Relationship between adverse events of adjuvant chemotherapy and survival outcomes: mediation analysis of Chinese colorectal cancer patients

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Abstract

Purpose We focus on adverse events in colorectal cancer patients with advanced age, high Eastern Cooperative Oncology Group scores and comorbidities.

Methods 408 Chinese colorectal cancer patients undergoing adjuvant chemotherapy at Peking Union Medical College Hospital were included. The cumulative incidences of different adverse events and mediation analyses were analyzed with respect to age, Eastern Cooperative Oncology Group status and comorbidities.

Results Young patients and patients with Eastern Cooperative Oncology Group score 1 had a significantly higher incidence of digestive adverse events related to adjuvant therapy. There were no significant mediation effects of adverse events on survival.

Conclusion Advanced age did not directly lead to poor survival outcomes and adverse events. Although higher Eastern Cooperative Oncology Group scores and comorbidity led to impaired survival and higher incidence of adverse events, the latter had no mediation effects on survival outcomes.

Introduction

Colorectal cancer (CRC) has long been the third most commonly diagnosed cancer and the second leading cause of cancer death worldwide [1]. In China, both the incidence and mortality of CRC have increased in recent decades, with estimated rates of 376.3 and 191.0 per 100,000 patients, respectively [2]. Most CRC patients in China are diagnosed between 60 and 74 years of age [2]. As the population is aging [3], older patients will be exposed to the risks of CRC. Combination of surgery and postoperative adjuvant chemotherapy is recommended as standard for resectable advanced-grade tumors [4–6]. 5-Fluorouracil (5-FU)/oxaliplatin (FOLFOX) and capecitabine/oxaliplatin (CAPEOX) are used as first-line adjuvant chemotherapy and improve overall survival (OS) compared with surgery alone [6–8]. 5-FU/leucovorin and 5-FU/irinotecan (FOLFIRI) are alternative choices in clinical practice.

When making clinical decisions, adverse events related to chemotherapy must be taken into consideration. However, few clinical trials have focused on the effects of adverse events, especially in patients with advanced age and high Eastern Cooperative Oncology Group (ECOG) scores, partly because those patients are generally excluded from clinical trials [9]. According to a European cohort, only a small percentage of older patients with stage III CRC received adjuvant chemotherapy [10]. In addition, advanced aged, more comorbidity, poor health status, and concern for adverse events are related to the choice of nonaggressive chemotherapy, which might lead to higher recurrence rates and mortality in older patients with CRC [11, 12]. Because of the lack of literature, clinicians have had to rely on their experience, which might result in undertreatment of patients in poor physical condition. Moreover, few studies have systematically investigated the adverse events related to adjuvant chemotherapy in Chinese CRC patients.

Patients with various clinicopathological parameters, such as different age and performance status, might respond differently to postoperative adjuvant chemotherapy [13]. Furthermore, adverse events related to chemotherapy could play an important role in this process, as their incidence may determine the outcomes of specific groups of patients.

The aim of our study was to calculate the cumulative incidences of adverse events in patients with different clinicopathological parameters and chemotherapy regimens. Furthermore, we conducted a mediation analysis to explore whether adverse events related to chemotherapy affected survival outcomes.

Methods

Population

This retrospective study included 408 CRC patients who received standard adjuvant chemotherapy according to the standard guidelines after tumor resection at the Department of Oncology, Peking Union Medical College Hospital (PUMCH) from 2015 to 2018. The records of each patient were reviewed independently by two researchers. We recorded basic characteristics including demographic data (sex and age); tumor characteristics (tumor location, differentiation level and TNM stage at diagnosis); ECOG score; comorbidity (hepatitis, diabetes mellitus and hypertension); and chemotherapy information (drugs and regimens). An age of 65 years, which is commonly accepted as the definition of old people in most nations including China, was selected as the cutoff age in the two groups.

All patients gave signed informed consent before the study. The study was approved by the Ethics Committee of PUMCH.

Follow-up

Overall survival (OS) was defined as the time from surgery until death or last follow-up. We compared the OS curves of different groups of

January 2019.

