Original Paper

EVALUATION OF THE COSTS OF COLORECTAL CANCER TREATMENT ACCORDING TO PHASE OF CARE IN AN ONCOLOGY REFERENCE CENTRE BEFORE COVID 19 PANDEMIC

AVALIAÇÃO DOS CUSTOS DO TRATAMENTO DO CANCRO COLORRETAL DE ACORDO COM A FASE DA DOENÇA NUM CENTRO DE REFERÊNCIA EM ONCOLOGIA ANTES DA PANDEMIA DE COVID 19

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ABSTRACT

Background: Colorectal cancer is the second most common cancer in Portugal, which imposes an economic burden in the restricted health care budget. The aim of this study was to estimate the effects of age, stage, gender, Eastern Cooperative Oncology Group performance status, Charlson Comorbidity Index and category of health care activity on the average colorectal cancer treatment costs based on hospital records before COVID19 pandemic.
Methods: The average monthly costs were estimated in three phases: initial, monitoring and final based on the costs of the patient's hospital activities. The Kruskal Wallis test was applied to identify treatment costs differences within groups.
Results: The study population included 3020 patients diagnosed with colorectal cancer. Hospitalization, younger patients and higher stages were the main contributors for colorectal cancer costs. Stage IV presented a distinctive cost profile. Significant cost differences were found between age groups and stage in all phases. In the first 24 months after diagnosis, treating a colorectal cancer patient in stage I, II, III and IV, cost in average, 5590, 9180, 13300 and 28450 euros, respectively. Patients with Charlson Comorbidity Index score 0 were more expensive than patients with higher scores.
Conclusion: Our findings illustrate the value of costs studies based on national databases. This study showed the impact of several variables in the costs of colorectal cancer treatment, before COVID 19 pandemic, which may be used to improve the budget distribution of the Portuguese health care system.

Keywords: *colorectal cancer, observational study, cost analysis, before pandemic COVID 19.*

RESUMO

Enquadramento: O cancro colorretal é o segundo cancro mais comum em Portugal, o que impõe um encargo económico importante no orçamento da saúde. O objetivo deste estudo foi estimar os efeitos da idade, estágio, sexo, índice proposto pela Eastern Cooperative Oncology Group, índice de comorbidade de Charlson e categoria de atividade de saúde nos custos médios de tratamento do cancro colorretal com base em registos hospitalares antes da pandemia de COVID19. **Métodos:** Os custos médios mensais foram estimados em três fases: inicial, acompanhamento e final com base nos custos das atividades hospitalares do paciente. O teste de Kruskal Wallis foi aplicado para identificar diferenças nos custos do tratamento dentro dos grupos. **Resultados:** A população do estudo incluiu 3.020 pacientes com diagnóstico de câncer colorretal. Hospitalização, pacientes mais jovens e estágios mais avançados foram os principais contribuintes para os custos do câncer colorretal. A Fase IV apresentou um perfil de custos distinto. Foram encontradas diferenças significativas de custos entre faixas etárias e etapas em todas as fases. Nos primeiros 24 meses após o diagnóstico, tratar um doente com cancro colorretal em estádio I, II, III e IV custa, em média, 5590, 9180, 13300 e 28450 euros, respetivamente. Pacientes com pontuação 0 no Índice de Comorbidade de Charlson eram mais caros do que pacientes com pontuações mais altas. **Conclusão:** Os nossos resultados ilustram o valor dos estudos de custos baseados em bases de dados nacionais. Este estudo mostrou o impacto de diversas variáveis nos custos do tratamento do cancro colorretal, antes da pandemia de COVID 19, e que podem ser utilizadas para melhorar a distribuição orçamental do sistema de saúde português.

