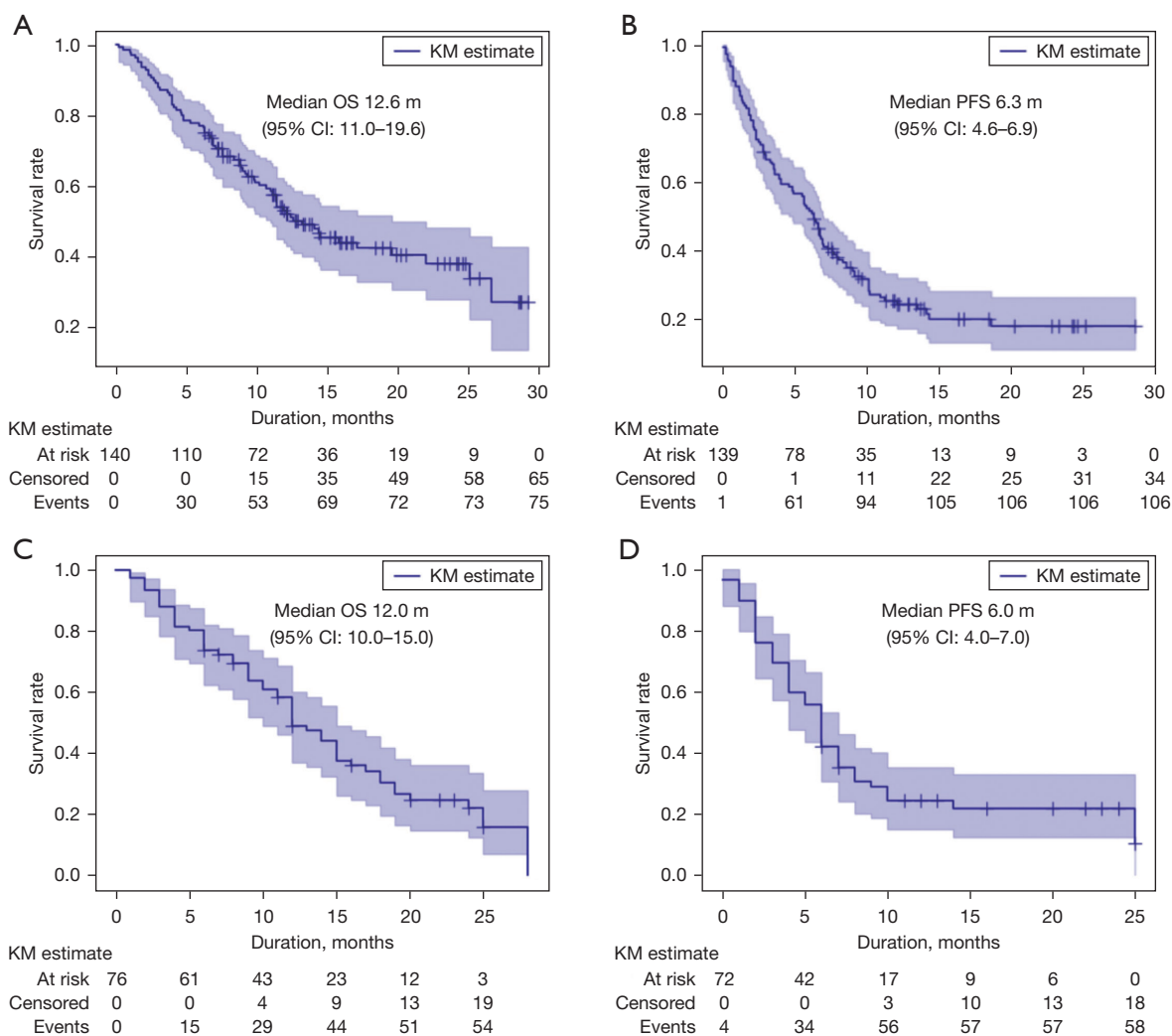


Figure 1 The patient’s OS and PFS results. (A) OS for 140 patients who were included in SMI analysis. (B) PFS for 140 patients who were included in SMI analysis. (C) OS for 76 patients. (D) PFS for 76 patients. KM, Kaplan-Meier; OS, overall survival; CI, confidence interval; PFS, progression-free survival; SMI, skeletal muscle mass index.

and the disease control rate (DCR) was 90.8%, which suggests that most patients could benefit from fruquintinib treatment. The mOS for the 140 patients was 12.6 months (Figure 1A), and the mPFS was 6.3 months (Figure 1B). In addition, the mOS for the 76 patients was 12.0 months (Figure 1C), and the mPFS was 6.0 months (Figure 1D).

