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ORIGINAL RESEARCH

A Cost Analysis of Adverse Event Management of Systemic Therapies for Metastatic Colorectal Cancer on Patients with at Least Two Previous Lines of Treatment in Spain

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Objective: First, to estimate the cost associated with the management of grade ≥3 adverse events (AEs) experienced by patients with metastatic colorectal cancer (mCRC) who had received late-line therapies (3L+) in Spain. Second, based on the tolerability profiles, the total AEs cost per therapy was estimated.

Methods: A cost-analysis was developed to estimate the economic impact associated with the patient management throughout the course of related-AEs of currently available 3L+ therapies for mCRC in Spain (regorafenib, fruquintinib, trifluridine/tipiracil (T/T) and T/T + bevacizumab). The National Health System (NHS) perspective was selected, thus only direct healthcare resources were considered (pharmaceutical treatments, specialist visits, hospital admissions and procedures). For each AE, a total management cost was calculated by multiplying resource consumption by its unitary cost. Finally, for each alternative, the total AEs cost was estimated multiplying the AEs incidence rate by its management cost. Unit costs (€, 2025) were obtained from national databases. AEs incidence rates were obtained from pivotal clinical trials. Anchored comparisons were calculated using a difference-in-differences (DID) approach with best-supportive care as a common reference.

Results: Total cost associated with AEs grade ≥3 occurring in patients with mCRC receiving 3L+ ranged from €300.19/patient for the management of hypertension to €3335.11/patient for increased bilirubin. Adjusting AEs for reported incidences, the total cost was €284.54 for fruquintinib (FRESCO), €301.82 for fruquintinib (FRESCO-2), €749.91 for T/T + bevacizumab (SUNLIGHT), €750.56 for T/T (SUNLIGHT), €1383.57 for T/T (RECOURSE) and €1158.57 for regorafenib (CORRECT). Fruquintinib in the anchored comparison based on FRESCO and FRESCO-2 shows: a cost reduction of €398.70 and €360.98 compared to regorafenib (CORRECT), and a cost reduction of €491.55 and €453.83 compared to T/T (RECOURSE).

Conclusion: The results of this analysis showed that fruquintinib was associated with lower management costs of AEs in patients with mCRC treated in late-line in Spain.

Keywords: metastatic colorectal cancer, safety, cost-management

Introduction

Colorectal cancer (CRC) is a type of tumour located in the colon or rectum, the average age of onset is 70–71 years, and most patients are over 50 years old at the time of diagnosis.[1] Worldwide, CRC is the third most frequent neoplasm, accounting for approximately 10% of all neoplasm cases, and currently is the second leading cause of cancer-related

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deaths (9.3%).[2,3] In Spain, CRC is considered the most frequent tumour, with an estimated 44,573 new cases in 2025.[4] Regarding mortality, 15,401 deaths were reported in the year 2024, with a rate of 32 deaths per 100,000 inhabitants.[5]

The prognosis of CRC is directly related to the clinical stage at the time of diagnosis. Five-year survival in patients with early diagnosis when the tumour remains localized exceeds 90%, while in more disseminated stages it is around 15–70%.[6,7] Metastases cases account for the lowest rates of survival, approximately 15–30% of patients with CRC present with metastases at the time of diagnosis, and approximately 20–50% of patients develop metastases during the course of their disease.[7–9] In Spain, in 2021, the 3-year survival in patients with metastatic CRC (mCRC) was around 29%.[10,11]

Beyond the direct consequences on the survival or life expectancy, patients with mCRC face a high symptom burden related to severe adverse events (AEs) associated with the disease itself (fatigue, anxiety, constipation, diarrhea, etc)., with the location of the metastases, and with the treatments they receive. Therefore, treatments for these patients should not only focus on improving their survival, but also on trying, as far as possible, to improve or maintain their quality of life (QoL).[12–14]

Currently, first-line treatment for mCRC consists of doublets or triplets of irinotecan or oxaliplatin and fluorouracil combined with biological therapies (anti-VEGF or anti-EGFR) or immunotherapy according to the molecular characteristics of each tumour.[8,15,16] Once patients progress to subsequent lines, normally, targeted therapeutic options are no longer feasible, tending to have moderate responses to treatments,[8,15,16] thus, in these patients, a good prognosis is mainly predicted by low tumour burden, less aggressive and/or more chemosensitive disease.[17] Additionally, most patients do not have targetable driving genomic mutations and therefore cannot be treated with targeted therapies, leading to a limited number of effective and tolerable therapeutic options.[18,19] All these points highlight an unmet need in patients undergoing late-line treatment, more effective treatment options are needed to individualize treatments and improve the survival in these patients.