Palavras-chave: *cancro colorretal, estudo observacional, análise de custos, período prévio à pandemia COVID 19.*

INTRODUCTION

Colorectal cancer is the third most common cancer and the second in terms of mortality. In 2018 alone, 1.8 million new cases were expected with an 881 000 estimated number of deaths.[1] In Portugal, colorectal cancer is the second most frequent. According to the most recent data, mortality-to-incidence ratio is 35% and 41% for men and women, respectively.[2]

Cancer imposes a substantial economic burden on society. The direct costs[3] associated with the treatment of cancer patients have been increasing worldwide, in part due to the increasing number of prevalent cancer cases and the growing cost of drugs.[4]

The total cost of cancer in the European Union (EU) was estimated at 126 billion euro, representing an annual cancer care spend of 102 euro per citizen in 2009, but this value varied substantially from 16 euro per person in Bulgaria to 184 euro per person in Luxembourg. In Portugal it was 53 euros per person.[5] A recent study conducted in Portugal estimated that 867 million euros were spend annually in cancer treatments. The cost per person was 84 euros, an increase of 31 euros compared to the 2009 study.[4,5]

The reasons for these wide differences between countries across the EU were unclear and require further investigation. In Portugal, the direct costs related to cancer treatment in 2006 were estimated in about 565 million euro, accounting for 3.9% of the total health expenditures that year.[6] However, expenses with cancer health care in our country have increased and the resources available to finance new therapies are limited. The evaluation of cancer treatment costs is of paramount importance to help decisions about the allocation of resources to service provision, prevention strategies, and research funding.[7,8]

Treatment related costs also vary with cancer type. Studies performed in Ontario have shown that, for patients surviving at least one year, female breast and prostate cancers were among the cancers with lower cost while colorectal and lung cancers were in the top 10 of the most expensive.[9] In a decade,

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treatment costs had a 50% increase for prostate and lung cancers and doubled for breast and colorectal cancers.[10]

In order to better understand the burden of disease in a country's health system, it is important to evaluate the cancer survivors' population by phase of care, given that numerous studies have shown higher costs in the initial and the terminal phases of care, than in the monitoring phase.[11-14] The initial phase is usually considered as the first year after diagnosis, where treatment intensity is higher. The final phase is considered as the last year of life and the monitoring phase as the phase between the other two.

Different studies used diverse information sources to estimate costs. In Italy, a study on the cost profiles of colorectal cancer by phase of care was performed for two Italian regions[15] and costs were estimated based on reimbursements from the regional government corresponding to Diagnosis Related Group (DRG) codes. In the US, studies on the projection of costs associated with cancer care[12,16,17] obtained information on costs from the Medicare database. A study on the costs of cancer care for the 21 most common cancers in Ontario[9] used linked administrative databases to calculate costs of drugs, surgery, among others. The main sources for studies on cancer costs were cancer registries to select the eligible patients.[12,16,17]

In Portugal, there is no national database with information on treatment costs per patient. The few published studies in Portugal about costs evaluation, used Diagnosis-Related Group codes to value impact care, ambulatory surgery and some medical treatments.[6,18] However not all medical treatments have an associated Diagnosis-Related Group code. So, costs are underestimated using this approach. Furthermore, all the drugs treatments are coded in one or two Diagnosis-Related Group codes, but the cost range is very wide. So, in this way it is not possible to obtain an accurate estimate of the costs.

The goal of this article was to estimate the hospital costs with cancer treatment before COVID 19 pandemic. This methodology was applied to colorectal cancer. This cancer was chosen for this analysis as it is the most incident cancer detected in the North Region. According to cancer incidence projections for the North Region, it is expectable that colorectal will increase by 26% till 2020.[19]

MATERIALS AND METHODS

An observational study in Portuguese Oncology Institute of Porto (IPOP) was conducted to estimate the hospital costs of patients with colorectal cancer. To accomplish that goal, it was essential to merge the information of two sources: the Management Support Office of IPOP, which listed the individual costs of each health care activity, and the hospital's Cancer Registry data, which registers the data regarding the patients. All data analyses were performed with Microsoft Excel 2013 and RStudio v1.1.456.

Phase of care definition: Phase of care definitions were based in previous studies of cancer cost analysis.[15,20] The initial phase of treatment is defined as the first 12 months after diagnosis, the final phase corresponds to the last 12 months of life and all the months between those are the monitoring phase. In this work, priority is given to the third phase, i.e. if a subject is diagnosed in January 2014 and only survives 18 months, the first six months were assigned to the first phase and the remaining twelve months were assigned to the third phase.

Study population: A cohort of colorectal cancer patients diagnosed between January 1st 2008-December 31st 2015 that were treated at the IPOP in the analysed period (January 1st 2014 to December 31st 2015) were considered. For these patients information on date of diagnosis, age at diagnosis, gender, date of death (if applicable), stage at diagnosis classified with the TNM system, Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, comorbidities at diagnosis and health care activities were acquired.

