Age and Outcome in Gastrointestinal Cancers: A Population-Based Evaluation of Oesophageal, Gastric and Colorectal Cancer

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Keywords

Oesophageal cancer · Gastric cancer · Colorectal cancer · Elderly · Cancer registry

Summary

Background: With demographic changes and partial representativeness of randomized studies the question arises which results are achieved in the treatment of the elderly. The objective was to analyse population-based data on gastrointestinal cancers in terms of age. **Methods:** Analyses included data of the Munich Cancer Registry, i.e. 4,014, 10,127 and 42,809 invasive oesophageal, gastric and colorectal cancer patients, respectively, which were diagnosed between 1998 and 2014. Tumour characteristics and outcome were analysed by age groups and therapy. Overall survival was analysed using the Kaplan-Meier method, and relative survival was computed as estimation for cancer-specific survival. Additionally, conditional survival of patients surviving at least 6 or 12 months was analysed by age. **Results:** 21, 44 and 38% of oesophageal, gastric and colorectal cancer patients, respectively, were aged >75 years. Of these, 15, 46 and 73% were surgically treated with curative intent, respectively, which is significantly less than in younger patients. The total 5-year relative survival was 24, 33 and 66%, respectively. The differences in median survival by age group were diminished by selecting those surviving at least 6 or 12 months and those with curatively intended treatment. **Conclusion:** An adequate patient selection for therapies of these gastrointestinal cancers was demonstrated at large. If the patients' general conditions allowed curatively intended treatment, it was applied and led to similar outcomes irrespective of age.

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Introduction

In Germany, the absolute numbers of incident cancer cases prognosticated for the year 2016 are 7,200, 15,600 and 61,300 for oesophageal (C15), gastric (C16) and colorectal (C18–20) cancer, with a male/female proportion of 3.5, 1.4 and 1.2, respectively. Whereas C15 incidence and mortality were nearly stable for more than one decade, C16 incidence and mortality have decreased over more than three decades, and since the early 1990s, C18–20 mortality as well as since 2003, C18–20 incidence are decreasing likewise. However, these gastrointestinal cancers are still accountable for 2.0, 3.6 and 13.4% of new cancer cases in men and <1, 2.9 and 12.6% of new cancer cases in women, respectively [1].

Because of their peak incidence in the sixth and seventh decade in men and in the eighth and ninth decade in women [2], the absolute numbers and proportions of older patients with these cancers will increase with the expanding older population in industrial countries [3, 4].

Because the only option for cure in gastrointestinal cancers is complete tumour removal, and as the patients' surgical risk increases with age, fulfilling the requirements of adequate treatment will get more difficult for surgery than for other adjuvant treatment options. In times of demographic ageing, prospective randomised clinical trials do not represent the general population just yet. Therefore, their results cannot be extended to the elderly and transferred one-to-one to routine care. As a result, observational population-based cancer registry data offer a chance to fill the information gap due to lack of evidence from randomized controlled trials, to evaluate the advances in cancer therapy, and to examine whether the elderly do benefit from medical advances as well. In this context, it is the goal of comparative effectiveness research to inform clinical decisions between alternate treatment

Fig. 1. Cohort profiles of oesophageal, gastric and colorectal cancer cohorts (1998–2014).

strategies using data that reflect real patient populations and real-world clinical scenarios for the purpose of improving patient outcomes [5].

Hence, the objective of this study is to survey tumour characteristics, treatments, and outcome of oesophageal, gastric and colorectal cancer by age strata in a German population-based setting.

Material and Methods

Data Collection

The Munich Cancer Registry (MCR) is the population-based clinical cancer registry of Upper Bavaria and, partly, of Lower Bavaria (Southern Germany). Its catchment area has been enlarged from 2.3 million inhabitants in 1998 to 4.8 million nowadays. Pathology reports of solid tumours from all pathology laboratories in this catchment area are available. From these reports, the total number of gastrointestinal cancer patients in the region is systematically assessed and the main prognostic factors are ascertained. In parallel, clinicians complete standardised forms concerning the patients' domicile, age, primary disease characteristics such as TNM stage, histology, grade, as well as therapies or deliver these data online to the MCR. Additionally, the life status of patients with a cancer diagnosis is systematically maintained through death certificates. Thus, active follow-up data are available for about 95% of all cases.