By univariate analysis, we noticed that multiple parameters were associated with PFS, such as PS score, body mass index (BMI), brain metastasis, SMI decrease of >5%, baseline carcinoembryonic antigen (CEA) level (Table 3). Further multivariate analysis identified that brain metastasis, and baseline CEA level (>5 ng/L) were

independent predictors of PFS (Figure 2). Univariate and multivariate analysis regarding prognostic prediction of OS was performed. The results of univariate analysis indicated that PS score, BMI, primary tumor site, brain metastasis, nutritional prognostic index, SMI decrease of >5%, baseline CEA and carbohydrate antigen 19-9 (CA 19-9) levels (Table 4) can predict patients’ prognosis and survival. Multivariate analysis of these predictors suggested brain metastasis, decrease in SMI of >5%, and baseline CEA level as independent predictors of OS (Figure 3).

According to the above full-sample analysis and statistical results in this study, a total of two characteristics established

Table 3 Univariate analysis of progression-free survival

Variables	No. patients (%)	Median survival (months)	χ^2 value	P value
Age			0.172	0.67
<70 years	106 (75.7)	7.90		
\geq 70 years	34 (24.3)	7.67		
Gender			1.002	0.31
Male	92 (65.7)	8.60		
Female	48 (34.3)	6.30		
BMI, kg/m ²			6.093	0.01
<18.5	11 (7.9)	2.80		
\geq 18.5	129 (92.1)	8.60		
PS score			9.155	0.002
0 to 1	119 (85.0)	9.00		
2	21 (15.0)	2.33		
Lung metastases			0.063	0.80
Yes	82 (58.6)	6.77		
No	58 (41.4)	8.60		
Pelvic metastasis			0.857	0.35
Yes	32 (22.9)	6.43		
No	108 (77.1)	7.67		
Brain metastasis			5.533	0.01
Yes	5 (3.6)	3.30		
No	135 (96.4)	8.60		
Bone metastasis			0.958	0.32
Yes	25 (17.9)	6.77		
No	115 (82.1)	8.60		
Peritoneal metastasis			0.510	0.47
Yes	14 (10.0)	10.13		
No	126 (90.0)	6.93		
Primary tumor site			4.010	0.13
Rectum	72 (51.4)	9.37		
Colon	64 (45.7)	5.70		
Small intestine	4 (2.9)	–		
Gene			0.757	0.38
KRAS mutant	89 (65.4)	7.67		
KRAS wild type	47 (34.6)	9.00		
NLR			0.330	0.56
<3	55 (54.5)	10.13		
\geq 3	46 (45.5)	7.67		

Table 3 (continued)

Table 3 (continued)

Variables	No. patients (%)	Median survival (months)	χ^2 value	P value
NLR			0.023	0.88
<5	83 (82.2)	7.90		
≥ 5	18 (17.8)	10.90		
LMR			0.771	0.38
<3.75	86 (85.1)	7.90		
≥ 3.75	15 (14.9)	10.13		
Albumin			3.308	0.06
<35 g/L	19 (19.4)	4.80		
≥ 35 g/L	79 (80.6)	10.13		
PNI			2.601	0.10
<40	24 (23.5)	6.00		
≥ 40	78 (76.5)	10.13		
SMI baseline			0.128	0.72
Male ≥ 40.8 , female ≥ 34.9	33 (43.4)	10.90		
Male <40.8, female <34.9	43 (56.6)	7.90		
SMI change			4.730	0.03
Decrease $\leq 5\%$	55 (74.3)	–		
Decrease >5%	19 (25.7)	6.43		
CEA			8.084	0.004
≤ 5 ng/L	30 (31.3)	–		
>5 ng/L	66 (68.8)	6.23		
CA19-9			2.683	0.10
≤ 34 U/mL	49 (52.1)	10.13		
>34 U/mL	45 (47.9)	5.80		
Therapeutic drug			0.005	0.94
<3 rd line	21 (22.6)	7.67		
≥ 3 rd line	72 (77.4)	7.90		
Dose			6.054	0.10
2 mg	2 (1.4)	0.70		
3 mg	64 (45.7)	10.13		
4 mg	27 (19.3)	8.60		
5 mg	47 (33.6)	6.00		