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In this study, mortality included patients that died from any cause. The patients with a second cancer, except skin cancer (International Classification of Disease (ICD)-10: C44), with less than 18 years and treated in other hospitals were excluded from the study.

Health care resources: All the health care activities of the patients were obtained, and a cost was associated to each activity. The following categories of activities were acquired: drugs, radiotherapy, hospitalization, laboratory tests, radiology, ambulatory outpatient care, medical consultation and others.

Charlson Comorbidity Index: The Charlson Comorbidity Index (CCI) is a score that assigns weights to comorbidities.[21] In this study, 15 different comorbidities were taken into account at diagnosis. The CCI, graded from 0 to 6, was determined for each patient and then clustered in three levels: 0, 1 and >1.

Age groups: The age groups chosen (18-69; 70-79; 80-99) were based on previous study.[15]

ECOG performance status: The ECOG score was used to measure the patient status at diagnosis.[22] The ECOG score varies from 0 to 5, however in this work, the scores were grouped in three levels: 0, 1 and >1.

Treatment cost by phase of care: For each patient the follow up started on the date of diagnostic and ended on the date of death or the end of the observation period (December 31st 2015), whichever came first. To each health care activity, the corresponding month and phase were determined, considering the date of diagnosis and/or the death of the patient (if applicable), as explained in the *Phase of care definition* section.

To obtain the monthly average costs the total cost of the month was divided by the total number of persons in the same month. Note that the contribution for the denominator derive from patients that actually incurred in costs as well as patients at risk of doing so, i.e. a living patient that could had presented hospital costs. The average monthly costs were then stratified by age group, stage, gender, ECOG performance status, CCI and category of health care activity. Confidence intervals were calculated with the bootstrap method for all phases of care.

Treatment cost by month since diagnosis: For each health care activity the corresponding month since the diagnosis date was determined. The phase and the death of the patient (if applicable) were not considered in this approach. To obtain the monthly average costs the same procedure was followed as described in the *Treatment cost by phase of care* section. The average monthly costs were then stratified by stage.

Statistical analysis: For each patient the total cost of each month, in each phase, was determined. In order to find differences in the treatment costs between the different levels in age group, stage, gender, performance status and CCI, the Kruskal Wallis test was applied. We deemed the difference cost between levels to be significant if its p value was less than 0.01.

RESULTS

Initially 3029 patients were identified as possible candidates for the study. In total 9 patients were excluded from the study: 4 that also had breast cancer (ICD10: C50) and 5 that died in the first week of January 2014. The study included 324 618 health care activities performed from January 1st 2014 to December 31st 2015 in 3020 patients diagnosed with colorectal cancer. Table 1 summarizes the demographics of the study population.

Figure 1 shows the average monthly costs per patient in which all the patients were included regardless of age, gender or stage of the disease. The U-shape cost profile was evident, with the higher costs found near the time of diagnosis and death. The third month after the diagnosis was the most expensive reaching 1800 euros. The cost gradually decreased until the monitoring phase, where a

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Table 1 – **Patient demographics**

		N = 3020
Gender	Female	1 239 (41.0%)
	Male	1 781 (59.0%)
Age Group	18-69	1 708 (56.6%)
	70-79	886 (29.3%)
	80-99	426 (14.1%)
Stage	I	558 (18.5%)
	II	841 (27.9%)
	III	1 158 (38.3%)
	IV	448 (14.8%)
	Unknown	15 (0.5%)
ECOG	0	2 171 (71.9%)
	1	668 (22.1%)
	>1	180 (5.9%)
	Unknown	1 (<0.1%)
CCI	0	1 617 (53.5%)
	1	902 (29.9%)
	>1	501 (16.6%)

plateau was reached. The cost increased again in the final phase, reaching its peak at 2900 euros in the last month of life.

Costs by age group: In the initial and monitoring phase the monthly costs of younger patients were slightly higher, when compared to the older patients. In the final phase the difference between age groups was clearer where the younger patients presented a higher cost in most months. In the last month of life, the patients with age between 70-79 years reached cost a maximum of 3850 euros.