The patient pathway between subsequent line therapies will depend on prior treatment, available options and patient preferences.[15] At the moment, the drugs approved in Spain for the treatment of mCRC in patients previously treated with multiple lines of therapy are regorafenib (a multi-kinase inhibitor),[20] fruquintinib (a VEGFR 1, 2 and 3 selective inhibitor),[21] trifluridine/tipiracil (T/T) (a cytotoxic metabolite)[22] and T/T plus bevacizumab (a VEGF monoclonal antibody).[23]

Although outcomes have improved since the introduction of these new therapeutic alternatives, showing significant improvements in the survival and in the QoL of patients with mCRC,[1,6] these new therapies are not exempt from the occurrence of AEs. It is widely recognized that the severity and frequency of AEs directly affect the QoL of patients,[24,25] and, at this line of treatment where clinical response is limited, the maintenance of the QoL becomes particularly relevant.[16] Besides, it is reasonable to assume that AEs also interferes with the adherence and discontinuation of treatments and the failure to comply with treatment regimens may ultimately lead to worse clinical outcomes.

In addition, from the onset of those AEs, special patient management and follow-up is required, particularly with more severe cases (grade ≥3), which may imply additional costs for the National Health Systems (NHS).[26,27] Therefore, the objective of this study was to estimate the cost associated with the management of each of the most frequent grade ≥3 AEs experienced by patients with mCRC who had received at least two prior lines of treatment in Spain. Furthermore, based on the specific tolerability profiles of therapies, the total cost of managing all these AEs associated with the drug used in the late line of treatment (3L+) was also estimated.

Materials and Methods

An analytical decision model was conceived, designed and developed to estimate the economic impact of the management of AEs associated with late-line therapies (3L+) in patients with mCRC in Spain.

The project was carried out in the following main phases: 1) a first phase consisting of the identification of the AEs to be considered in the analysis; 2) a second phase for the identification and quantification of the direct healthcare resources required for the management of any of the selected AEs; 3) a third phase for the estimation of the total cost associated with the management of each of the AEs considered in the analysis; 4) finally a fourth phase consisting of the estimation

of the total cost for the management of the AEs of each of the different mCRC late-line treatments according to the different frequency of occurrence of the AEs.

Economic Model

The cost-analysis model was designed and programmed in Microsoft Excel®. The analysis was performed from the perspective of the Spanish NHS, therefore only costs related to direct healthcare resources were estimated. The time horizon considered in the model captured the resource utilization associated with managing the patient throughout the course of the AEs.

For the development of the model, a multidisciplinary expert panel composed of 4 oncologists, with wide experience in the management of patients with mCRC, and 3 health economics specialists was carried out to identify and validate the parameters to be considered in the analysis. For this purpose, a structured questionnaire was designed by the team of health economists and shared individually with each of the oncologists to be completed according to their experience in clinical practice. Subsequently, a consensus meeting was held with all members of the expert panel, in which the structure of the conceived model, as well as all the parameters and values necessary for the development of the analysis were presented, discussed, validated and agreed.

Adverse Events Considered

The analysis considered AEs reported in pivotal clinical trials of the currently available therapies (regorafenib, T/T, T/T + bevacizumab and fruquintinib), approved and reimbursed in Spain, for use in patients with mCRC who had received at least two prior lines of treatment. Treatment-related AEs of grade ≥3 reported in at least 5% of patients in any of the following clinical trials were selected for inclusion in the model: FRESCO,[28] FRESCO-2,[10] CORRECT,[29] RECOURSE[30] and SUNLIGHT.[31] Grade 1 and 2 AEs were excluded from the analysis, as it was assumed that AEs of grade ≥3 are those associated with the highest resource consumption for their management, thus accounting for most of the overall economic impact.

Therefore, the following grade ≥3 AEs were identified in the aforementioned trials: anemia, asthenia, diarrhea, fatigue, hand-foot syndrome, hypertension, leukopenia, neutropenia, rash, thrombocytopenia, increased alanine aminotransferase, increased alkaline phosphatase, increased aspartate aminotransferase and increased bilirubin (Figure 1).

Resource Consumption and Management

In line with the perspective considered in the analysis, only direct healthcare resources associated with the management of grade ≥3 AEs in patients with mCRC were accounted.

