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ORIGINAL ARTICLE

Role of pre-existing type 2 diabetes in colorectal cancer survival among older Americans: a SEER-Medicare population-based study 2002–2011

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Abstract

Purpose Type 2 diabetes mellitus (diabetes) is a common comorbid condition among older adult colorectal cancer (CRC) patients, yet its effects on CRC mortality have not been adequately examined. This study aims to investigate the association between pre-existing diabetes, with and without complications, and CRC mortality.

Methods Medicare beneficiaries 67 years and older diagnosed with CRC between 2002 and 2011 were studied using the Surveillance, Epidemiology, and End Results (SEER)-Medicare datasets. Pre-existing diabetes was ascertained using validated algorithms. Cox proportional hazards models were used to compare all-cause and CRC-cause-specific death risk differences in relation to prior diabetes diagnosis and diabetes severity (with and without complications) with adjustment for relevant patient demographics and disease characteristics.

Results Analyses included 93,710 CRC patients. Among the study population, 22,155 (24%) had diabetes prior to CRC diagnosis and 4% had diabetes-related complications (neuropathy, nephropathy, retinopathy, or peripheral circulatory disorders). All-cause CRC mortality was significantly higher among diabetic patients compared with non-diabetic patients (hazard ratio (HR) = 1.20; 95% confidence interval (CI) = 1.17–1.23). The results were more pronounced for diabetes with complications (HR = 1.47; 95% CI = 1.34–1.54). Diabetic patients with complications were 16% more likely to die of colorectal cancer compared with patients without diabetes (HR = 1.16; 95% CI = 1.08–1.25).

Conclusion Pre-existing diabetes contributes to poorer all-cause mortality among CRC patients and increased mortality from CRC among those with diabetes and complications. Opportunities exist to incorporate diabetes prevention and management interventions during CRC treatment phases among older adults.

Keywords Cancer · Colorectal cancer · Type 2 diabetes · Survival · Medicare · Mortality

Introduction

Colorectal cancer (CRC) and type 2 diabetes mellitus (referred to as diabetes) are major causes of morbidity and death in the Unites States (U.S.) [1, 2]. Both diseases are preventable through lifestyle changes, and their complications can be attenuated through screening and early detection [3, 4]. CRC and diabetes share many common risk factors that characterize

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the Western lifestyle such as poor eating habits and prolonged sedentary behavior [5, 6]. Colorectal cancer is the second leading cause of cancer death among older adult (i.e., age 65 years and older) males and third leading cause of cancer death among older adult females [2]. More than 25% of the older adults suffer from diabetes [7]. Consequently, diabetes is a common comorbid condition among CRC patients, particularly among older adults, with estimated co-occurrences ranging from 5 to 26% [8–11]. Despite these high rates of comorbidity, the effects of diabetes on CRC outcomes have not been adequately examined, with less being known about the potential influence of diabetes on CRC risk of death and associated risk variations by diabetes severity (complications vs. no complications).

Study purpose

The purposes of this study were to, first, investigate whether diabetes is an independent predictor of poorer survival from all-cause and CRC-specific mortality and second, assess whether variations of CRC survival outcomes exist by diabetes complication status. We hypothesized that mortality risk among CRC patients is higher among those with pre-existing diabetes with and without complications, compared with CRC patients without diabetes.

Methods

Data source and cohort

The Surveillance, Epidemiology, and End Results (SEER)-Medicare linked datasets were used for this study [12]. The SEER cancer registries include 20 U.S. geographic areas and covers approximately 28% of the domestic population [13]. The National Cancer Institute, in partnership with the Centers for Medicare and Medicaid Services (CMS), performs linkage of the SEER data with Medicare claims for Medicare beneficiaries every 2 years, and each linkage successfully matches 95% SEER cases for persons age 65 years and older to their Medicare enrollment and claims files [14]. Both SEER and CMS actively follow patients: SEER registries follow cancer patients and record death/alive status at the end of each data submission while CMS reports information about all beneficiaries from entitlement to death regardless of place of residence.

Demographic and clinical information were extracted for each person from the Patient Entitlement and Diagnosis Summary file (PEDSF) SEER file. Example variables of interest included age, date of death, sex, race, state of residence, date of diagnosis, survival in months, stage at diagnosis, and source of diagnosis. Medicare enrollment information and clinical claims data were extracted from the Medicare Provider Analysis and Review (MEDPAR) for inpatient stays and from the Outpatient Claims file for outpatient stays.