During the data statistics, it was found that some baselines were missing, resulting in a non-uniform total number of cases. Because of the different domain values explored, the NLR grouping is repeated. BMI, body mass index; PS, performance status; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index; SMI, skeletal muscle mass index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

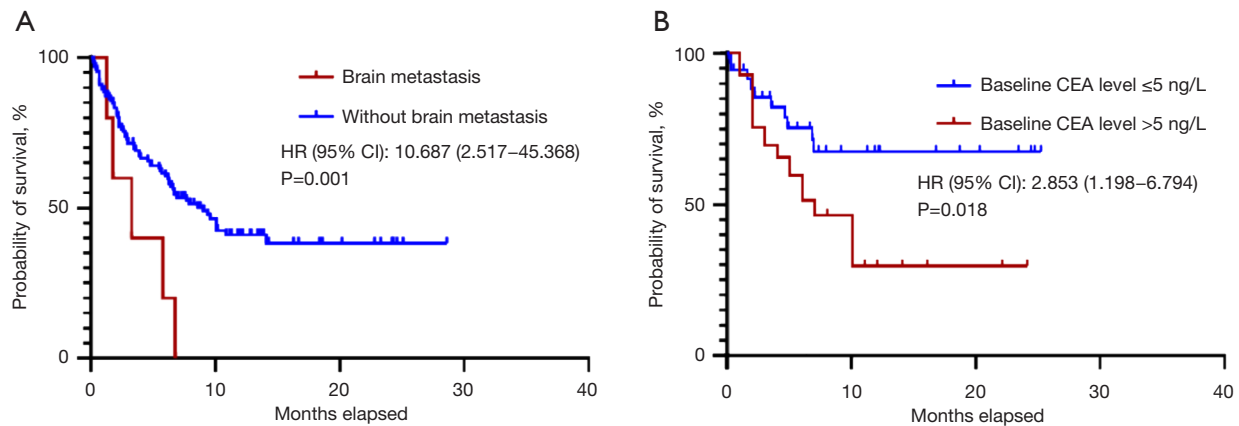


Figure 2 Kaplan-Meier curves showing PFS for brain metastasis and without brain metastasis groups (A); and baseline CEA level >5 or ≤5 ng/L subgroups (B). HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; PFS, progression-free survival.

the nomogram, brain metastasis, and baseline CEA level (>5 ng/L) with statistical significance (Figure 4A). According to the above full-sample analysis and statistical results in this study, a total of 3 characteristics established the nomogram: brain metastasis, SMI decrease of >5%, and baseline CEA level (>5 ng/L) with statistical significance (Figure 4B).

Safety

According to CTCAE v 5.0, 78 (55.7%) of the 140 patients experienced at least 1 any grade treatment-emergent adverse event (TEAE), among whom, 12 (8.6%) experienced ≥ grade 3 TEAE. Some 78 (55.7%) of the 140 patients experienced at least 1 treatment-related adverse event (TRAE), among whom 8 (5.7%) experienced ≥ grade 3 TEAE. The most common TEAEs were hypertension (24, 17.1%), hand-foot syndrome (20, 14.3%), fatigue (21, 15%), oropharyngeal pain (10, 7.1%), and decreased appetite (10, 7.1%). The most common TRAEs were hypertension (24, 17.1%), fatigue (21, 15%), hand-foot syndrome (20, 14.3%), oropharyngeal pain (10, 7.1%), and decreased appetite (10, 7.1%) (Table 5). There were 9 (13.6%) patients who had a dose reduction due to TRAEs, and 15 (10.7%) patients had treatment discontinuation due to TRAEs. Cox regression analysis showed that hand-foot syndrome, asthenia, and oral mucositis were associated with OS; asthenia, hoarseness, and mucositis oral were associated with PFS prognosis (Table 6).