The structured questionnaire used for collection of resource consumption included the identification of each of the health care resources, which were grouped into the following categories: specialist visits, hospital admissions (duration and unit of hospitalization), surgical procedures (type and duration), diagnostic procedures (laboratory and imaging), medications and other relevant resources associated with the management of the AEs considered in the analysis. For each resource considered, the questionnaire collected quantities and frequencies of use, as well as the proportion of patients with these consumptions.

Supplementary Table 1 shows, for each resource, the frequency and percentage of patients estimated by the expert panel for each of the AEs that can occur in patients with mCRC receiving a late-line treatment.

Cost Estimation

The total cost associated with the management of each of the AEs was calculated by multiplying the resources consumption by the unitary cost of each resource. Finally, for each of the alternatives considered in the model, the economic impact was estimated by multiplying the incidence rate by the management cost for each AE. As AEs were assumed to occur independently of each other, to calculate the total cost associated with the management of AEs for each treatment, the costs of all AEs were added together, as follows:

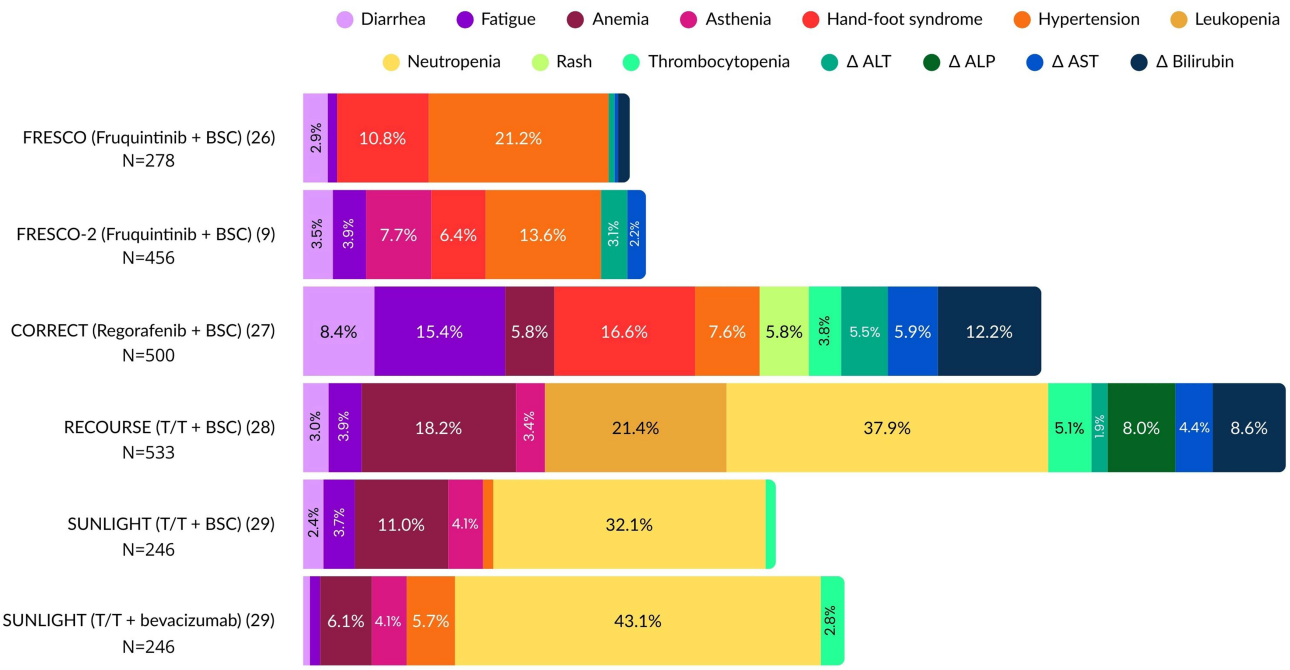

Figure 1 Incidence of grade ≥3 AEs observed in ≥5% of patients during pivotal clinical trials.
Abbreviations: Δ, Increased; BSC, Best Supportive Care; AEs, Adverse Events; ALP, Alkaline Phosphatase; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BSC, Best Supportive Care; T/T, Trifluridine/Tipiracil.

$$Total\ cost = (AE1\ incidence\ rate\ x\ AE1\ cost) + (AE2\ incidence\ rate\ x\ AE2\ cost) + (AE3\ incidence\ rate\ x\ AE3\ cost) + \ldots + (AEn\ incidence\ rate\ x\ AEn\ cost)$$

In line with previously published studies,[32] anchored comparisons of AEs management costs were also conducted using a difference-in-difference (DID) approach with best supportive care (BSC) as the common reference. Incremental AEs costs for each treatment versus BSC were estimated within each trial, and then comparisons of fruquintinib (FRESCO and FRESCO-2) versus T/T (RECOURSE) and regorafenib (CORRECT) were derived from the differences in these incremental costs. As the SUNLIGHT trial lacked a BSC arm, AEs costs for T/T + bevacizumab could not be anchored.