Patient Sample

A total of 4,432 oesophageal, 13,297 gastric and 48,386 colorectal malignant tumour patients with residence in the catchment area were diagnosed between 1998 and 2014 (fig. 1). Patients with a non-invasive carcinoma, neuroendocrine tumour, gastrointestinal stroma tumour, and other sarcoma or lymphoma as well as death certificate only (DCO) cases (6.2, 9.5 and 6.7%, respectively) were excluded from the analyses. Thus, the analyses of the three epidemiological cohorts of 4,014, 10,127 and 42,809 patients provide a current and population-based survey of invasive oesophageal, gastric and colorectal carcinoma, respectively.

Patients with evidence of another previous or synchronous malignant tumour were excluded from survival analyses to eliminate overlaying tumour effects and treatment restrictions. Thus, the cohorts of the survival analyses comprised 3,186, 8,381 and 34,861 patients. It was assured by preliminary analyses that survival differences between these reduced cohorts and the total cohorts including patients with synchronous and preceding tumours are about 1.5 percent points in colorectal cancer and even smaller in oesophageal and gastric cancer, confirming that the effects of preceding and synchronous other competitive tumours can be neglected.

In order to examine the effects of treatment, a variable 'surgery with curative intent' was generated for each cancer, considering all surgical procedures which are suitable for complete tumour removal, such as oesophagectomy, gastrectomy, and hemicolectomy, or considering the status of tumour residual R0 if other specifications were missing. The extent of lymph node removal was not evaluated.

Statistics

The MCR organises data in an Oracle database. Statistical analyses were run in SAS (Statistical Analysis System 9.4; SAS Institute, Cary, NC). Frequency data were analysed using the chi-square test. The percentages of the presented subcategories were related to the sum of each item with available data; missing values were not taken into account.

Observed (unadjusted overall) survival was estimated by the Kaplan-Meier method and curves were drawn up to 10 patients at risk. Relative survival was calculated by the ratio of the observed survival rate to the expected survival rate. The expected survival time of age- and sex-matched individuals was calculated using life tables of the general German population. Relative survival can be interpreted as survival from cancer after correction for other causes of death and is therefore used as an estimate for cancer-specific survival. To adjust for effects of age on treatment outcome, such as postoperative mortality, a conditional survival analysis was calculated for those who survived at least half a year in oesophageal and gastric cancer and at least 12 months in colorectal cancer, according to the landmark method proposed by Anderson et al. [6]. These landmarks approximately represent the median survival of the primarily metastasized patients (M1). The significance level α was set at 0.05 in all statistical tests.

Table 1. Epidemiologic measures in oesophageal, gastric and colorectal cancer

	Oesophageal cancer	Gastric cancer	Colorectal cancer
<i>Incidence male/female</i>			
1998–2014 MCR, per 100,000 and year WS	5.4/1.2	11.0/6.1	40.9/25.5
AAPC 2000–2013 MCR, %	–1.7/±0	–2.5/–2.9	–2.3/–2.5
2016 Germany, n per year [1]	5,600/1,600	9,200/6,400	33,700/27,600
2009–2013 Germany, per 100,000 and year WS [12]	6.3/1.4	10.8/5.7	38.3/23.8
2009–2013 USA, per 100,000 and year WS [13]	5.1/1.0	5.6/2.8	29.0/21.8
AAPC 2004–2013 USA, % [13]	–0.7/–0.6	–1.5/–0.6	–3.4/–3.0
<i>Age, years</i>			
Median male/female MCR	65.8/68.8	71.8/76.5	70.1/74.1
25-/75-percentile MCR	58.9/74.1	63.9/73.6	63.1/80.1
<i>Death certificate only (DCO) cases</i>			
Patients MCR, %	6.2	9.5	6.7
Median age of DCO cases MCR, years	75.2	83.7	84.0
<i>Lifetime risk, %</i>			
Germany, age > 65 [1]	0.7/0.2	1.7/1.1	6.3/4.9
USA, age > 60 [13]	0.80/0.21	0.91/0.49	4.1/3.7
<i>5-year relative survival, %</i>			
1998–2006/2007–2014 MCR	20.1/26.6	32.5/34.6	66.0/65.1
1999–2005/2006–2012 USA [13]	17.6/19.2	24.1/29.2	66.1/65.8
Europe 2005–2007 [14]	15.2	26.2	60.5
WS = World standard; MCR = Munich Cancer Registry; AAPC = average annual percentage change.			