Costs by stage at diagnosis: Figure 2 shows the average monthly costs of the stage at diagnosis. Patients diagnosed with stage I presented the lowest costs of all stages, being 1360 euros, in the third month after diagnosis, its maximum value in the initial phase. Stage I, II and III costs decreased quickly after the diagnosis, rising only in the final phase. Stage IV costs declined slowly in the initial and monitoring phase, a distinctive cost behaviour profile. The patients in stage III in the last month of life had the highest cost, 3350 euros.

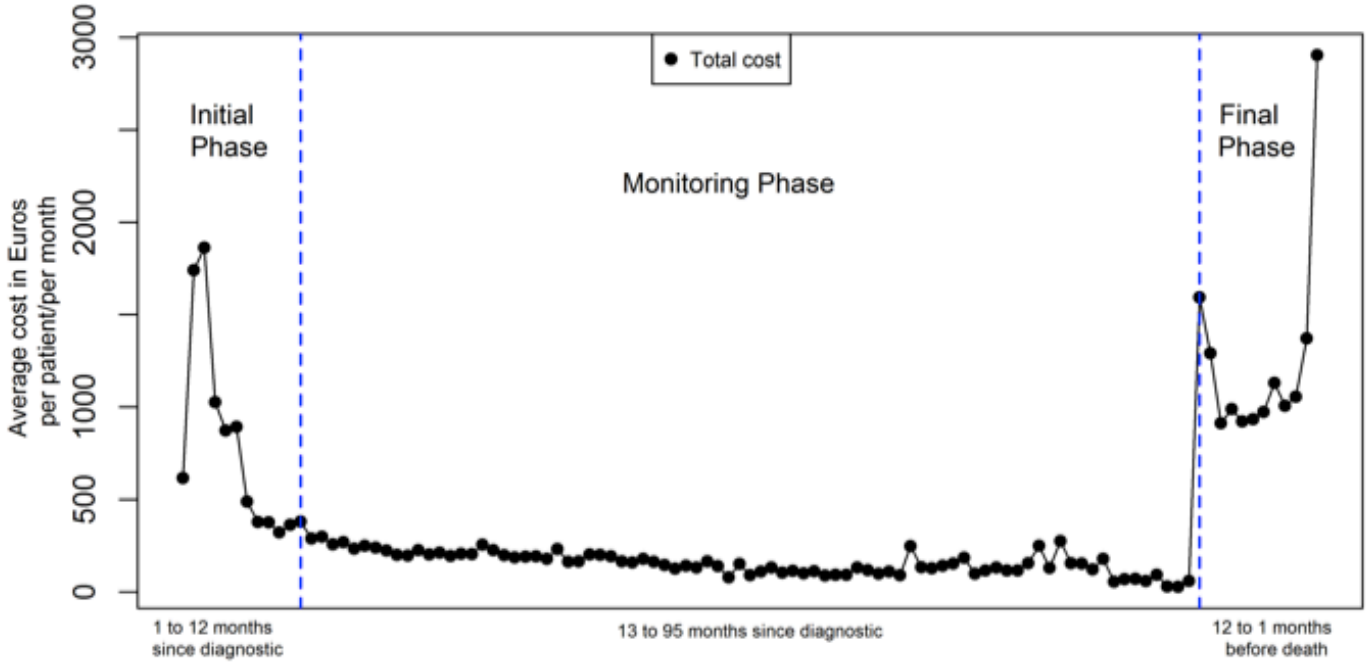

Figure 1 – **Average monthly costs (in Euros) per patient by phase of care.**

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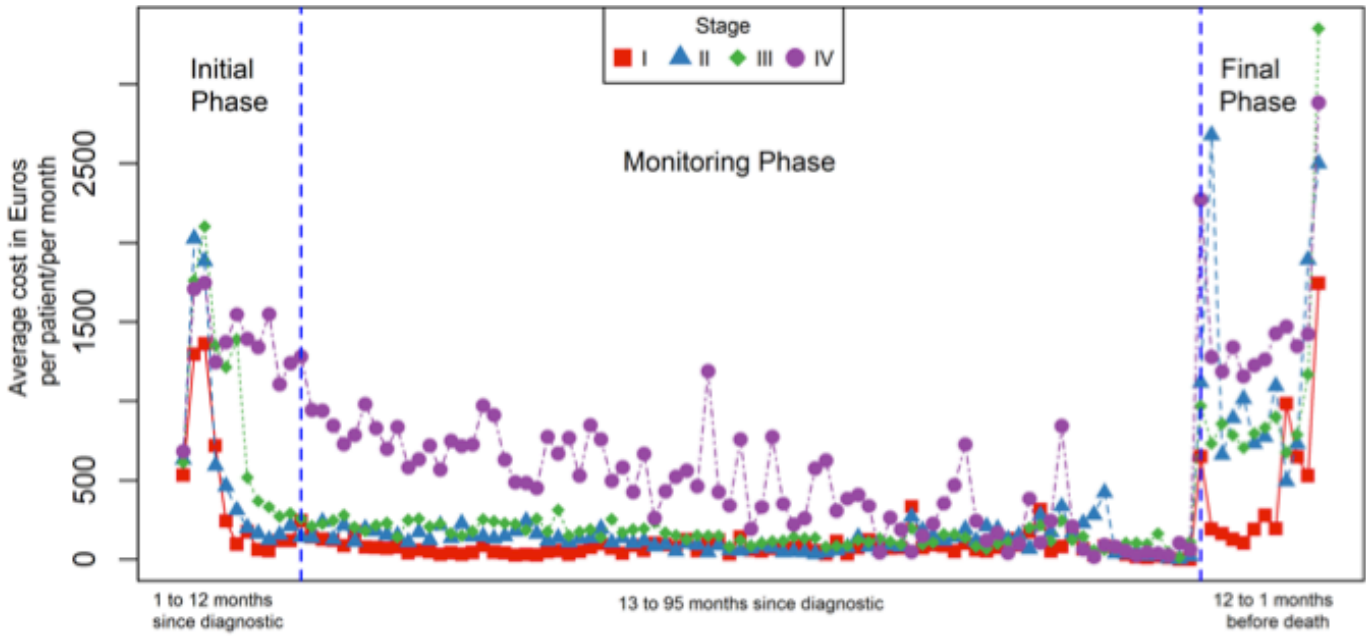

FIGURE 2 – **Average monthly costs (in Euros) per patient by phase of care and stage at diagnosis.**

Costs by health care activity: Drugs and hospitalization had the highest costs in all phases. Radiotherapy presented a cost peak in the first months after diagnosis, 570 euros. Hospitalization costs followed the typical U-shape form, reaching its highest values in the last month of life, around 2600 euros. Hospitalization represented most of the costs. Drugs costs rise slightly in the beginning of the initial phase, staying overall steady throughout the monitoring phase. In the final phase, drugs costs gradually decreased until the last month of life. Radiotherapy costs showed a peak in the first months after diagnosis. The remaining health care activities (laboratory tests, ambulatory outpatient care, medical consultation and others) presented a steady low-cost profile (between 50 to 130 euros) throughout the three phases.

Costs by gender: The cost profiles were very similar in the three phases. In the initial phase, both genders reached a peak in the third month after diagnosis, with a total cost of 1810 and 1930 euros for male and female patients, respectively. The final month of life was the most expensive for both genders.

Costs by CCI: The patients with in the level >1 had the highest cost of the initial phase in the third month, reaching 2180 euros. In the monitoring phase, the cost profiles of the three levels were very similar, even though some peaks were present in late months of this phase. In the final phase, differences can be found in the cost profiles of each level. The patients with CCI 0 presented higher costs, followed by the ones with 1 and >1, showing that patients with lower Charlson Comorbidity Indexes, in the final phase, were more costly to the IPOP. In the final month of life, the patients CCI 1 were the most expensive reaching 3160 euros.

Costs by ECOG performance status: Patients diagnosed with ECOG >1 presented the highest cost of the initial phase, 3900 euros in the third month after diagnosis. ECOG levels costs followed the typical U-shape cost profile. In the final phase, ECOG 0 was the most expensive followed by ECOG 1 and ECOG >1.