The unitary costs of the healthcare resources were obtained from a database containing information on healthcare costs published for Spain.[33] The pharmaceutical costs for each of the drugs were calculated from the ex-factory prices published by the General Council of Official Associations of Pharmacists in Spain,[34] applying the national mandatory deduction established in Royal Decree-Law 8/2010.[35]

All costs included in the model are expressed in euros valued for the year 2025 (€, 2025). Tables 1 and 2 detail the unitary cost of the healthcare resources and pharmaceutical treatment included in the analysis, respectively.

Results

Considering the resource consumption estimated by the expert panel for each of the AEs included in this analysis, the total cost associated with the management of grade ≥3 AEs occurring in patients with mCRC receiving 3L+ of treatment ranged from € 300.19 per patient for the management of hypertension to € 3335.11 per patient for the management of increased bilirubin. In most cases, AEs were managed by visits to specialists or to the emergency department, except for diarrhea, neutropenia and increased bilirubin, where the highest cost was associated with hospital admissions. Regarding visits, the oncologist was the specialist with the highest number of visits to resolve an AE. Among all AEs, hand-foot syndrome and hypertension had the highest rate of specialist visits, with these visits representing 99.5% and 98.0% of the total cost, respectively (Table 3).

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Table 1 Unitary Cost of the Healthcare Resources

Healthcare Resource	Unitary Cost (€, 2025)
Specialist visits	
Cardiology	€ 187.68
Day hospital	€ 414.60
Dermatology	€ 107.04
Emergency room	€ 230.11
Nursing care	€ 24.18
Nutritionist	€ 153.94
Oncology	€ 225.98
Primary care physician	€ 75.70
Hospital admissions	
Oncology admission	€ 626.42 per day
Procedures	
Abdominal ultrasound	€ 86.99
Biochemistry	€ 85.10
Blood culture	€ 20.54
Computed Axial Tomography scan	€ 152.17
Echocardiogram	€ 119.17
Hemogram	€ 7.68
Microbiological faeces analysis	€ 17.98
Urine culture	€ 10.50
Other resources	
Blood transfusion	€ 201.38 per pouch
Platelet transfusion	€ 94.75

Table 2 Price per mg or IU of Pharmaceutical Treatments (€, 2025)

Pharmaceutical Treatments	Ex-Factory Price per mg/IU	Pharmaceutical Treatments	Ex-Factory Price per mg/IU
Ciprofloxacin	€ 0.0002	Minocycline	€ 0.0029
Dexamethasone	€ 0.0500	Morphine	€ 0.0115
Epoetin alpha	€ 0.0058	Octreotide	€ 13.880
Ferric carboxymaltose	€ 0.2000	Oral clindamycin	€ 0.0006
Filgrastim	€ 0.1137	Prednisone	€ 0.0027
Fluconazole	€ 0.0137	Pregabalin	€ 0.0022

(*Continued*)

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Table 2 (Continued).

Pharmaceutical Treatments	Ex-Factory Price per mg/IU	Pharmaceutical Treatments	Ex-Factory Price per mg/IU
Ibuprofen	€ 0.0001	Topic betamethasone	€ 0.0300
Levofloxacin	€ 0.0024	Topic clindamycin	€ 0.0070
Loperamide	€ 0.1563	Topic clobetasol	€ 0.1100
Megestrol	€ 0.0048	Valacyclovir	€ 0.0015

Abbreviations: IU, International Units; mg, milligrams.