Survival Analysis

Median OS was 71 months in the young and 56 months in the old patients ($p = 0.33$). Median OS was 59 months in the ECOG score 0 group and 56 months in the ECOG score ≥1 group ($p = 0.05$) (Supplementary Fig. 1). We investigated whether comorbidity affected OS in all patients (Supplementary Fig. 2 and Supplementary Fig. 3). Hepatitis, diabetes and hypertension did not influence OS significantly. In subgroup analysis, old patients with hepatitis tended to have shorter OS ($p = 0.16$) compared with those without hepatitis, while young patients with hepatitis had significantly longer OS compared with those without hepatitis ($p = 0.088$). Diabetes was another predictor for old patients with shorter OS ($p = 0.044$).

Adverse Events

Adverse events were defined according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, 2017, and included: myelosuppression (grade I–IV), digestive adverse events (nausea, vomiting and diarrhea), fever and numbness. For patients who received more than 1 chemotherapy programs in different time periods, we only included adverse events took place the first time in each program. The specific chemotherapy cycle in which an adverse event took place for first time was recorded. The incidence for each type of adverse events related to different drugs in all cycles and the first 4 cycles were calculated and compared among different groups.

Mediation Analysis

Nausea, vomiting and diarrhea had significant different incidences in different patient populations, and were chosen as potential mediators that might influence survival outcomes. No significant mediation effects were found (Fig. 1 and Fig. 2).

Results

Population

Basic characteristics of the 408 CRC patients enrolled in this study are presented in Table 1. Patients were divided into groups according to age and ECOG score. There was no significant difference in clinicopathological characteristics between young (≤65 years, N = 119) and old (> 65 years, N = 289) patients, except that the latter had a significantly higher incidence of hepatitis. Patients with higher ECOG scores ≥1 (N = 60) had comparable clinicopathological characteristics to patients with lower ECOG score 0 (N = 95). The rates of different chemotherapy regimens utilized in clinical practice were also counted: for the old, irinotecan alone was more commonly used compared to the young (p = 0.002); for those with higher ECOG scores, capecitabine was more commonly used (p = 0.003). (Table 1)

Table 1
Basic characteristics of patients included in different age groups and ECOG groups

	Age groups			ECOG groups		
Characteristics	**Young(≤ 65)**	**Old (> 65)**	p **value**	**ECOG = 0**	**ECOG ≥ 1**	p **value**
	N = 289	**N = 119**		**N = 95**	**N = 60**	
Sex, male/female	165/124	75/44	0.325	58/37	31/29	0.325
Age, mean ± SE	54.53 ± 9.71	70.15 ± 3.84		58.43 ± 9.83	61.31 ± 11.16	
Location of tumor						
Colon	140	65	0.338	56	27	0.126
Right colon	66	35	0.457	22	17	0.073
Left colon	74	29		34	10	
Rectum	149	54		39	33	
Differentiation level			0.438			0.799
Low	29	17		2	2	
Medium	162	64		54	29	
High	23	8		15	9	
x	77	31		24	20	
T stage			0.104			0.762
1	8	1		1	0	
2	18	9		3	4	
3	157	45		50	29	
4	70	36		27	16	
x	36	28		14	11	
N stage			0.064			0.189
0	46	16		14	5	
1	128	47		30	26	
2	72	23		33	16	
3	0	2		0	0	
x	43	31		18	13	
M stage			0.468			0.066
0	143	54		43	19	
1	77	40		32	30	
x	68	25		20	11	
ECOG			0.175			
0	73	22		/	/	
1	31	20		/	/	
2	5	2		/	/	
3	3	1		/	/	
x	179	75		/	/	
Comorbidities						
	38	18	0.716	27	16	0.957

	Age groups			ECOG groups		
Diabetes	20	7	0.88	9	12	0.104
Hepatitis	17	18	**0.004**	17	7	0.414
Chemotherapy regimens						
FOLFOX	66	28	0.983	25	16	0.999
CAPEOX	158	67	0.848	34	13	0.092
FOLFIRI	37	22	0.184	13	5	0.450
Capecitabine	25	11	0.999	2	9	**0.003**
Irinotecan	7	12	**0.002**	5	5	0.511

Adverse Events In Different Age Groups

There was significantly higher incidences of digestive adverse events in the young and old patients: the incidence of nausea were 40% versus 27% ($p = 0.014$) and the incidence of vomiting were 28% versus 13% ($p = 0.002$) (Table 2). There was no significant difference in other adverse events (diarrhea, hematological toxicity, numbness and fever) between young and old patients. The rates of adverse events related to different drugs are summarized in Table 3. In the oxaliplatin group, young patients had higher rates of digestive adverse events including nausea (36% versus 22%, $p = 0.024$) and vomiting (23% versus 10%, $p = 0.011$) for all cycles. In the 5-FU group, 27% of young patients experienced vomiting during treatment compared with 10% of old patients ($p = 0.028$). In the capecitabine and irinotecan group, no significant difference was observed between the young and old patients.