Discussion

The latest Chinese cancer epidemiology study reported

that CRC ranks second with 517,100 new cases per year (3). When it comes to such a huge patient population, the treatment of CRC patients is particularly important. Fruquintinib is used as the standard third-line treatment regimen for advanced CRC (4). The FRESCO (7) and FRESCO-2 (14) studies demonstrated a consistent PFS of 3.7 months in the fruquintinib group, and the PFS observed in other small-sample real-world studies is around 5–7 months (15,16). In this study, a PFS of 6.3 months and an OS of 12.6 months was achieved, which may be related to individualized treatment strategy, and experienced AE management in our centers. Patients have a higher average duration and intensity of medication, thus resulting in better efficacy and survival prognosis. We aimed to identify the specific patients who can achieve significant survival benefits from fruquintinib treatment. This study analyzed 140 real-world cases of advanced CRC treated with fruquintinib, and for the first time analyzed the prognostic predictive relationship between sarcopenia and fruquintinib, identifying independent predictors associated with prognosis through Cox regression, forming an effective predictive model.

Sarcopenia is an important marker of malnutrition and a study has used the SMI of the third lumbar spine to diagnose sarcopenia in patients (17). Sarcopenia is a syndrome characterized by progressive, generalized SML and hypofunction. The European Working Group on Sarcopenia in the Elderly Patients considered that sarcopenia is a progressive, systemic skeletal muscle disorder that may increase the likelihood of adverse outcomes such as falls, fractures, physical disability, and

Table 4 Univariate analysis affecting overall survival

Variables	No. patients (%)	Median survival (months)	χ^2 value	P value
Age			1.933	0.16
<70 years	106 (75.7)	14.47		
\geq 70 years	34 (24.3)	11.37		
Gender			0.969	0.32
Male	92 (65.7)	14.47		
Female	48 (34.3)	12.37		
PS score			11.731	0.001
0 to 1	119 (85.0)	15.83		
2	21 (15.0)	8.90		
BMI, kg/m ²			5.951	0.015
<18.5	11 (7.9)	6.93		
\geq 18.5	129 (92.1)	14.43		
Lung metastases			1.027	0.31
Yes	82 (58.6)	13.17		
No	58 (41.4)	12.37		
Pelvic metastasis			2.360	0.12
Yes	32 (22.9)	8.43		
No	108 (77.1)	14.43		
Brain metastasis			5.044	0.02
Yes	5 (3.6)	8.90		
No	135 (96.4)	14.07		
Bone metastasis			0.589	0.44
Yes	25 (17.9)	11.03		
No	115 (82.1)	13.17		
Peritoneal metastasis			0.029	0.86
Yes	14 (10.0)	19.57		
No	126 (90.0)	12.57		
Primary tumor site			8.081	0.01
Rectum	72 (51.4)	17.13		
Colon	64 (45.7)	9.83		
Small intestine	4 (2.9)	–		
Gene			0.002	0.96
KRAS mutant	89 (65.4)	14.43		
KRAS wild type	47 (34.6)	13.17		
NLR			0.216	0.64
<3	55 (54.5)	17.13		
\geq 3	46 (45.5)	12.57		

Table 4 (continued)

Table 4 (continued)

Variables	No. patients (%)	Median survival (months)	χ^2 value	P value
NLR			0.005	0.94
<5	83 (82.2)	12.57		
≥ 5	18 (17.8)	26.73		
LMR			0.515	0.47
<3.75	86 (85.1)	17.13		
≥ 3.75	15 (14.9)	11.90		
Albumin			3.640	0.05
<35 g/L	19 (19.4)	8.80		
≥ 35 g/L	79 (80.6)	19.57		
PNI			4.798	0.02
<40	24 (23.5)	8.80		
≥ 40	78 (76.5)	19.57		
SMI baseline			0.127	0.72
Male ≥ 40.8 , female ≥ 34.9	33 (43.4)	26.73		
Male <40.8, female <34.9	43 (56.6)	17.13		
SMI change			6.038	0.01
Decrease $\leq 5\%$	55 (74.3)	26.73		
Decrease >5%	19 (25.7)	11.37		
CEA			9.119	0.003
≤ 5 ng/L	56 (40.0)	–		
>5 ng/L	84 (60.0)	10.20		
CA19-9			3.832	0.050
≤ 34 U/mL	49 (52.1)	22.03		
>34 U/mL	45 (47.9)	9.90		
Therapeutic drug			0.003	0.95
<3 rd line	21 (22.6)	12.37		
$\geq 3^{\text{rd}}$ line	72 (77.4)	12.57		
Dose administered			5.850	0.11
2 mg	2 (1.4)	7.57		
3 mg	64 (45.7)	15.83		
4 mg	27 (19.3)	19.57		
5 mg	47 (33.6)	9.83		

