

Predictors of Survival Among Colorectal Cancer Patients in a Low Incidence Area

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Background: Colorectal cancer is the third most common malignancy in Saudi Arabia. The best therapeutic regimen for colorectal cancer is a matter of ongoing debate and data on its treatment in Saudi Arabia are limited.

Purpose: The objective of this study was to explore the predictors of survival and to compare the risk of mortality among colorectal cancer patients treated with different therapeutic modalities.

Patients and Methods: The study utilized data from the electronic colorectal cancer registry of a university-affiliated tertiary care hospital. The Kaplan-Meier survival analysis was used to estimate the survival rates over 36 months of follow-up across rectal and colon cancer patients as well as different sociodemographic and medical characteristics. Bivariate and multiple Cox proportional-hazards regressions were conducted to estimate the risk of mortality among rectal and colon cancer patients undergoing different treatments.

Results: The number of patients in the registry who were followed up for 36 months was 143 patients. The majority of patients had colon cancer (74.13%). Rectal cancer patients had generally better survival estimates compared to their colon cancer counterparts. Colon cancer patients treated with chemotherapy had a significantly lower risk of mortality controlling for the use of surgery, radiotherapy, and other variables including age, gender, stage of cancer, and family history of colorectal cancer (HR=0.33; $P=0.03$). Additionally, colon cancer patients with a family history of colorectal cancer had significantly higher risk of mortality (HR=3.40; $P=0.02$).

Conclusion: The findings of this study highlight the value of chemotherapy in managing colon cancer patients.

Keywords: colorectal cancer, surgery, chemotherapy, survival, Saudi Arabia

Introduction

Colorectal cancer is the first most frequent type of cancer in men and the second most frequent in women.¹ According to the World Health Organization, 1.8 million people were diagnosed worldwide with colorectal cancer in 2018.^{1,2} In the same year, colorectal cancer resulted in 862,000 deaths globally, making it the second leading cause of cancer-related mortality.¹⁻³ The incidence of this disease varies markedly among different geographic regions. The highest incidence rates were observed in Europe,⁴ while the lowest rates were observed in Asia.⁵ However, a growing trend is seen in many low- and middle-income countries.⁶ In the Kingdom of Saudi Arabia, colorectal cancer is the third most common malignancy and one of the leading causes of cancer-related deaths.⁷ Moreover, colorectal cancer age-adjusted mortality has been increasing over the past few years, and this trend is likely to continue in the future.⁷

According to the National Saudi Cancer Registry, only 253 colorectal cancer cases were reported in 1994, but this number increased to 1033 cases in 2010. The age-adjusted incidence has increased from 5.0/100,000 in 1994 to 9.6/100,000 in 2010, and to 11.1/100,000 in 2012.^{8,9} At the King Faisal Specialist Hospital and Research Center (Riyadh, Saudi Arabia) alone, 622 cases were diagnosed with colorectal cancer from 1975 to 1989.¹⁰ The five-year survival of colorectal cancer patients varies widely between countries, ranging from 28% in developing African and Asian countries to 60% in Japan, United States, and Switzerland,^{11–13} whereas five-year survival rate of approximately 44% was reported in Saudi Arabia between 2000 and 2004.¹⁴ In the United States, men are diagnosed at a younger age than women; however, in Saudi Arabia men are diagnosed at an older age compared to women.⁸ According to a study that was conducted at the King Faisal Specialist Hospital, the mean age of diagnosis for women was 47.8 years compared to 53.5 years for men.¹⁰ Although the same study suggested that the incidence of colorectal cancer in Saudi Arabia is higher in males (383 cases, 61.6%) than in females (239 cases, 38.4%),¹⁰ a recent analysis in 40 European countries demonstrated that the incidence and mortality rates are comparable in both sexes.¹⁵ In contrast, the five-year survival rate among Saudi male colorectal cancer patients (41.0%) is significantly lower than their female counterparts (50.6%).¹⁴

Metastasis of colorectal cancer affects the likelihood of survival dramatically.^{16,17} Recent studies in the Netherlands have found that approximately 15–25% of colorectal cancer patients had metastases at the time of diagnosis.^{18,19} In Saudi Arabia, similar rates, ranging from 16% to 29%, have been reported.⁸ Distant metastases, together with the older age (≥ 65 years), were found to be significant risk factors of mortality among Saudi patients with colorectal cancer, however, gender and the cancer grade were not associated with mortality.¹⁴