Costs by month since diagnosis: An analysis of the costs since diagnosis was also performed. In Figure 3 the costs by month after the diagnosis,

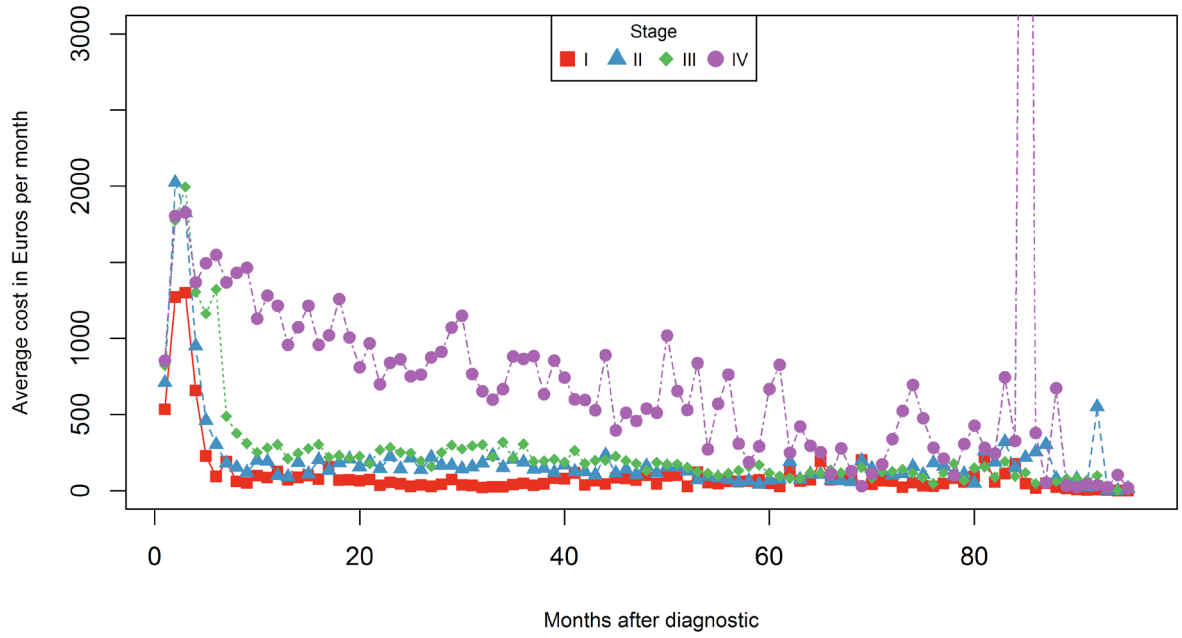

FIGURE 3 – **Average monthly costs (in Euros) per patient by months after diagnosis.**

stratified by stage, are represented. Treating a patient diagnosed with colorectal cancer in the first 24 months cost, in average, 5590, 9180, 13300 and 28450 euros for the stage I, II, III and IV, respectively. The average monthly cost increased, until the third month after the diagnosis when a peak was reached. The cost started to stabilize in the eighth month after diagnosis.

Figure 4 displays the average cost analysis by phase with 95% confidence intervals. Regarding age, CCI and ECOG no pattern of average costs was found. The average costs of cancer increased with stage in all phases and male patients had slightly more costs than female patients in all phases.

Statistical analysis: The Kruskal Wallis test was applied to determine if cost differences between levels were significant in the stage, age group, gender, ECOG performance status and CCI. The results are displayed in Table 2.

DISCUSSION

In this study, the IPOP costs of colorectal cancer were estimated based in administrative and Cancer Registry data before COVID 19 pandemic. These costs were then stratified by age group, stage, heath care activity, gender, ECOG performance status CCI. This study was undertaken from the hospital perspective, therefore indirect or intangible costs were not included.

We found that the mean of colorectal cancer costs followed a U-shaped curve which is consistent with previous studies results.[15,11,23] However our estimates differ from previous studies in which the first month after the diagnosis was the most expensive. In our results the third month was the most expensive. This result could be explained by the higher hospitalization and radiotherapy costs in that month. Within phase of care, the costs varied by age group, stage and heath care activity.