During the data statistics, it was found that some baselines were missing, resulting in a non-uniform total number of cases. Because of the different domain values explored, the NLR grouping is repeated. PS, performance status; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index; SMI, skeletal muscle mass index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

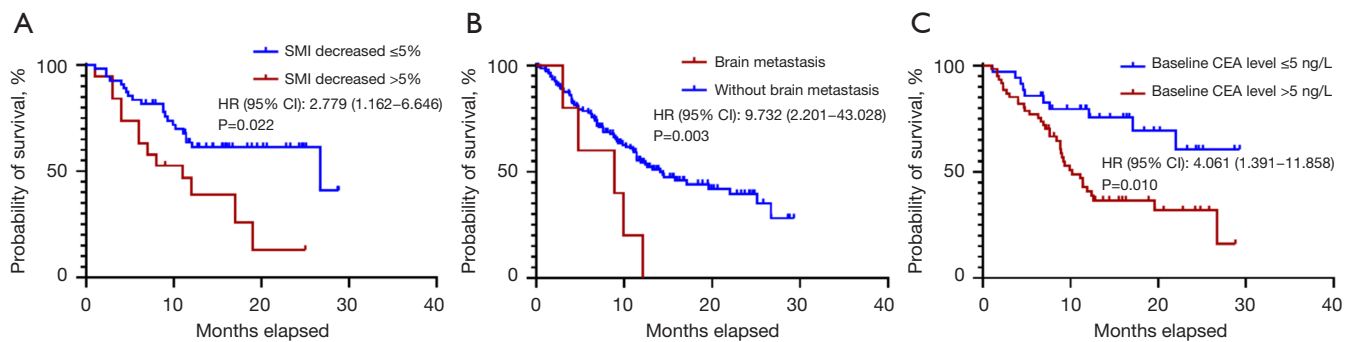


Figure 3 Kaplan-Meier curves showing OS for SMI decreased $\leq 5\%$ or $> 5\%$ subgroups (A); brain metastasis and without brain metastasis groups (B); and baseline CEA level > 5 or ≤ 5 ng/L subgroups (C). SMI, skeletal muscle mass index; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; OS, overall survival.