Table 3 Management Mean Cost per AE and by Type of Resource

Adverse Event	Specialist Visits, € (%)	Hospital Admissions, € (%)	Procedures, € (%)	Pharmaceutical Treatment, € (%)	Other Resources, € (%)	Total € (%)
Anemia	€ 912.58	€ 187.92	€ 185.56	€ 300.28	€ 463.17	€ 2049.51
	44.53%	9.17%	9.05%	14.65%	22.60%	100%
Asthenia	€ 396.08	€ 187.92	€ 148.44	€ 7.67	–	€ 740.12
	53.52%	25.39%	20.05%	1.04%		100%
Diarrhea	€ 682.38	€ 1566.04	€ 228.83	€ 10.71	–	€ 2487.96
	27.43%	62.94%	9.20%	0.43%		100%
Fatigue	€ 396.08	€ 187.92	€ 148.44	€ 7.67	–	€ 740.12
	53.51%	25.39%	20.06%	1.04%		100%
Hand-foot syndrome	€ 789.80	–	–	€ 3.73	–	€ 793.53
	99.53%			0.47%		100%
Hypertension	€ 294.23	–	€ 5.96	–	–	€ 300.19
	98.01%		1.99%			100%
Leukopenia	–	–	–	–	–	–
Neutropenia	€ 497.98	€ 626.42	€ 21.56	€ 92.62	–	€ 1238.57
	40.20%	50.58%	1.74%	7.48%		100%
Rash	€ 621.66	€ 313.21	–	€ 2.57	–	€ 937.43
	66.32%	33.41%		0.27%		100%
Thrombocytopenia	€ 463.46	€ 37.58	€ 15.36	–	€ 4.74	€ 521.14
	88.93%	7.21%	2.95%		0.91%	100%
Δ ALT	€ 463.46	€ 50.11	€ 192.95	€ 0.72	–	€ 707.24
	65.53%	7.09%	27.28%	0.10%		100%
Δ ALP	€ 463.46	€ 50.11	€ 192.95	€ 0.72	–	€ 707.24
	65.53%	7.09%	27.28%	0.10%		100%

(*Continued*)

Table 3 (Continued).

Adverse Event	Specialist Visits, € (%)	Hospital Admissions, € (%)	Procedures, € (%)	Pharmaceutical Treatment, € (%)	Other Resources, € (%)	Total € (%)
Δ AST	€ 463.46	€ 50.11	€ 192.95	€ 0.72	–	€ 707.24
	65.53%	7.09%	27.28%	0.10%		100%
Δ Bilirubin	€ 454.02	€ 2,505.66	€ 374.00	€ 1.43	–	€ 3335.11
	13.61%	75.13%	11.22%	0.04%		100%

Abbreviations: Δ, Increased; AE, Adverse Event; ALP, Alkaline Phosphatase; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

In relation to leukopenia, the expert panel consulted mentioned that its management does not represent an additional cost as it is usually related to neutropenia; therefore, in the analysis, it was assumed that any potential cost related to leukopenia would be implicitly included in the cost associated with the management of neutropenia.

Figure 2 shows the total cost associated with the management of each of the AEs considered in the model.

Adjusting AEs for reported incidence in the main studies, the total cost associated with the management of AEs with fruquintinib in FRESCO and FRESCO-2 was € 284.54 and € 301.82, respectively. For regorafenib (CORRECT), the total cost was € 1158.76. With T/T, the total cost was € 750.56 and € 1383.57 in SUNLIGHT and RECOURSE, respectively.