The youngest age group (18-69) had higher costs than the oldest ones (70-79; 80-99), primarily in the final phase. This tendency has been reported in

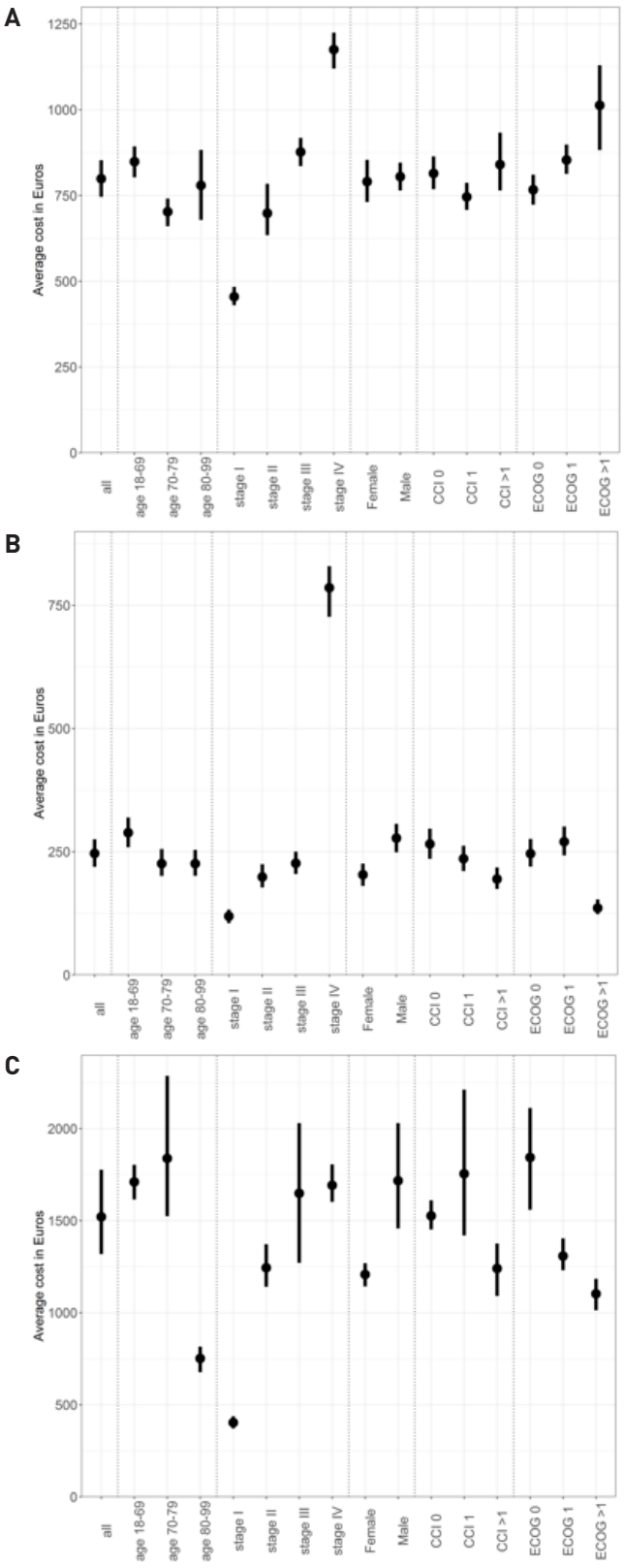

Figure 4 – **Average costs (in Euros) per patient with 95% confidence intervals for: (A) Initial phase, (B) Monitoring phase, (C) Final phase.**

Table 2 – **Average cost of colorectal cancer treatment by phase of care (in Euros) and Kruskal Wallis Test P value Results**

		Initial Phase		Monitoring Phase		Final Phase	
		average cost	p value	average cost	p value	average cost	p value
Gender	Female	749	0.20	114	<0.01	1 182	0.42
	Male	797		185		1 304	
Age Group	18-69	847	<0.01	194	<0.01	1 587	<0.01
	70-79	690		134		1 178	
	80-99	611		58		570	
Stage	I	417	<0.01	75	<0.01	483	<0.01
	II	574		126		1 215	
	III	872		154		1 047	
	IV	1 351		458		1 522	
CCI	0	830	0.56	166	0.34	1 354	<0.01
	1	713		159		1 214	
	>1	742		124		1 072	
ECOG	0	755	0.09	158	<0.01	1454	<0.01
	1	841		174		1172	
	>1	816		58		742	

earlier studies.[24,25] Clerc et al.[26] and Ramsey et al.[24] hypothesized that some expensive and aggressive treatments could be given only to younger patients since them are "deemed more able to support their adverse effects".[26] However Sargent et al.[27] concluded that older patients with colon cancer could receive the same benefit from adjuvant drugs as the younger patients, without a significant increase in toxic effects.