Age cut-offs at 65, 70 or 75 years are common in the literature [7–11]. Therefore, three age groups (<60, 60–75, >75 years) were chosen for evaluation. In addition, survival was examined in five age groups (<50, 50–59, 60–69, 70–79, ≥80 years) to provide further detailed information about the effects of age. Relative survival in the oldest age group, i.e. ≥80 years, fluctuates more and more with longer follow-up. The expected 1-year survival in this group is lower than 90%. The decreasing absolute patient numbers after the 90th year lead to an unstable quotient of observed and expected survival which may even increase.

Results

Incidence and Survival

Epidemiologic measures comparing the MCR catchment area, Germany, and the USA are presented in table 1. Overall, the age-adjusted incidences are higher in the German and the MCR population compared to the USA [12, 13]. The MCR gastric cancer incidence is double in males and 2.2-fold higher in females (11.0 and 6.1 vs. 6.5 and 2.8). The oesophageal cancer incidences are between 20 and 40% higher in the German population (6.3 and 1.4 vs. 5.1 and 1.0). The colorectal cancer incidence is 40% higher in MCR males and 17% higher in MCR females (40.9 and 25.5 vs. 29.0 and 21.8).

The median age in the MCR population is always about 3–4 years higher in females, the youngest in oesophageal cancer (65.8 and 68.8 years), and the oldest in gastric cancer (71.8 and 76.5 years).

The lifetime risk to get diagnosed with oesophageal cancer is nearly similar in Germany and the USA, while it is twice as high to get diagnosed with gastric cancer in Germany.

The 5-year relative survival is higher in the MCR population with 20.1 and 26.6% for males and females with oesophageal cancer compared to 17.6 and 19.2% in the USA. In gastric cancer, these differences are even higher with 32.5 and 34.6% compared to 24.1 and 29.2%. In this regard, the DCO rates in the MCR area of 6.2, 9.5 and 6.7% for oesophageal, gastric and colorectal cancer, respectively, with a median age of DCO cases always above the 75%-percentile should be commemorated. In colorectal cancer, the 5-year relative survival is nearly the same with 66 and 65.1% in the area of the MCR and 66.1 and 65.8% in the USA.

Patient and Tumour Characteristics

The population-based cohorts of oesophageal, gastric and colorectal cancer comprise 4,014, 10,127 and 42,809 cases from 1998 to 2014, respectively. Selected patient and tumour characteristics stratified by three age groups are described in table 2–4.

In all three tumour entities, men are overrepresented, with a slight change towards women in the oldest age group. In general, the younger (<60 years) have higher proportions of primary M1 tumours. In oesophageal and gastric cancer, their tumours show a worse tumour grade (G3). The oesophageal cancers of the elderly (>75 years) are adenocarcinomas in nearly 50% of cases compared to 35% in the younger age groups, while the distribution of tumour site and stage is nearly the same in every age group. In general, the proportion of unavailable specifications is always highest in the oldest age group.

In gastric cancer, the younger show higher proportions of tumours of the gastro-oesophageal junction and of signet cell carci-

Table 2. Oesophageal cancer: selective characteristics by three age groups (epidemiologic cohort 1998–2014, n = 4,014)