Table 2
Adverse events in different age and ECOG groups.

	Old	**Young**	***p* value**	**ECOG = 0**	**ECOG ≥ 1**	***p* value**
	N = 119	**N = 289**		**N = 95**	**N = 60**	
I	4(3%)	10(3%)	0.254	4(4%)	5(8%)	0.361
II	11(9%)	15(5%)		11(12%)	3(5%)	
III	5(4%)	22(8%)		6(6%)	4(7%)	
IV	2(2%)	4(1%)		3(3%)	3(5%)	
Digestive toxicity						
Nausea	32(27%)	116(40%)	**0.014**	28(30%)	28(47%)	**0.049**
Vomit	15(13%)	80(28%)	**0.002**	21(22%)	24(40%)	**0.026**
Diarrhea	19(16%)	46(16%)	1	13(14%)	21(36%)	**0.003**
General toxicity						
Numb	20(17%)	50(18%)	1	16(17%)	11(18%)	1
Fever	15(13%)	39(13%)	1	14(15%)	16(27%)	0.104

Table 3
Adverse events related to specific chemotherapeutics in different age groups

	Oxaliplatin			5-Fluorouracil			Capecitabine			Irinotecan		
	Old	Young	p value	Old	Young	p value	Old	Young	p value	Old	Young	p value
	N = 95	N = 224		N = 50	N = 103		N = 78	N = 183		N = 34	N = 44	
Hematologic			0.457			0.104			1			0.559
toxicity												
I	2(2%)	7(3%)		1(2%)	5(5%)		2(3%)	3(2%)		1(3%)	2(5%)	
II	8(8%)	10(5%)		5(10%)	7(7%)		5(6%)	7(4%)		2(6%)	1(2%)	
III	5(5%)	15(7%)		0(0%)	8(8%)		5(6%)	9(5%)		1(3%)	3(7%)	
IV	0(0%)	2(1%)		2(4%)	2(2%)		0(0%)	1(1%)		3(9%)	1(2%)	
Digestive toxicity												
Nausea	21(22%)	80(36%)	**0.024**	11(22%)	35(34%)	0.184	16(21%)	61(33%)	0.072	8(24%)	12(27%)	0.968
Vomit	9(10%)	52(23%)	**0.011**	5(10%)	28(27%)	**0.028**	9(12%)	40(22%)	0.087	5(15%)	11(25%)	0.424
Diarrhea	5(5%)	20(9%)	0.322	6(12%)	22(21%)	0.257	6(8%)	12(7%)	0.981	9(27%)	15(34%)	0.677
General toxicity												
Numb	13(14%)	32(14%)	1	8(16%)	14(14%)	0.933	9(12%)	24(13%)	0.985	2(6%)	3(7%)	1
Fever	9(10%)	26(12%)	0.748	7(14%)	15(15%)	1	4(5%)	17(9%)	0.395	5(15%)	4(9%)	0.492

Adverse Events In Groups With Different Ecog Scores

The rates of digestive adverse events were significantly higher in patients with ECOG score ≥1 compared with ECOG score 0 ($p = 0.049$ for nausea, $p = 0.026$ for vomiting and $p = 0.003$ for diarrhea) (Table 2). The rates of adverse events related to different drugs are summarized in Table 4. No significant different incidences were observed between patients with ECOG scores 0 and ≥1.

Table 4
Adverse events related to specific chemotherapeutics in different ECOG groups