Several epidemiological studies have found that diabetes mellitus may increase the risk of various types of cancer, such as pancreatic and liver cancers.^{20,21} The presence of a link between diabetes and colorectal cancer was hypothesized more than 20 years ago,²² and was recently recognized by the American Diabetes Association.²³ However, the correlation between these two pathologic conditions has not been confirmed, indicating that country-specific factors may be involved.²⁴ Importantly, recent epidemiologic studies have demonstrated that diabetic

patients affected by colorectal cancer have poorer overall survival rates compared to their nondiabetic counterparts,^{25,26} in particular when complications of diabetes were present.²⁷ However, other studies did not identify a similar association.^{28,29}

Several therapeutic options are currently used for colorectal cancer treatment.³⁰ However, surgery is the most common approach,³¹ although the perception of ideal surgical technique differs between the Western and Asian countries.³² Data available from Saudi Arabia indicate that rectal cancer patients undergoing curative surgery have a significantly higher survival rate, 54%, compared to 5% for those not treated surgically.³³ The use of chemotherapy was associated with better survival rates compared to patients who were only treated by surgery.^{34,35} Although more recent data indicate that only 5% of patients benefit from adjuvant chemotherapy,³⁰ this type of treatment is strongly recommended in case of high-grade tumors.³⁶ Interestingly, over a period of 20 years, from the 1980s to 2000s, the median survival rate of colorectal cancer patients increased almost three-fold, and this improvement has been attributed to a more frequent use of chemotherapy.³⁷ Radiotherapy has also been shown to improve the survival rate and reduce the probability of tumor recurrence, but with the introduction of new treatment modalities, its use became controversial.³⁸

In view of the existing controversies and the paucity of data on colorectal cancer treatment in Saudi Arabia, the objective of the present study was to explore the predictors of survival and compare the risk of mortality among a sample of colorectal cancer patients in the Kingdom who were treated with different therapeutic modalities.

Materials and Methods

Study Design

The present study was designed as a retrospective cohort study. The data were extracted from an electronic colorectal cancer registry maintained in the division of gastroenterology in the department of medicine at a university-affiliated tertiary care hospital in Riyadh, Saudi Arabia. The registry included patients who were diagnosed with colorectal cancer since January 2014 based on colonoscopy and histological confirmation; patients were followed for 36 months. The study was approved by the institutional review board of the College of Medicine at King Saud University (approval number E-11-538).

The retrieved information from the database included age, gender, history of smoking and alcohol, the presence of comorbidities (diabetes, hypertension, inflammatory bowel disease), family history of colorectal cancer, histological type of colorectal cancer (non-mucinous adenocarcinoma, mucinous adenocarcinoma, poorly differentiated tumor), number of polyps detected during the index colonoscopy, and the presence of metastases. The treatments were categorized as surgery, chemotherapy, and radiotherapy. No personal identifiers were collected and no patient interviews were involved; therefore, written informed consent form was waived per the institution policy. Moreover, the collected data were coded to protect the confidentiality of the patients in accordance with the ethical principles of the declaration of Helsinki.

Statistical Analysis

All statistical analyses were conducted using SAS[®] version 9.2 (SAS Inc., Cary, NC, USA). The survival analysis was conducted using the Kaplan–Meier method, and the survival estimates across different variables were compared by the log-rank test. In order to explore the predictors of survival among colorectal cancer patients, bivariate Cox proportional-hazards regressions were conducted among rectal and colon cancer patients separately. A multiple Cox proportional-hazards regression model was conducted among colon cancer patients to examine the impact of different treatment modalities (surgery, chemotherapy, and radiotherapy) on mortality controlling for age, gender, family history of colorectal cancer, number of polyps, and stage of cancer. Statistical significance was considered at $\alpha < 0.05$, and 95% confidence intervals were reported for all hazard ratios.

Results

The study enrolled 143 patients, of which 106 (74.13%) and 37 (25.87%) had colon and rectal cancers, respectively. Approximately, 57% of the study sample were male and the mean age was 59.41 ± 12.84 years (Table 1). The most frequent comorbidities were diabetes (31.47%), hypertension (32.87%), and a small group of patients had inflammatory bowel disease (2.79%). Only 21 patients (14.69%) reported a family history of colorectal cancer (Table 1).