	Age, years			Total	p-value
	<60	60–75	>75		
Oesophageal cancer, n (%)	1,155 (28.8)	2,013 (50.2)	846 (21.1)	4,014 (100) ^a	
Male/female, %	82.7/17.3	80.5/19.5	72.1/27.9	79.4/20.6	<0.0001
Grade 3, %	52.1	49.1	45.8	49.3	<0.0001
c/p UICC Stage, %					<0.0001
I	6.5	7.1	5.1	6.5	
II	10.6	10.7	7.8	10.0	
III	28.2	29.1	21.8	27.3	
IV	25.5	23.1	18.0	22.7	
Stage not available/M0	29.2	30.1	47.4	33.5	
Histology, % ^b					<0.0001
Squamous cell carcinoma	64.2	62.8	48.5	60.2	
Adenocarcinoma	34.0	35.4	49.0	37.8	
Other carcinomas	1.8	1.8	2.7	2.0	
Not available	1.6	1.8	3.2	2.0	
Tumour site, %/proportion adenocarcinoma, %					<0.0001
Upper third	13.9/3.1	12.4/2.4	9.8/4.8	12.3/3.0	
Middle third	19.9/6.5	20.8/5.7	16.9/22.4	19.7/9.0	
Lower third	51.3/56.4	50.2/57.9	51.0/69.1	50.7/59.9	
NOS	15.0/19.1	16.6/25.1	22.3/35.4	17.3/26.4	
Therapy, %					
Surgery with curative intent	36.4	27.2	14.8	27.2	<0.0001
Life status, %					
Deceased within 1 year	40.2	46.9	58.9	47.5	<0.0001

^aRow and column percentages can differ slightly from 100% due to rounding.
^bMissing values were excluded from calculations of frequency distribution.
NOS = Not otherwise specified.

noma. Similarly, the stage distribution does not substantially differ by age.

In colorectal cancer, the oldest age group (>75 years) comprises more women than men as well as less rectal cancers (28.9 vs. 44.3% in the youngest age group).

Therapy

Information on surgery with curative intent differs strongly: it is least, i.e. 27.2%, in oesophageal cancer, 57% in gastric cancer, and 78.8% in colorectal cancer. In all tumour entities it is shown that the proportion of patients treated with surgical procedures with curative intent decreases with higher age. In colorectal cancer, the guideline-recommended adjuvant and neoadjuvant treatments are cautiously carried out in the oldest age group. Primarily, the proportion of ‘stage not available’ is attributable to the non-surgically treated patients.

Survival

Overall (or observed), relative, expected survival and relative survival in two periods of diagnosis (1998–2006, 2007–2014) as well as comparative SEER data are presented in fig. 2a–c. The different curves of expected survival reflect the different age distribu-

tion of each cancer. Patients with oesophageal cancer are the relatively youngest, so their expected survival is higher compared to that of gastric cancer patients who are the oldest. Fig. 2d–f shows that the worsening prognostic effect of age is seen in patients of 70 years and older in all tumour entities.

Oesophageal Cancer

The 5-year relative survival is 24%. There has been a slight survival improvement over the two time periods with a median survival of 11 months in the period of 1998–2006 and of 16 months in the period of 2007–2014 (fig. 2a). The median survival worsens continuously with increasing age: it is 1.5 years in the youngest age group (<50 years) and 6 months in the oldest (≥80 years). The difference between overall and relative survival in the first year from initial diagnosis is very low in every age group, indicating that nearly all patients die of their cancer (fig. 2d). The 5-year relative survival is 31.3, 26.0, 25.2, 21.9 and 13.0% in the five age groups. The condition of having survived at least 6 months slightly reduces these differences in 5-year relative survival (38.8, 32.2, 37.5, 31.4 and 26.3%, as shown in fig. 2g). Relative survival by age and tumour stage is presented in fig. 3a: in the most advanced stage IV, the age has no substantial effects, with an observed median survival

Table 3. Gastric cancer: selective characteristics by three age groups (epidemiologic cohort 1998–2014, n = 10,127)

	Age, years			Total	p-value
	<60	60–75	>75		
Gastric cancer, n (%)	1,851 (18.3)	3,787 (37.4)	4,489 (44.3)	10,127 (100) ^a	
Male/female, %	61.9/38.1	63.5/36.5	49.4/50.6	57.0/43.0	<0.0001
Grade 3, %	80.1	67.6	61.6	67.3	<0.0001
GEJ, %	25.0	21.9	17.6	20.7	<0.0001
c/p UICC Stage, % ^b					<0.0001
I	22.2	25.1	18.9	21.8	
II	16.3	13.4	10.4	12.6	
III	13.1	12.4	10.9	11.9	
IV/M0	5.4	5.2	3.2	4.4	
IV/M1	32.5	29.9	20.7	26.3	
Stage not available/M0	10.5	13.9	35.8	23.0	
Histology, %					<0.0001
Adenocarcinoma	57.5	71.9	79.8	72.8	
Signet cell carcinoma	40.0	25.9	17.3	24.7	
Other carcinomas	2.6	2.2	2.9	2.6	
Not available	1.4	1.7	2.2	1.9	
Therapy, %					
Surgery with curative intent	68.5	63.9	46.3	57.0	<0.0001
Life status, %					
Deceased within 1 year	29.6	37.2	56.5	44.4	<0.0001

^aRow and column percentages can differ slightly from 100% due to rounding.
^bMissing values were excluded from calculations of frequency distribution.
GEJ = Gastro-oesophageal junction.