	Oxaliplatin			5-Fluorouracil			Capecitabine			Irinotecan		
	ECOG = 0	ECOG ≥ 1	p value	ECOG = 0	ECOG ≥ 1	p value	ECOG = 0	ECOG ≥ 1	p value	ECOG = 0	ECOG ≥ 1	p value
	N = 59	N = 29		N = 38	N = 21		N = 36	N = 22		N = 18	N = 10	
Hematologic toxity												
I	3(5%)	3(10%)	1	3(8%)	2(10%)	0.697	1(3%)	1(5%)	1	2(11%)	0(0%)	0.232
II	3(5%)	2(7%)		4(11%)	0(0%)		2(6%)	2(9%)		2(11%)	0(0%)	
III	4(7%)	2(7%)		2(5%)	0(0%)		2(6%)	2(9%)		0(0%)	1(10%)	
IV	1(2%)	0(0%)		1(3%)	0(0%)		0(0%)	0(0%)		0(0%)	0(0%)	
Digestive toxicity												
Nausea	19(32%)	12(41%)	0.562	17(45%)	9(43%)	1	7(19%)	8(36%)	0.258	4(22%)	6(60%)	0.097
Vomit	14(24%)	11(38%)	0.284	12(32%)	9(43%)	0.576	7(19%)	8(36%)	0.258	5(28%)	5(50%)	0.412
Diarrhea	6(10%)	4(14%)	0.724	7(18%)	8(38%)	0.167	3(8%)	3(14%)	0.664	4(22%)	5(50%)	0.211
General toxicity												
Numb	7(12%)	5(17%)	0.768	3(8%)	3(14%)	0.656	5(14%)	3(14%)	1	0(0%)	0(0%)	1
Fever	7(12%)	5(17%)	0.768	8(21%)	3(14%)	0.754	1(3%)	4(18%)	0.063	3(17%)	2(20%)	1

Adverse Events In Different Comorbidity Groups

Hepatitis and diabetes were negative predictors for OS in old patients; therefore, we divided patients according to comorbidity in old and young patients. The incidence of adverse events did not differ significantly in old patients with or without hepatitis (Supplementary Table 1). Although not significant, there was a trend towards more adverse events in old patients with diabetes compared with those without diabetes (Supplementary Table 2). Consistent with survival analysis in which hepatitis was a predictor for longer OS, when adverse events were compared in young patients with or without hepatitis, there was a trend towards less digestive toxicity in patients with hepatitis (Supplementary Table 3).

Discussion

To our knowledge, this is the first Chinese population-based study to explore the adverse events related to adjuvant chemotherapy in CRC patients. We found that the incidence of adverse events differed according to age, ECOG score and comorbidity, and adverse events had no mediation effects on survival outcomes.

Distant metastasis [15], lymph node metastasis [16, 17], and performance scores [15, 18, 19] have been reported as prognostic factors for CRC patients. We found some other factors that may influence survival outcomes in certain groups of patients. For example, impaired survival outcomes were observed in old patients with diabetes compared with those without diabetes. As previously reported, the increased mortality in diabetes patients was mainly related to cardiovascular diseases [20] and cancer-specific complications [21]. However, we found no significantly high incidence of treatment-related adverse events in patients with diabetes. We suppose that diabetes may lead to impaired survival by causing more cardiovascular events or infections rather than treatment-related toxicity.

We observed a trend that young patients with hepatitis tended to have longer survival outcomes than those without hepatitis. As previously reported, chronic HBV infection may be associated with reduced hepatic metastasis of CRC [22, 23] and prolonged survival of CRC patients [22]. After HBV infection, hepatic microenvironment may change, including gene products about immune function [24]. Cytotoxic T lymphocytes and Kupffer cells are activated during HBV replication and may play important roles in preventing hepatic metastasis [25]. In addition, patients with hepatitis may have sufficient supportive cares in their family, which leads to better treatment results. The positive effect of hepatitis on survival of young patients was not observed in old patients, partly because of the less-functional immune system in the latter. Moreover, there was no significant difference in adverse events between the groups, which means that hepatitis may not reduce the incidence of treatment-related toxicity in young CRC patients.

In the literature, it is controversial whether CRC patients with advanced age and/or higher ECOG scores have more adverse events after receiving adjuvant chemotherapy [13]. For example, a pooled analysis of 3351 patients showed that 5-FU- or capecitabine-based adjuvant chemotherapy benefitted older patients to the same extent as younger patients, without a significant increase in adverse events [26]. Hamza et al. reported no significant difference in adverse events among old compared with young patients, which meant that tolerance to FOLFOX regimen was comparable among old and young patients [27]. Lund et al. reported that age had no impact on disease-free survival and CRC mortality [28]. In a recent study, advanced age and poor performance status were negative predictors of severe adverse events and long hospitalization [29]. In the present study, the incidence of adverse events was comparable between the old and young patients, except for digestive adverse events, which were more common among young patients using oxaliplatin and 5-FU. Digestive adverse events, especially nausea, are related to subjective sensations; therefore, old patients might ignore the discomfort caused by weak gastrointestinal function. However, a trend towards higher frequency of digestive toxicity in older patients was reported by Hamza et al. [27]. The inconsistent results might have originated from racial differences among the patients and the small sample size of both studies. In addition, we found more digestive adverse events in patients with ECOG score ≥1, which was consistent with previous studies that showed that patients with poor performance scores were less responsive to chemotherapy [18, 29]. However, mediation analysis showed that the incidence of digestive adverse events did not lead to poor survival. We suggest that, as long as patients receive proper treatment on time, the occurrence of digestive adverse events does not lead directly to death. However, it is possible that those adverse events may impair quality of life or lead to longer hospitalization and higher expense for cancer patients.