The most frequent tumor type was non-mucinous adenocarcinoma, which occurred in 134 patients (93.71%) (Table 1). Mucinous adenocarcinoma and poorly differentiated adenocarcinoma were present in 2.79% and 3.49%

Table 1 Baseline Characteristics of Study Sample

Characteristic	N (%)
Gender	
Male	82 (57.34)
Female	61 (42.66)
Age, years (mean \pm SD)	59.41 ± 12.84
Colon cancer	106 (74.13)
Rectal cancer	37 (25.87)
Comorbidities	
Diabetes	45 (31.47)
Hypertension	47 (32.87)
Inflammatory bowel disease	4 (2.79)
Family history of colorectal cancer	21 (14.69)
Type of Colorectal Cancer	
Non-mucinous adenocarcinoma	134 (93.71)
Mucinous adenocarcinoma	4 (2.79)
Poorly differentiated	5 (3.49)
Number of polyps (mean \pm SD)	0.91 ± 1.93
Stage of Cancer	
Stage I	14 (9.79)
Stage II	40 (27.97)
Stage III	60 (41.96)
Stage IV	29 (20.28)

Note: Data are presented as mean \pm standard deviation.

of patients, respectively. A large variation was seen in the number of polyps, with a mean of 0.91, median of 0, and interquartile range of 1. Surgery and chemotherapy were the most often used therapeutic modalities, with 99 (69.23%) and 96 (67.13%) patients treated with these approaches, respectively. Fifteen patients (10.48%) underwent radiotherapy, and always in combination with surgery and chemotherapy. Sixty-seven patients (46.85%) underwent both surgery and chemotherapy; while the number of patients who either underwent surgery or chemotherapy only were 32 (22.38%) and 29 (20.28%) patients, respectively.

The overall survival rate of the study sample over the 36-month follow-up period is shown in Figure 1. The median survival in months for diabetic patients across the four stages of cancer was significantly lower than their non-diabetic counterparts as shown in Table 2. Similarly, the median survival in months across the four stages of cancer was significantly lower among patients with a family history of colorectal cancer compared to their counterparts with no family history of colorectal cancer (Table 2). The overall survival rates of colorectal cancer patients are shown in

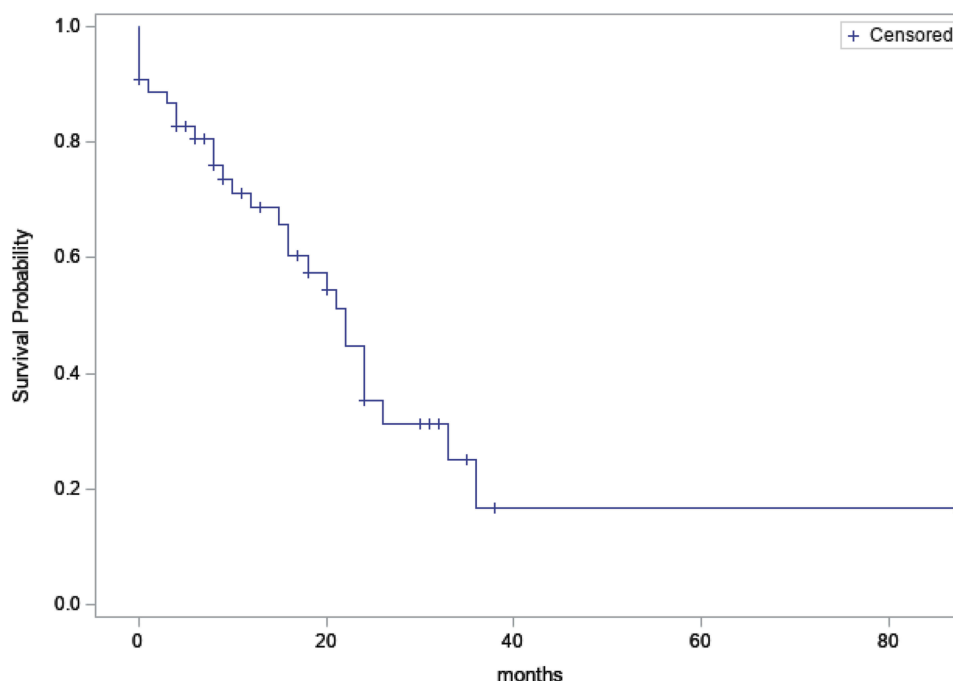


Figure 1 The survival rates of colorectal cancer patients over 36 months.

Figure 1 and the survival rates across different cancer stages are shown in Figure 2. Rectal cancer patients with stage III and IV had higher Kaplan–Meier (KM) survival estimates (0.751 and 0.540, respectively) compared to their counterparts with colon cancer (0.366 and 0.120, respectively) as shown in Table 3.