The cohort under study included older adult patients aged 67 years and older diagnosed with CRC between 2002 and 2011. The age was limited to 67 years and older to allow at least 2 years of claims to be analyzed. Patients had to have 24 months continuous enrollment in Part A and Part B to be included [15]. Patients were excluded if the month of CRC diagnosis was missing or if CRC was diagnosed at autopsy or by death certificate. To classify CRC diagnosis, CRC International Classification of Diseases for Oncology 3rd edition (ICD-O-3) codes C18.0–C18.9, C19.9, and C20.9 were used.

Outcomes and predictors

Death risk was assessed using all-cause mortality and CRC-cause-specific mortality. Information about date of death is tracked in both SEER and Medicare enrollment files. Therefore, subjects were included in analyses if their month of death was the same in both files or only differed by a maximum of 1–3 months. Survival in months is provided by the SEER program based on active follow up. Patients were censored if they were "alive" at the cut-off date (December 31, 2011) or if they died after the cut-off date. In addition, for cause-specific mortality, patients were censured if a non-CRC cause of death was documented prior to the cut-off date.

Pre-existing diabetes was ascertained from the Medicare inpatient and outpatient claims using a validated algorithm (algorithm #1) with 74.4% sensitivity and 97.5% specificity [16]. Based on the Hebert algorithm, claims were searched 24 months prior to a CRC diagnosis. The identification period was expanded to 3 months after CRC diagnosis to capture patients who may not have had a healthcare encounter before their cancer diagnosis [15]. To avoid "rule out" diagnoses, a flag was assigned to a record if a diabetes diagnosis code appeared in a single hospital claim and two or more outpatient claims separated by more than 30 days. Applying the rule out algorithm helps to avoid overestimating conditions when they are identified from claims. Medication was not included in the algorithm for identifying patients with diabetes because CMS started covering medication in Part D only since 2006. To classify type 2 diabetes diagnoses, the following ICD-9-CM codes were used: 250.00, 50.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, and 250.33. Diabetes with complications included neuropathy, nephropathy, retinopathy, or peripheral circulatory disorders. Patients with no diabetes diagnosis served as the referent group in all analyses.

Demographic covariate variables controlled for in analyses were classified at the time of CRC diagnosis. The covariates included age groups (67–75, 76–85, and 85 years old and

older), marital status (single, married, separated/divorced, widowed, and unknown), and race/ethnicity (White non-Hispanic, Black non-Hispanic, Hispanic, non-Hispanic Asian Pacific Islander, and non-Hispanic American Indian/Alaska Native). Poverty level, was computed from the 2000 U.S. Census and the 2012 American Community Survey for all cases using median household income, then ranked and grouped into quartiles (low, medium, medium high, and high poverty level) [17].

The comorbidity score, which excludes diabetes, was calculated based on an updated version of the Charlson index by the National Cancer Institutes, which is a cancer-specific index including 14 conditions (e.g., acute myocardial infarction, congestive heart failure, and cerebrovascular diseases) and excludes solid tumors, leukemias, and lymphomas [18].

Clinical covariates included tumor site (proximal colon consisting of the cecum to the splenic flexure, distal colon consisting of the descending and sigmoid colon, colon not otherwise specified (NOS), and rectum), histology (adenocarcinomas, carcinomas, and carcinomas NOS), stage at diagnosis (localized, regional, and distant), and comorbidity score (no comorbidity, 1 comorbidity, and 2 or more comorbidities). Treatment was not controlled for in analyses because treatment decisions are affected by patient cancer stage and concurrent existing comorbid conditions. We controlled for both these confounding variables.

Statistical analyses

Descriptive analyses were used to compare demographic and clinical information for colorectal cancer patients by their diabetes status and the presence of diabetes-related complications. Chi-square tests assessed differences between groups for categorical variables. Significant differences in survival were tested with the log-rank tests. All-cause and CRC-cause-specific death risk differences were compared using Cox proportional hazards models, and hazard ratios (HR) were compared in relation to prior diabetes diagnosis and diabetes complications status. All models were adjusted for relevant covariates. Tied data were adjusted using the Efron approximation. The proportional hazards assumption was tested and met based on the graphed Schoenfeld residuals for predictors and covariates [19]. The 95% confidence intervals (CI) for HRs were generated and reported. All statistical analyses were performed using version 9.4 of the SAS statistical software (SAS Institute).