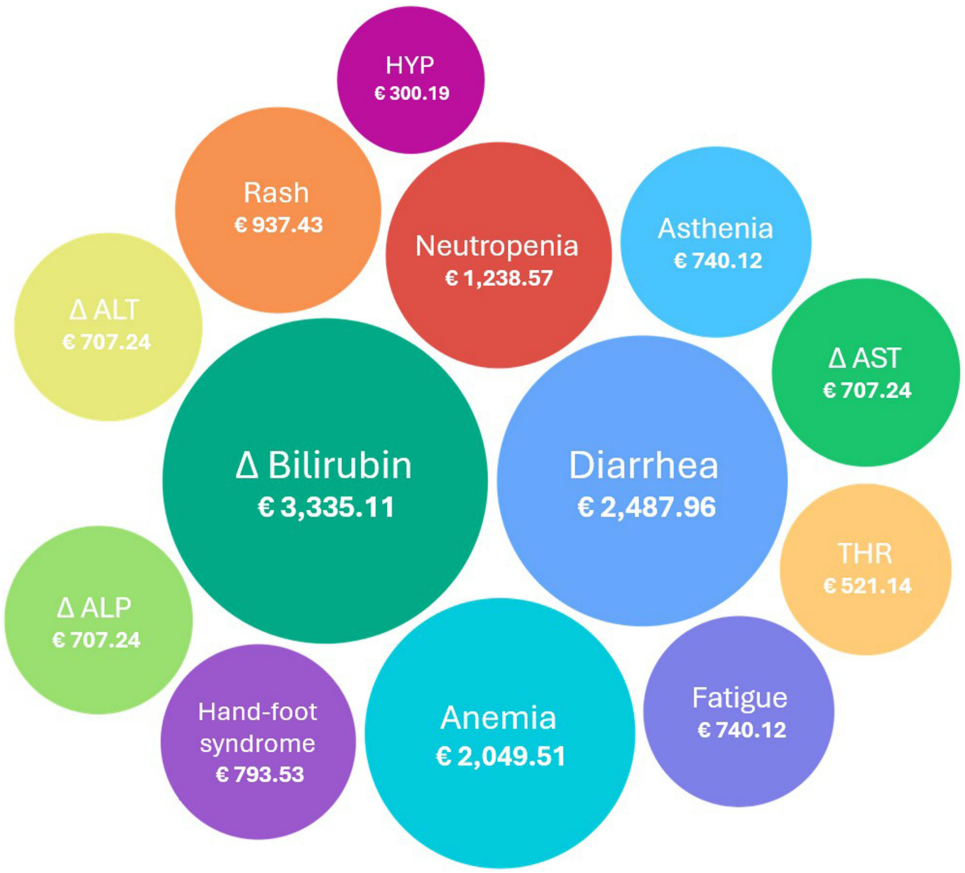

Figure 2 Total cost associated with the management of each of the AE assessed.
Abbreviations: Δ, Increased; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; HYP, Hypertension; THR, Thrombocytopenia.

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The total cost for T/T + bevacizumab was € 749.91 in SUNLIGHT. Those AEs with the greatest economic impact were hand-foot syndrome (€ 85.63) and diarrhea (€ 71.60) for fruquintinib in FRESCO and FRESCO-2 respectively; increased bilirubin (€ 407.55) for regorafenib in CORRECT; neutropenia (€ 397.75 - € 469.16) for T/T in RECOURSE and SUNLIGHT; and finally, neutropenia (€ 533.69) for T/T plus bevacizumab in SUNLIGHT. Table 4 and Figure 3 shows the total mean cost of grade ≥3 AE between the studies.

When comparing the results across the different studies, fruquintinib showed the lowest incremental costs among the respective treatment arms. For its part, the DID method associated fruquintinib in FRESCO and FRESCO-2 with a cost reduction of € 360.98 - € 398.70 and € 453.83 - € 491.55 compared to regorafenib in CORRECT and T/T in RECOURSE, respectively. Table 5 shows the anchor-based comparison of AEs cost with placebo + BSC as the common comparator.

Discussion

CRC is an ongoing public health problem and is the second leading cause of cancer deaths worldwide and the first leading cause of cancer deaths in Spain in the coming years.[2,3,36] Advances in therapies have improved both survival and QoL for patients. However, longer survival also increases healthcare resource use due to extended treatment and patient follow-up. Also, because these patients have already received multiple prior lines of therapy, they are often more vulnerable, and managing advanced stages of diseases such as mCRC requires closer monitoring and greater resource utilization.

This analysis provided detailed estimates about the health resource consumption and the total cost, associated with the management of the most frequent grade ≥3 AEs related to late-line treatments (fruquintinib, regorafenib, T/T and T/T + bevacizumab) of patients with mCRC from the Spanish NHS perspective. The type and proportion of those grade ≥3 AEs reported for fruquintinib, when comparing to regorafenib, T/T, and T/T plus bevacizumab in their respective pivotal trials, reflected a decrement in healthcare resource use associated with AEs management cost. Among the assessed clinical trials, the three AEs with the highest economic impact related to their management in the mCRC population due to late-line therapies were increased bilirubin, diarrhea and anemia, in which the economic expenditure was normally driven by inpatient care and secondly by specialist visits. For the rest of the AEs, given that most of cases were managed through specialist visits, these yielded the least impact on costs.

For the present analysis, the most common grade ≥3 AEs were considered, and validated by an expert panel. Other cost analyses conducted within the context of the Spanish healthcare system in the field of oncology have also included the management cost of AEs as part of broader economic evaluations.[37–39] However, the large differences observed—such as the type of illness, drug therapy, population treated, AEs considered, year of evaluation, and others—cause substantial cost disparities in the results, making it difficult to compare our findings directly with these studies. In some adverse events, such as hypertension, costs may be underestimated because these conditions can evolve into chronic episodes requiring follow-up in primary care. However, based on expert opinion, these long-term management costs were not considered clinically or economically significant within the scope of this study. Therefore, only the acute, treatment-related costs of severe AEs were included in the analysis.