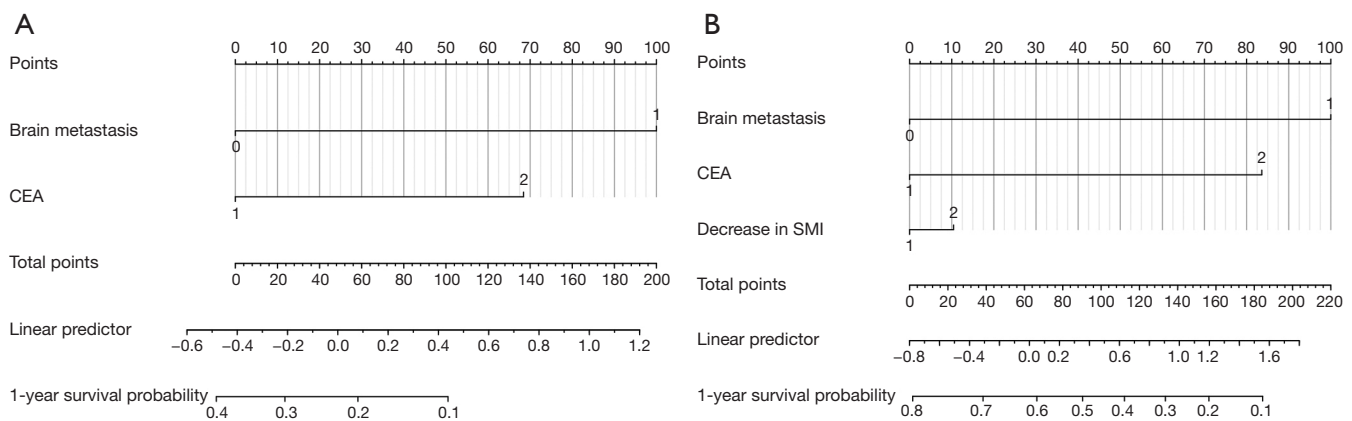


Figure 4 Nomogram predicting 1-year PFS probability (A) and OS probability (B) of 140 mCRC patients. CEA, carcinoembryonic antigen; SMI, skeletal muscle mass index; PFS, progression-free survival; OS, overall survival; mCRC, metastatic colorectal cancer.

death (18). Tumor-associated sarcopenia not only affects the normal metabolism of body components, but also reduces the therapeutic efficacy, quality of life, and survival of patients (19). Studies have suggested that release of inflammatory cytokines such as interleukin 1 (IL-1), tumor necrosis factor- α (TNF- α), and interleukin 6 (IL-6) may be associated with sarcopenia, and alterations in these parameters may affect the prognosis of advanced CRC (20,21).

Several small studies have indicated that patients with advanced CRC who developed sarcopenia after treatment with TAS-102 or regorafenib had a lower 1-year survival rate. Sarcopenia is considered a poor prognostic factor in patients with CRC (22-24), but no studies have confirmed any specific values or proportion of muscle decrease can predict the survival prognosis of patients with CRC. The

analysis in this study showed that sarcopenia and other clinical indicators were associated with survival prognosis in advanced CRC treated with fruquintinib. In prognosis prediction of PFS and OS, PS score 2, BMI < 18.5 kg/m², and SMI decrease $> 5\%$ all showed shorter OS; conversely, PFS and OS were significantly prolonged by PS scores 0–1, BMI ≥ 18.5 kg/m², and SMI reduction $\leq 5\%$, which means that good general condition and good maintenance of nutritional status during treatment will bring longer survival benefits. Further multivariate analysis identified that SMI reduction $> 5\%$ was an independent predictor of OS. Therefore, during fruquintinib treatment, we should continuously monitor the nutritional status of patients, conduct timely nutritional risk assessment and intervention, and maintain a good SMI, to ensure that patients are keep benefiting from the treatment.

Table 5 Summary of adverse events

Adverse events	TEAE, n (%)		TRAE, n (%)	
	All grade	Grade 3–4	All grade	Grade 3–4
All adverse events	78 (55.7)	12 (8.6)	78 (55.7)	8 (5.7)
Hypertension	24 (17.1)	6 (4.3)	24 (17.1)	4 (2.9)
Hand-foot syndrome	20 (14.3)	1 (0.7)	20 (14.3)	1 (0.7)
Fatigue	21 (15)	0	21 (15)	0
Hoarseness	12 (8.6)	0	5 (3.6)	0
Oropharyngeal pain	10 (7.1)	2 (1.4)	10 (7.1)	2 (1.4)
Appetite decreased	10 (7.1)	0	10 (7.1)	0
Diarrhea	8 (5.7)	0	8 (5.7)	0
Dysphonia	7 (5)	0	7 (5)	0
Mucositis oral	5 (3.6)	1 (0.7)	5 (3.6)	0
Proteinuria	4 (2.9)	1 (0.7)	4 (2.9)	0
Abdominal pain	4 (2.9)	0	4 (2.9)	0
Myalgia	4 (2.9)	0	4 (2.9)	0
Constipation	3 (2.1)	0	2 (1.4)	0
Arthralgia	3 (2.1)	0	3 (2.1)	0
Weight decreased	3 (2.1)	0	3 (2.1)	0
Fever	2 (1.4)	1 (0.7)	1 (0.7)	0
Platelet count decreased	2 (1.4)	1 (0.7)	2 (1.4)	1 (0.7)
Peripheral sensory nerve disorder	2 (1.4)	0	2 (1.4)	0
Eczema	2 (1.4)	0	2 (1.4)	0
Myocardial infarction	1 (0.7)	1 (0.7)	0	0
Diabetes	1 (0.7)	0	1 (0.7)	0
Intestinal obstruction	1 (0.7)	0	1 (0.7)	0
Cold	1 (0.7)	0	0	0
Anorectal infection	1 (0.7)	0	1 (0.7)	0
Hyperuricemia	1 (0.7)	0	1 (0.7)	0
Testicular pain	1 (0.7)	0	1 (0.7)	0
Hypothyroidism	1 (0.7)	0	1 (0.7)	0
Urinary tract infection	1 (0.7)	0	1 (0.7)	0
Pruritus	1 (0.7)	0	1 (0.7)	0
Cognitive disorder	1 (0.7)	0	1 (0.7)	0
Headache	1 (0.7)	0	1 (0.7)	0
Vertigo	1 (0.7)	0	1 (0.7)	0
Alopecia	1 (0.7)	0	1 (0.7)	0
Hematuria	1 (0.7)	0	1 (0.7)	0
Back pain	1 (0.7)	0	1 (0.7)	0