Results

The study analyses included 93,710 CRC patients followed for a total of 320,087 person-years. The mean age of the study population was 78 (± 7) years and the median age was 77 years (range 67 to 108 years). Among the study population, 22,155 (24%) had diabetes prior to CRC diagnosis. Among those with diabetes, 17% (3,827) had diabetes-related complications. A significantly larger proportion of diabetic patients were less than 85 years old, female, and White (Table 1). A large proportion of diabetic patients also lived in medium to high poverty level areas, had at least one or more comorbidities, and had tumors in the proximal colon (Table 2).

At the end of the study period, 44,688 subjects-representing 48% of the initial cohort- died of all causes. CRC-specific deaths, a sub-part of all deaths, amounted to 26,037 deaths. Among patients who died of all causes, 20% had diabetes without complications and 5% had diabetes with complications. Among those who died specifically of CRC, 18% had diabetes without complications and 4% had diabetes with complication (Table 3). The median survival for all-cause mortality was 61 months (95% CI = 60–62). The overall 5-year survival rate for the study cohort was 51% (Standard error (SE) = 0.00186). Diabetes with complications had the most unfavorable crude survival followed by those with diabetes without complications (Kaplan Meier log-rank test $P < 0.0001$).

In the univariate Cox regression model, CRC patients with diabetes had 21% increased risk of mortality from all causes (HR = 1.21; 95% CI = 1.18–1.23). The mortality risk was particularly higher among diabetic patients with complications (HR = 1.69; 95% CI = 1.62–1.76) (Table 4, Model 1). Significant results were only observed for diabetes with complications in CRC-cause-specific mortality (HR = 1.14; 95% CI = 1.07–1.22). Similar results were observed when adjusted for age and comorbidities, although the magnitude of effects attenuated after the introduction of comorbidities (Table 4, Models 2 and 3).

In the fully adjusted model, colorectal cancer patients were more likely to die if they had diabetes (HR = 1.20; 95% CI = 1.17–1.23), particularly those with complications (HR = 1.47; 95% CI = 1.34–1.54), compared with those with no prior diabetes diagnosis. Diabetes patients with complications were 16% more likely to die of CRC compared with patients without diabetes (HR = 1.16; 95% CI = 1.08–1.25) (Table 4, Model 4).

Discussion

This study shows that the impact of diabetes on survival rates among older adult CRC patients is substantial. Moreover, not unexpected, the specific groups of CRC patients with diabetes and complications had almost a 50% higher risk of all-cause death and a 16% higher risk of CRC-cause-specific death. These findings are unique in that most studies that examine the association of CRC and diabetes have not parsed out the effects of diabetes status by severity [20–29].