A cost analysis model conducted with a methodological approach and population similar to those used in the present study has been published in the USA.[32] Although the study population consisted of patients with mCRC treated with late-line therapies, likewise, structural differences between healthcare systems and currency exchange rates make direct comparison difficult. Nevertheless, our findings appear to be in line with the referenced publication. The study showed that fruquintinib was less costly relative to managing AEs compared to the other late-line treatments for mCRC. Both studies also highlight that the treatment of grade ≥3 hematologic AEs was a cost driver, with the highest prevalence rates reported in T/T and T/T + bevacizumab.

Beyond the economic impact, severe AEs equally affect QoL, which is also an important input to consider. At the point of latest line treatments, the best treatment has to consist not only in improving overall survival, but also in improving the

Table 4 Total Mean Cost of AEs Between FRESCO, FRESCO-2, CORRECT, RECOURSE and SUNLIGHT Studies

Adverse Event	FRESCO[28]		FRESCO-2[10]		CORRECT[29]		RECOURSE[30]		SUNLIGHT[31]	
	Fruquintinib + BSC	Placebo + BSC	Fruquintinib + BSC	Placebo + BSC	Regorafenib + BSC	Placebo + BSC	T/T + BSC	Placebo + BSC	T/T + BSC	T/T + bevacizumab
Anemia	-	-	-	-	€ 118.87	€ 72.91	€ 372.64	€ 62.34	€ 224.95	€ 124.97
Asthenia	-	-	€ 56.81	€ 28.96	-	-	€ 24.99	€ 22.34	€ 30.09	€ 30.09
Diarrhea	€ 71.60	-	€ 87.30	-	€ 208.99	€ 49.17	€ 74.69	€ 9.39	€ 60.68	€ 20.23
Fatigue	€ 7.99	-	€ 29.22	€ 6.44	€ 113.98	€ 76.06	€ 29.16	€ 41.89	€ 27.08	€ 9.03
Hand-foot syndrome	€ 85.63	-	€ 50.47	-	€ 131.73	€ 3.14	-	-	-	-
Hypertension	€ 63.71	€ 6.57	€ 40.81	€ 2.61	€ 22.81	€ 2.37	-	-	€ 3.66	€ 17.08
Leukopenia	-	-	-	-	-	-	€ 0.00	-	-	-
Neutropenia	-	-	-	-	-	-	€ 469.16	-	€ 397.75	€ 533.69
Rash	-	-	-	-	€ 54.37	€ 3.71	-	-	-	-
Thrombocytopenia	-	-	-	-	€ 19.80	€ 2.06	€ 26.65	€ 1.98	€ 6.36	€ 14.83
Δ ALT	€ 5.09	€ 10.32	€ 21.71	€ 3.07	€ 38.89	€ 22.45	€ 13.45	€ 26.89	-	-
Δ AST	-	-	-	-	-	-	€ 56.47	€ 75.58	-	-
Δ ALP	€ 2.54	€ 5.16	€ 15.51	€ 9.22	€ 41.77	€ 36.48	€ 31.04	€ 43.19	-	-
Δ Bilirubin	€ 47.99	€ 48.69	-	-	€ 407.55	€ 277.93	€ 285.32	€ 394.61	-	-
Total Cost	**€ 284.54**	**€ 70.75**	**€ 301.82**	**€ 50.31**	**€ 1158.76**	**€ 546.27**	**€ 1383.57**	**€ 678.23**	**€ 750.56**	**€ 749.91**

Abbreviations: Δ, Increased; BSC, Best Supportive Care; AEs, Adverse Events; ALP, Alkaline Phosphatase; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