It is reported that older patients might suffer from undertreatment when receiving chemotherapy, mainly because of the reluctance of doctors, risk of severe adverse events, and comorbidity [30–32]. However, based on our study, advanced age and higher ECOG scores do not directly lead to poor survival outcomes and adverse events. In addition, mediation analysis showed that adverse effects do not influence survival outcomes. Therefore, we suggest that concern about treatment-related adverse events in patients with advanced age, higher ECOG scores and comorbidity should not be considered as an independent indicator for less-aggressive treatment.

There were some limitations to this research. First, this was a single-center retrospective study, which could have led to selection bias. Besides, the medical records of several patients were not complete, such as only 155 patients in our study had ECOG scores. However, we had compared the basic characteristics and survival outcomes between those with and without ECOG scores and found no selectin bias in most indexes (Supplementary table 4) .Prospective studies are required to explore the potential adverse events and efficiency of adjuvant chemotherapy in Chinese CRC patients. Moreover, physicians will always choose to adjust the dose of chemotherapy regimens once adverse events occurred in clinical practice. Although we only recorded the incidence of adverse events which took place the first time, the change of dose may influence the survival outcomes. Finally, long-term survivals could not be analyzed because of the short follow-up. We are keeping contact with the patients included in our study and we intend to report the updated survival outcomes in the future.

In conclusion, this is believed to be the first Chinese population study to focus on adverse events related to adjuvant chemotherapy in CRC patients. We found that advanced age did not directly lead to poor survival outcomes and adverse events. Although higher ECOG scores and comorbidity led to impaired survival and higher incidence of adverse events, the latter had no mediation effects on survival outcomes. Therefore, we propose a more aggressive treatment strategy for patients with advanced age, poor ECOG score and comorbidity, without undue concern about the possible adverse events after chemotherapy. We believe that monitoring adverse events related to chemotherapy instead of potential undertreatment may help prolong survival and improve quality of life for more patients.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Peking Union Medical College Hospital, and the informed consent were signed by patients when they admitted into hospital. The procedure in this study was performed in accordance to the Code of Conduct of the China Medical Scientific Societies.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during the current study are not publicly available since they will contain patient data and the informed consent agreement does not include sharing data publicly. An anonymized form of the data could be made available from the corresponding author upon reasonable request.

Competing interests

None

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Authors' contributions

W.Y. contributed to the study conception and design, G.C. and T.Y. collected the clinical data, G.C., T.Y. and Z.N. wrote the main manuscript and prepared figures and tables. All authors reviewed the manuscript.