Table 1 Demographic characteristics by diabetes status

	Total (%)	No diabetes (% total)	Diabetes (% total)	Diabetes with complications (% diabetes)	Diabetes without complications (% diabetes)	*P* value
Patient demographics	93,710	71,555 (76)	22,155 (24)	3827 (17)	18,328 (83)	
Age						< .0001
67–75	39,364 (42)	29,471 (41)	9893 (45)	1720 (45)	8173 (45)	
76–85	40,137 (43)	30,589 (43)	9548 (43)	1672 (44)	7876 (43)	
86+	14,209 (15)	11,495 (16)	2714 (12)	435 (11)	2279 (12)	
Sex						< .0001
Male	42,626 (45)	32,104 (45)	10,522 (47)	1875 (49)	8647 (47)	
Female	51,084 (55)	39,451 (55)	11,633 (53)	1952 (51)	9681 (53)	
Race/ethnicity						< .0001
White NH	74,931 (78)	58,645 (82)	16,286 (74)	2622 (69)	13,664 (75)	
Black NH	8217 (9)	5488 (8)	2729 (12)	627 (16)	2102 (11)	
Hispanic	5180 (6)	3461 (5)	1719 (8)	323 (8)	1396 (8)	
American Indian/Alaska Native	266 (0)	174 (0)	92 (0)	22 (0)	70 (0)	
Asian or Pacific Islander	4745 (5)	3479 (5)	1266 (6)	222 (6)	1044 (6)	
Unknown	371 (0)	308 (0)	63 (0)	*	52 (0)	
Marital status						0.0052
Single	7631 (8)	5824 (8)	1807 (8)	344 (9)	1463 (8)	
Married	45572 (49)	34941 (49)	10631 (48)	1701 (44)	8930 (49)	
Separated/divorced	6563 (7)	4892 (7)	1671 (8)	335 (9)	1336 (7)	
Widowed	29,792 (32)	22,720 (32)	7072 (32)	1277 (33)	5795 (32)	
Unknown	4152 (4)	3178 (4)	974 (4)	170 (4)	804 (4)	
Poverty level						< .0001
0 to < 5% poverty	43,276 (46)	34,076 (48)	9200 (42)	1568 (41)	7632 (42)	
5 to < 10% poverty	24,800 (26)	18,804 (26)	5996 (27)	1014 (27)	4982 (27)	
10 to < 20% poverty	17,331 (18)	12,728 (18)	4603 (21)	800 (21)	3803 (21)	
20 to 100% poverty	7801 (8)	5551 (7)	2250 (10)	422 (422)	1828 (10)	
Unknown	502 (1)	396 (1)	106 (0)	23 (1)	83 (0)	

NH non-Hispanic

*The number of cases is too few to report

This study found a significant association between pre-existing diabetes and all-cause mortality among a cohort of older adult CRC patients. In a population-based study, Groß et al. found a 23% increase in risk from all-cause mortality among patients with comorbid diabetes [21]. Patients in a clinical trial had poorer prognosis if they had diabetes at the time of CRC diagnosis; a 42% increased risk of all-cause death [22]. Similarly, patients with pre-existing diabetes from the Connecticut cancer registry were found to have a 38% elevated risk of all-cause mortality [26]. Bella et al. found a 41% increased risk of all-cause mortality among CRC adult Italian patients with comorbid diabetes irrespective of sex or sub-site [25]. Other similar results have been reported in systematic reviews [30, 31].

In the present study, although we found a significant association between pre-existing diabetes and CRC-cause-specific mortality, the effect size was minimal. This small effect aligns with the lack of concordance within the current literature, which indicates mixed results about the association of pre-existing diabetes with CRC-cause-specific mortality. For instance, for non-U.S. populations [2, 25, 32] and in some meta-analyses [27, 33], authors have reported significant relationships between comorbid diabetes and CRC mortality. In contrast, other researchers did not identify elevated risk for CRC mortality among diabetic patients [26, 31].

The exact pathophysiological mechanism through which diabetes may affect CRC prognosis is not clear; however, some proposed pathways include hyperinsulinemia and hyperglycemia. These are known factors that contribute to increased risk of cancer and tumor metastasis [29, 34, 35], and may also directly affect the outcomes of CRC. Moreover, diabetes may increase the risk of CRC recurrence, which may partly contribute to the observed poorer prognosis among diabetic patients with CRC [22, 28, 33].