The higher costs for later cancer stages found in this study complement the existing literature. This may point to that more expensive treatments may be administered to these patients.[25] Given the substantial cost differences between stages it may be important to focus on earlier detection policies of colorectal cancer in order to decrease health care expenses.[28] In Portugal, a cancer-screening program was implemented to population between

50-74 years. It is estimated that the program will be able to reduce the colorectal cancer mortality by 20%.[29] In this study, mortality from any cause was considered which could explain the lower cost of the early stages in the final phase.

Hospitalization accounted for most of the costs. This result is similar to those found in previous studies made in France, USA and Switzerland.[26,30,31]

In regard of the costs stratified by gender, no expressive differences were found in the graphic analysis. At the best of our knowledge, no other study presented the colorectal average monthly costs stratified by gender.

The patients with lower CCI levels presented the highest costs. Yoon et al.[32] studied the association between CCI and different cancer costs. They found no significant relation between a higher CCI and an increase of colon cancer costs. The researchers also reported a protective effect of comorbidities, since these patients frequently have hospital visits that led to early cancer detection.[32]

ECOG performance status 0 was the most expensive followed by ECOG 1 and ECOG >1. No other study was found that presented the colorectal average costs stratified by ECOG performance status.

Higher costs in stage IV were found in this study when analysing the months since the diagnostic. Stage IV had a distinctive cost profile, where the costs decreased slowly even in the monitoring phase. Identical results were previously reported in a Portuguese study.[33] The researchers found costs disparities between different stages and cancer types, with later stages being more costly.[33]

The Kruskal Wallis test was implemented to determine if there were differences between the different levels for stage, age group, gender, ECOG performance status and CCI. For both stage and age group significant cost differences were found between different age groups and different stages in the three phases. Regarding the gender analysis significant differences between levels were found in the monitoring phase. ECOG performance status showed significant differences between levels in the monitoring and final phase. In the CCI analysis significant differences between levels were found in the final phase.

Some studies have evaluated the cost of cancer treatment in Portugal. Araujo et al. [6] compared the budget allocation to cardiovascular diseases and cancer, since these are the first and second leading death causes in Portugal, respectively. The Burden of Disease indicator was the Disability-adjusted life-year and in order to determine the cancer treatment costs, medical consultation and hospitalization data based on DRG was used. They concluded that cancer treatment seemed to be under-funded when compared to the leading death cause in Portugal. Pinto et al.[34] provided an overview of the Portuguese cancer registries and the management of colorectal cancer. They found regional disparities in access to health care facilities however a restructuration of the health care services was being implemented to adopt more efficient policies. Lopes et al.[4] estimated the direct medical costs of treatment of cancer in Portugal. Researchers found that cancer treatment represented 5.5 percent of the total health expenditure. This 867-million-euro cost has been increasing since the Araujo et al. study.

In this study all health care activities from diagnosed colorectal cancer patients were included though it was not possible to distinguish cancer related activities and comorbidities ones. Clerc et al.[26] found that comorbidities did not significantly influence the global cost of colorectal cancer. No distinction was made in the cost analysis between colon cancer (ICD10: C18) and rectal cancer (ICD10: C19-20). Tilson et al.[28] and Lang et al.[25] have reported that rectal cancer costs are higher than colon cancer costs. Our approach may had led to an overestimation of the costs in patients with colon cancer and an underestimation in patients with rectal cancer.

Few scientific articles on the cost analysis of colorectal cancer are available, especially regarding the Portuguese health care system. Even less discriminate the impact of different health care

activities in the overall cost of colorectal cancer, making this study an important contribution for the understanding of the resource's distribution in colorectal cancer care.

CONCLUSION

An estimation of the health care costs for colorectal cancer patients of the northern region of Portugal, before COVID 19 pandemic was provided. Colorectal cancer costs vary considerably with age, stage and health care activity where younger patients, stage IV and hospitalization were the most expensive in each category. As expected, the initial and final phases corresponded to the highest cost, and the monitoring phase to the lowest, creating the characteristic U-shape cost profile. Significant differences were found in age groups and stages in the initial, monitoring and final phases. This study provided useful information for future research of cost analysis that may be used to improve the budget distribution of the Portuguese health care system.

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