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Figures

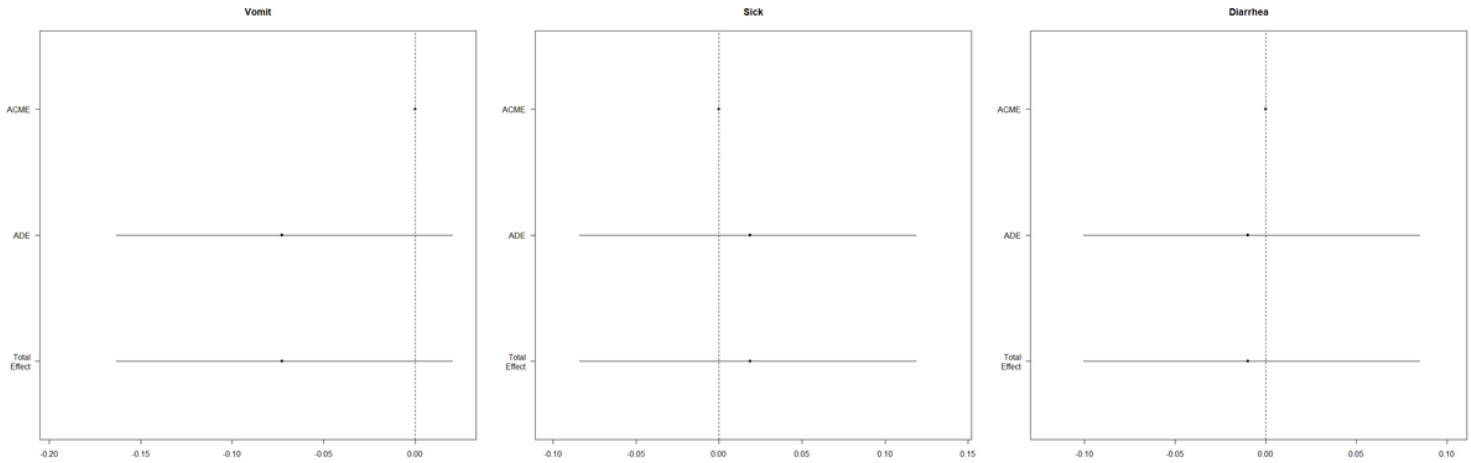

Figure 1

Results of mediation analysis of age-adverse events-survival outcomes. Three adverse events (vomit, sick and diarrhea) with significant rates in the young and old group were analyzed. The happen of vomit, sick and diarrhea played no mediation effects in causing different survival outcomes in different age groups. ADE: Average Direct Effect, ACME: Average Causal Mediation Effect, Total Effect=ADE+ACME.

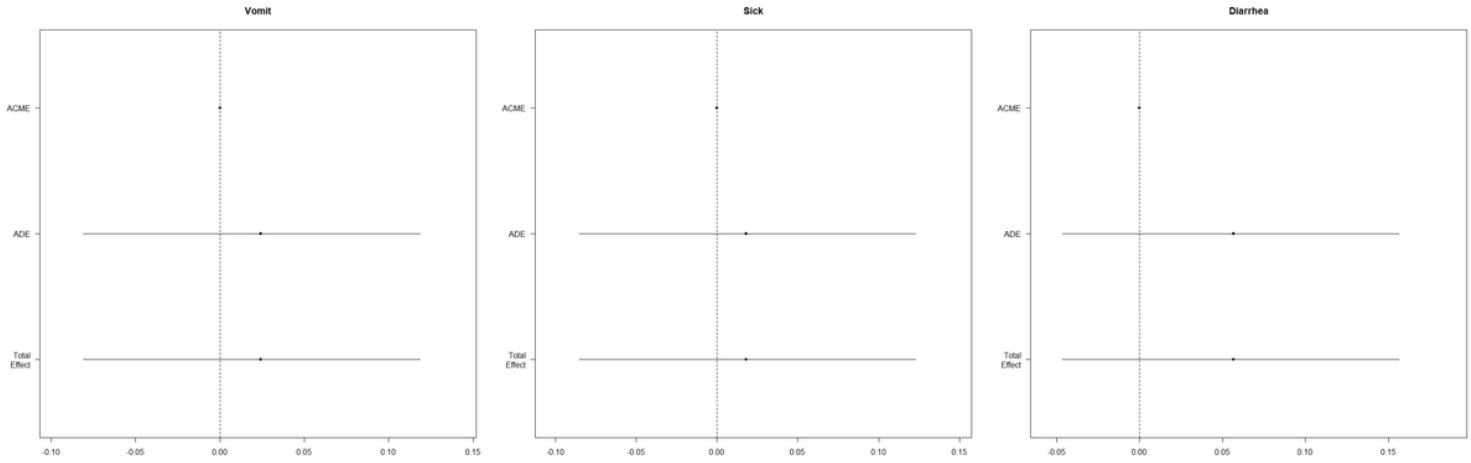

Figure 2

Results of mediation analysis of ECOG-adverse events-survival outcomes. Three adverse events (vomit, sick and diarrhea) with significant rates in patients with ECOG=0 and ECOG ≥1 were analyzed. The happen of vomit, sick and diarrhea played no mediation effects in causing different survival outcomes in different ECOG groups. ADE: Average Direct Effect, ACME: Average Causal Mediation Effect, Total Effect=ADE+ACME.

Supplementary Files

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- SupplementaryFigure1.tif
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- SupplementaryFigurelegends.docx
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