Table 2 Clinical characteristics by diabetes status

	Total (%)	No diabetes (% total)	Diabetes (% total)	Diabetes with complication (% diabetes)	Diabetes without complication (% diabetes)	*P* value
Total patients	93,710	71,555 (76)	22,155 (24)	3827 (17)	18,328 (83)	
Comorbidities						< .0001
No comorbidity	70,023 (75)	56,397 (79)	13,626 (62)	1510 (39)	12,116 (66)	
One comorbidity	18,031 (19)	12,213 (17)	5818 (26)	1225 (32)	4593 (25)	
Two or more comorbidities	5656 (6)	2945 (4)	2711 (12)	1092 (29)	1619 (9)	
CRC stage						< .0001
Localized	41,785 (45)	31,766 (44)	10,019 (45)	1768 (46)	8251 (45)	
Regional	34,037 (36)	25,854 (36)	8183 (37)	1351 (35)	6832 (37)	
Distant	13,513 (14)	10,554 (15)	2959 (13)	507 (13)	2452 (13)	
Unknown stage	4375 (5)	3381 (5)	994 (5)	201 (5)	793 (4)	
CRC site						<.0001
Proximal	46,896 (50)	35,413 (49)	11,483 (52)	2063 (54)	9420 (51)	
Distal	21,236 (23)	15,958 (22)	5278 (24)	915 (24)	4363 (24)	
Rectum	22,712 (24)	17,990 (25)	4722 (21)	726 (19)	3996 (22)	
Colon, NOS	2866 (3)	2194 (3)	672 (3)	123 (3)	549 (3)	
Grade						<.0001
Well differentiated	8312 (9)	6360 (9)	1952 (9)	353 (9)	1599 (9)	
Moderately differentiated	57,464 (61)	43,529 (61)	13,935 (63)	2376 (62)	11,559 (63)	
Poorly differentiated	15,361 (16)	11,818 (17)	3543 (16)	604 (16)	2939 (16)	
Undifferentiated	1392 (1)	1055 (1)	337 (2)	56 (1)	281 (2)	
Unknown grade	11,174 (12)	8788 (12)	2386 (11)	437 (11)	1949 (11)	
Histology						0.0003
Adenocarcinomas	80,066 (85)	60,987 (85)	19,079 (86)	3297 (86)	15,782 (86)	
Carcinomas	11,194 (12)	8624 (12)	2570 (12)	439 (11)	2131 (12)	
Carcinomas, NOS	2443 (3)	1944 (3)	506 (2)	91 (2)	415 (2)	

CRC, colorectal cancer; *NOS*, not otherwise specified

In addition, diabetes might increase general mortality as well as death from diabetes-related diseases (e.g., stroke, ischemic heart disease, hypertension, chronic renal failure). A study of multimorbidity and survival among persons with CRC found that among CRC deaths, 9% were attributable to congestive heart failure and more than 5% were attributable to chronic obstructive pulmonary disease [21]. Another study using a large U.S. cohort found a twofold increase of death from cardiovascular diseases among patients with self-reported diabetes and CRC [27]. Moreover, there are potential indirect influences of diabetes on cancer management and treatment. Comorbid diabetes among CRC patients might influence treatment decisions, treatment response, and treatment-related side effects. Researchers found that older patients with diabetes and other comorbidities were less likely to see an oncologist in the first six months after diagnosis [36, 37], less likely to start and/or complete recommended CRC adjuvant chemotherapy [38, 39] or neoadjuvant therapy for

Table 3 Distribution of CRC deaths by diabetes status and mortality outcome

Mortality	Total deaths	Diabetes status		
		No diabetes (%)	Diabetes without complications (%)	Diabetes with complications (%)
Overall mortality	44,688	33,510 (75)	8905 (20)	2273 (5)
CRC-cause-specific death	26,037	20,306 (78)	4733 (18)	998 (4)

Table 4 Effect of pre-existing diabetes on total mortality and CRC-cause-specific mortality in patients with colorectal cancer

Parameter	Cause-specific mortality			All-cause mortality		
	Hazard ratio	95% confidence interval		Hazard ratio	95% confidence interval	
		Lower limit	Upper limit		Lower limit	Upper limit
Model 1: univariate with diabetes						
No diabetes	Referent			Referent		
Diabetes	0.99	0.96	1.02	1.21[a]	1.18	1.23
Diabetes without complications	0.97	0.94	1	1.13[a]	1.1	1.16
Diabetes with complications	1.14[a]	1.07	1.22	1.69[a]	1.62	1.76
Model 2: Model 1 + age						
No diabetes	Referent			Referent		
Diabetes	1.02	0.99	1.05	1.27[a]	1.24	1.29
Diabetes without complications	0.99	0.96	1.02	1.18[a]	1.15	1.21
Diabetes with complications	1.18[a]	1.11	1.26	1.78[a]	1.71	1.86
Model 3: Model 2 + comorbidity						
No diabetes	Referent			Referent		
Diabetes	0.99	0.96	1.02	1.16[a]	1.13	1.18
Diabetes without complications	0.97	0.94	1	1.11[a]	1.08	1.13
Diabetes with complications	1.10[a]	1.03	1.17	1.43[a]	1.37	1.5
Model 4: fully adjusted model						
No diabetes	Referent			Referent		
Diabetes	1.05[a]	1.02	1.09	1.20[a]	1.17	1.23
Diabetes without complications	1.04	0.99	1.08	1.15[a]	1.12	1.18
Diabetes with complications	1.16[a]	1.08	1.25	1.47[a]	1.4	1.54