Table 4. Colorectal cancer: selective characteristics by three age groups (epidemiologic cohort 1998–2014, n = 42,809)

	Age, years			Total	p-value
	<60	60–75	>75		
Colorectal cancer, n (%)	8,031 (18.8)	18 579 (43.4)	16,199 (37.8)	42 809 (100) ^a	
Male/female, %	58.3/41.7	62.6/37.4	46.0/54.0	55.5/44.5	<0.0001
Grade 3, %	23.4	21.4	23.4	22.5	<0.0001
Rectal cancer, %	44.3	37.7	28.9	35.6	<0.0001
c/p UICC Stage, % ^b					<0.0001
I	18.3	20.8	16.3	18.6	
II	21.9	25.2	28.4	25.8	
III	28.7	25.7	23.5	25.4	
IV	23.0	19.5	18.3	19.7	
Stage not available/M0	8.1	8.8	13.5	10.4	
Therapy, %					
Surgery with curative intent	83.3	81.6	73.2	78.8	<0.0001
Life status, %					
Deceased within 1 year	8.9	13.8	30.0	19.0	<0.0001

^aRow and column percentages can differ slightly from 100% due to rounding.
^bMissing values were excluded from calculations of frequency distribution.

Fig. 2. a–c Overall, relative and expected survival, relative survival by period of diagnosis and tumour, d–f relative survival by age and tumour, and g–i conditional relative survival for those who have survived at least 6 months in C15 and C16 and at least 12 months in C18–20.

of 7 months in those <60 years and less than 4 months in those >75 years. In stage III, those >75 years have a slightly worse prognosis with a median survival of 11 months compared to 18 months for the younger age groups. Fig. 3d presents the relative survival stratified by age and therapy. Here, it is shown that the adequate surgical therapy – if applicable – overrules the effects of age.

Gastric Cancer

The 5-year relative survival is 33.4%, and there may be an improvement for those who survive at least 5 years (fig. 2b). As in oesophageal cancer, death in the first year after diagnosis is completely due to cancer. Stratified by age, the median survival is between 7 months and 2.7 years. The 5-year relative survival differs between 41.2% in the age group of 50–59 years and 23.5% in those ≥80 years (fig. 2e). Again, for those who have survived at least 6 months the effects of age are diminished (fig. 2h). Fig. 3b demonstrates the by far worst prognosis of the elderly >75 years irrespective of tumour stage. Fig. 3e underlines the desperate outcome of those without feasible adequate surgery with a median survival below 1 year irrespective of age.

Colorectal Cancer

The 5-year relative survival is 65.6%, and substantial improvements since 1998 cannot be seen in the total cohort (fig. 2c). The better prognosis of colorectal cancer leads to stronger effects of age. Overall and relative survival divide after 6 months, and relative median survival is not yet reached in all age groups after 15 years of observation (fig. 2f). The conditional relative survival of those who survived at least 1 year is nearly the same in all age groups of 50 years and older. Only the youngest, i.e. <50 years, have a slightly worse prognosis (fig. 2i). Fig. 3c shows that only the oldest, i.e. ≥80 years, do not similarly benefit from adequate surgical treatment as those younger than 80 years.

Post-Progression Survival from First Distant Metastasis

Fig. 3g–i demonstrates the impact of age on post-progression survival after first distant metastasis which strengthens with improved prognosis: in oesophageal cancer with the worst prognosis, the median survival of the youngest is 2.3-fold longer than that of the oldest, in gastric cancer it is 2.7-fold longer, and in colorectal cancer it is 4.2-fold longer.

Fig. 3. Relative survival by **a-c** stage, age, and tumour as well as by **d-f** age, therapy, and tumour and **g-i** post-progression survival by age and tumour.