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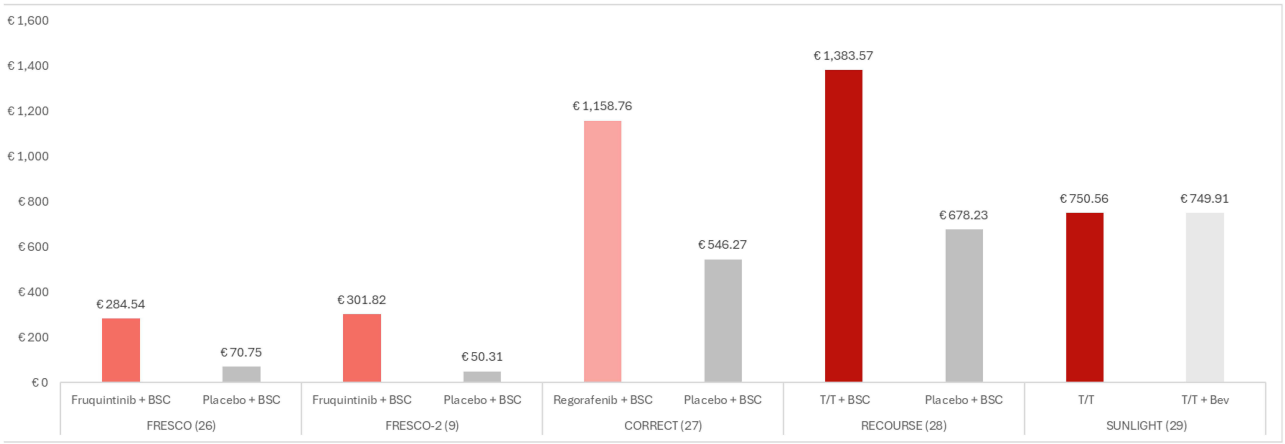

Figure 3 Total costs of AEs management for each therapeutic alternative.
Abbreviations: AEs, Adverse Events; ALP, Alkaline Phosphatase; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BSC, Best Supportive Care; T/T, Trifluridine/Tipiracil.

patient's QoL, making them feel as comfortable and self-sufficient as possible.[40] The AEs associated with mCRC treatments may worsen patient's QoL, and as a result, different Health Technologies Assessments bodies currently recognize QoL and patient reported outcomes as a key endpoint to assess in the approval process of oncology therapies.[27,41]

The current study is not exempt from limitations. First, AEs management costs were estimated only for those graded 3 or more. Thus, costs associated with grade 1 or 2 AEs and costs incurred in outpatient settings were not considered in the model. However, this approach is supported by the fact that, typically, only AEs grade ≥3 requires close follow-up of the patient, as well as that grade ≥3 AEs are commonly the only ones that require treatments/procedures in the hospital setting. Also, in this cost analysis, hospital admissions and specialist visits accounted for the major expense in the management of AEs. Despite all, this approach may result in underestimation of the actual costs incurred during AEs management. Another limitation inherent to healthcare economic models is the need for assumptions and therefore the uncertainty of values such as those associated with standard clinical practice. Therefore, in this analysis, due to the lack of published data, the resource consumption had been estimated based on an expert panel opinion.

Table 5 Difference-in-Differences Analysis of AEs Management Costs by Treatment

	FRESCO[28]	FRESCO-2[10]	CORRECT[29]	RECOURSE[30]
Incremental total cost between treatment arms and placebo	+ € 213.79 Fruquintinib + BSC vs. Placebo + BSC	+ € 251.51 Fruquintinib + BSC vs. Placebo + BSC	+ € 612.49 Regorafenib + BSC vs. Placebo + BSC	+ € 705.34 T/T + BSC vs. Placebo + BSC
Difference-in-differences for fruquintinib + BSC				
Based on FRESCO	-	-	- € 398.70 vs. regorafenib + BSC	- € 491.55 vs. T/T + BSC
Based on FRESCO-2	-	-	- € 360.98 vs. regorafenib + BSC	- € 453.83 vs. T/T + BSC

Abbreviations: AEs, Adverse Events; BSC, Best Supportive Care; T/T, Trifluridine/Tipiracil.

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Conclusions

In conclusion, despite the limitations mentioned above, the results of this analysis show the economic impact for the NHS in the management of each of the selected AEs experienced by patients with mCRC who had received at least two prior lines of treatment in Spain. Furthermore, this analysis proves that the costs associated with AEs are widely different between treatments for patients with mCRC in advanced stages of the disease. Considering the incremental cost between study arms, fruquintinib may lead to a range of cost reductions of € 448 - € 465 compared to T/T + bevacizumab, € 857 - € 874 versus regorafenib and € 466 - € 1099 compared to T/T. Therefore, the use of fruquintinib could reduce the costs associated with the management of AEs for the NHS, as fruquintinib achieves lower AEs incidence rates compared to the other late-line therapeutic alternatives in mCRC considered in the analysis. Finally, this analysis could be useful for clinical decision-making on treatment optimization in mCRC, providing information on AEs and associated management costs that may complement clinical efficacy.

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Data Sharing Statement

The data presented in this study are available upon reasonable request from the corresponding author.

Ethics Approval

Ethical approval is considered not applicable and unnecessary according to national regulations, as this is not a study collecting patient-level data. Therefore, as it is not a study, informed consent does not apply.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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