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Table 6 Univariate analysis of adverse reactions and OS or PFS

Variables	Median survival (months)	χ^2 value	P value
Univariate analysis of adverse reactions and OS			
Hand-foot syndrome		4.428	0.03
Yes	22.03		
None	11.90		
Asthenia		3.986	0.04
Yes	7.60		
None	14.07		
Oral mucositis		5.417	0.02
Yes	8.43		
None	14.07		
Univariate analysis of adverse reactions and PFS			
Asthenia		5.003	0.02
Yes	2.97		
None	8.60		
Hoarseness		4.340	0.03
Yes	2.13		
None	8.60		
Oral mucositis		8.976	0.003
Yes	2.50		
None	9.00		

OS, overall survival; PFS, progression-free survival.

As a classical tumor marker in CRC patients, the application value of CEA is widely known in clinical practice. Subgroup analysis of the FRESCO study noticed that early alterations in CEA might be a potential predictor (25). In this study, we noticed that baseline CEA may associate with the PFS and OS of patients who underwent fruquintinib treatment: baseline CEA levels ≤ 5 ng/L compared with >5 ng/L, mOS: not yet reached (NR) *vs.* 10.2 months ($P=0.003$), mPFS: NR *vs.* 6.23 months ($P=0.004$); further multivariate analysis identified baseline CEA level as an independent predictor of fruquintinib treatment in patients with advanced CRC.

From the clinical characteristics of patients, primary tumor site, brain metastasis could affect the OS, whereas brain metastasis was independent predictors of PFS and OS. This means that patients with this clinical characteristic

can receive early interventional therapy with fruquintinib to improve their condition.

In this study, the incidence of any grade or \geq grade 3 TEAEs and TRAEs is lower than that in the FRESCO and other studies (7,9,10). This difference could be explained by the nature of real-world studies. A prospective randomized trial requires a very specific follow up visit plan, in which the regular laboratory test can help physicians identify many asymptomatic AEs, such as proteinuria, elevated transaminases, abnormal blood cells, and so on. In the real-world setting, patients are not strictly followed and most of the AEs are collected from their chief complaint during follow up consultation. The most common TEAEs in this study were hypertension (24, 17.1%), hand-foot syndrome (20, 14.3%), and fatigue (21, 15%) the incidences of which were similar to those in a previous report (7). Patients with an underlying medical history had a higher incidence and grade of TEAEs. Therefore, very careful AE monitoring and management is particularly required for this population. In addition, this study found that the occurrence of fatigue and oral mucositis was associated with PFS and OS, but the incidence of this two AEs were low and independent predictive factor analysis could not be performed, which could be used as a clinical prompt. When this AE occurs in the future treatment process, patients should be encouraged to adhere to the medication and cannot arbitrarily discontinue the drug or reduce the dose, to ensure the efficacy of the treatment.

Conclusions

In conclusion, the real-world efficacy and safety are numerically superior to those in the FRESCO study. This study firstly clarified the relationship between sarcopenia and prognosis prediction of these patients. We also noticed that brain metastasis, SMI decrease of $>5\%$, and baseline CEA level (>5 ng/L) may indicate prognosis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-24-559/rc>

Data Sharing Statement: Available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-24-559/dss>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-24-559/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ningbo No. 2 Hospital Human Research Ethics Committee (No. PJ-NBEY-KY-2019-146-01) and informed consent was taken from all the patients. All participating hospitals/institutions were informed and agreed with this study.

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