[a] Statistically significant at $P < 0.05$

Model 4 is adjusted for age (categorical), sex, marital status, race/ethnicity, poverty level, stage at diagnosis, site, comorbidities, histology, grade, year of diagnosis, and registry

metastasized cancer [39], and less likely to receive aggressive cancer treatment [20]. These treatment disparities may be attributed to increased cancer treatment-related side effects, real or perceived by clinicians, which indicates a potential clinician bias towards cancer patients with multimorbidity [22].

As seen in the current study, patients with diabetes-related complications were more likely to die of CRC. Reasons for this effect have not been fully explored. However, this finding suggests that poor diabetes control is unfavorable for CRC patients, and patients could benefit from controlling diabetes and preventing its complications. Uncontrolled diabetes is a known independent risk factor for diabetes complications [40]; hence, clinicians play a large role in aiding their patients to manage their diabetes through regular HbA1c testing, education about lifestyle changes, and medication. For instance, it has been demonstrated that cancer patients who receive diabetes education are less likely to visit emergency departments, have fewer hospital admissions, and are more likely to manage their diabetes with more frequent HbA1c tests [41].

To complement clinical care provided by physicians, CRC patients with diabetes may also benefit from evidence-based chronic disease self-management education programs delivered in community settings. Such programs are widely available nationwide [42, 43] and are effective to reduce physical and mental health ramifications [44, 45] as well as direct costs associated with emergency room visits and hospitalizations [46].

Strengths and limitations

The strength of this study lies in its inclusion of a large number of patients from a nationally representative database. The SEER-Medicare data offer a combination of clinical information from the cancer registries as well as diagnoses and procedures from the Medicare claims data. These data are population-based and enable the tracking of patients longitudinally. The integration of various data elements and ability to follow patients throughout the duration of their cancer experience is important in that it facilitates in-depth studies such as these to examine aspects associated with survivorship and mortality.

Findings from this study should be interpreted considering certain limitations. Administrative data are not inherently designed for research. Therefore, some information on lifestyle behaviors and patient characteristics were not available for the current study which may have affected the magnitude of the effects. However, other studies that controlled for these factors did not observe a weakening in the association under study [10, 27]. Moreover, colon and rectal cancers behave differently and have different prognosis based on cancer stage. While findings could have been stratified by cancer site, previous research reports no indication of differences in mortality outcomes by diabetes status (i.e., diabetes vs. no diabetes) [47].

Further, identifying diabetes from administrative data introduced additional limitations. First, diabetes cases may have been overlooked if the individual did not have a health system encounter. To mitigate this limitation, we allowed a 24-month period before CRC diagnosis and 3 months after CRC diagnosis to identify previously undiagnosed diabetes [15]. Second, the dataset lacked information about cases with prediabetes (impaired fasting glucose and/or impaired glucose tolerance); therefore, hazard ratios in the current study might have been underestimated. This remains a concern because the prevalence of prediabetes is on the rise in the U.S. [1]. Third, we were unable to identify diabetes duration; however, this has not shown to be impactful of survival in similar studies [27].

Conclusion

In summary, this study used population-based data and the findings indicate that pre-existing diabetes contributes to poorer all-cause survival among patients with CRC and increased mortality from CRC for patients with diabetes and associated complications. These findings are relevant in the context of the rising prevalence of diabetes among the aging U.S. population. Because CRC and diabetes (and their comorbidity) are more prevalent among older adults, these complex patients may require additional clinical interactions and support, which will entail the development of care plans that are interdisciplinary and take into consideration the added burden of diabetes among CRC patients. In addition, findings also underscore lack of understanding about how diabetes affects CRC outcomes. Particular attention is needed for patients with diabetes complications as they suffer from the worst outcomes. Increased focus on diabetes education, diabetes self-management, and improved diabetes control are critical to improve survival among colorectal patients with comorbid diabetes.

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Compliance with ethical standards

Human and animal rights and informed consent The study did not involve research on human subjects and it did not require informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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