Discussion

The age-standardised incidences of oesophageal cancer in males and of gastric and colorectal cancers in general have continuously decreased. In oesophageal cancer, this is likely to reflect the decreasing tobacco consume and runs parallel to the decrease of male lung cancer incidence. In colorectal cancer, the establishment of screening could perhaps show its effects.

Absolutely, however, numbers have not decreased because of the increasing age of cancer patients, especially in oesophageal and colorectal cancer [2, 14]. This bears challenges for all health care providers, particularly for the fields of surgery, oncology, and radiotherapy.

The choice of any more or less invasive treatment does mostly depend on tumour prognosis and the patients' general condition which is strongly related to age, besides lifestyle factors such as alcohol and tobacco abuse which can be seen more often in oesophageal cancer patients. Therefore, aged patients above 75 years are rightly underrepresented in the curatively treated groups, with the lowest proportion in oesophageal cancer with 15% and the highest in colorectal cancer with 73%.

The survival analyses show an improvement of relative survival over two time periods similar to SEER data in oesophageal cancer. In oesophageal cancer, this may be explained by a shift to 15% more adenocarcinoma since 1998 and to localisation in the lower oesophagus, thus yielding a better prognosis than squamous cell carcinoma of the middle and upper parts. Essential improvements of survival in the first 6 months due to a quantum leap in treatment are not seen. The major advances in colorectal cancer treatment were presented with fluorouracil-based chemotherapy and total mesorectal excision in the late 1980s and 1990s and with neoadjuvant radiochemotherapy in locally advanced rectal cancer in the early 2000s [15–18]. While patients were on average 2 years older in the latter time period, one may state a further minor improvement.

Because age, frailty, and sarcopenia are associated with risk of perioperative morbidity and mortality in gastrointestinal cancers, the survival differences of age groups are explained [19, 20]. However, there is evidence that minimally invasive techniques can be safely performed with functional and oncological equivalent in older colorectal cancer patients and may be an option for gastric cancer therapy in the near future [21, 22].

Remarkable is the survival of those patients who were treated with surgery appropriate for complete tumour removal and cure. In gastric cancer, the 5-year relative survival differs by age between 55 and 50%. This small difference argues for a reliable indication for surgery, because 71% of those <50 years and 39% of those ≥80 years are treated in this way with almost similar results. If an essentially greater proportion of the elderly was treated in this way, the survival would be worse because of greater postoperative morbidity and mortality. If the indication for surgery was improved by excluding the very early deceased patients, the survival of the patients treated surgically with curative intent would further improve. This can also be seen in the conditional survival of colorectal cancer patients where the exclusion of those who survive 1 year at most leads to an improved survival of more than 5%, also for the oldest. Thus, in all cancers the challenge is posed to identify those with an unfavourable prognosis of a few months and to apply less invasive therapies.

We acknowledge several limitations of this study which must be considered in the interpretation of the results. The study is a cohort study with all the well-established drawbacks. A DCO rate of more than 5% as well as DCO patients who are in median 10 years older than the non-DCO cases and also missing values may mask selections. Complementary data to the conducted treatments with decided information on deliberately not conducted or not indicated treatments would be desirable. This also applies to comorbidities or desperate prognosis which do not allow the implementation of a recommended therapy, even if such data could not be permanently collected in a population-specific and valid manner for all therapies in a cancer registry. Despite these drawbacks, the presented results on the age dependency of treatment seem valid because of their plausibility, the marginal variability between hospitals, and missing contradictions in comparison to the literature [23–25].

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Conclusion

Hence, it can be stated that the substandard implementation of curatively intended surgical procedures in the treatment of elderly patient cohorts need not be a sign of deficiency in health care but a sign for reasonable considerations of tumour prognosis, patients' life expectancy, and calendrical and physical age. Current guidelines and established tumour boards, which have been available in recent years, may also have contributed to a reliable health care, a low inter-hospital variability, and a stable long-term survival. The treatment and care of oesophageal, gastric and colorectal cancer in elderly patients seem to be balanced and appropriate in the efforts to discriminate between those who benefit from forced invasive therapies and those who do not. At least, the oldest who are treated in curative intent present similar outcomes as their younger fellow sufferers.

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Disclosure Statement

The authors indicated no potential conflicts of interest.

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