Neither surgery nor chemotherapy or radiotherapy were significantly associated with lower risk of mortality among rectal cancer patients as shown in Table 4. With the exception

of family history of colorectal cancer, which was significantly associated with higher risk of mortality ($HR=3.14$; $P=0.02$), none of the tested variables in the bivariate Cox regression analysis was significantly associated with the risk of mortality among colon cancer patients as shown in Table 5. Moreover, the risk of mortality was not significantly associated with either surgery ($HR=0.84$; $P=0.88$) or chemotherapy ($HR=0.43$; $P=0.38$) among colon cancer patients with stage II. Likewise, chemotherapy ($HR=0.26$; $P=0.34$) and surgery

Table 2 Median Survival in Months Across the Four Stages of Cancer

Characteristic	Stage I	Stage II	Stage III	Stage IV	P-value
Overall	35 (16–36)	21 (4–24)	22(15–33)	16 (3–26)	0.111
Rectal cancer	-	-	33(22–33)	10 (1–24)	0.547
Colon cancer	31(25–36)	21(12–24)	18 (8–24)	12 (3–24)	0.173
Gender					
Male	36(26–36)	10(1–24)	20(8–33)	16 (3–24)	0.115
Female	-	21(21–21)	26(18–28)	26(12–26)	
Diabetes					
Yes	-	24(12–24)	15(8–18)	9(3–12)	0.021*
No	36(36–36)	21(4–24)	22(15–33)	22(0–36)	
Family History of Colorectal Cancer					
Yes	-	-	19(13–24)	3.5(1.5–10)	0.011*
No	-	21(10–24)	33(15–36)	24(12–26)	

Notes: *Indicates statistically significant difference. Data are presented as median with quartile I and quartile 3 (Q1–Q3).

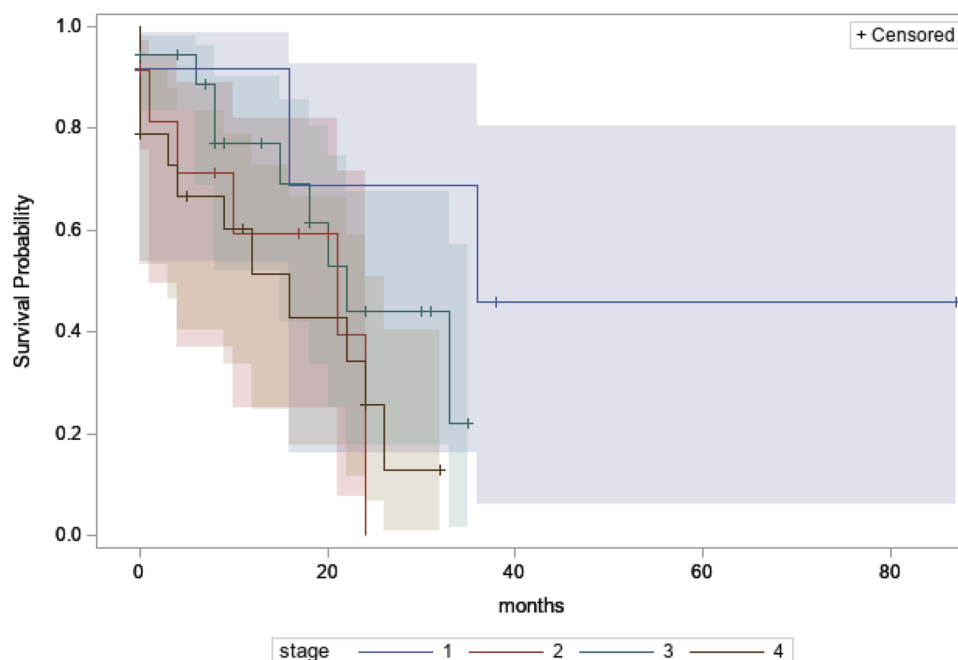


Figure 2 The survival rates among colorectal cancer patients of different stages of cancer over 36 months with 95% confidence limits.

(HR=0.67; $P=0.73$) were not associated with risk of mortality among stage III colon cancer patients. However, chemotherapy was significantly associated with lower risk of mortality (HR=0.33; $P=0.03$) among colon cancer patients in the multiple Cox proportional-hazards model as shown in Table 6.

Discussion

The current work focused on the identification of survival predictors and the risk of mortality among colorectal cancer patients subjected to different therapies. To the best of our knowledge, this is the first effort to obtain information on the predictors of survival as well as the risk of mortality among

colorectal cancer patients in Saudi Arabia since 2005. The relevance of acquisition of such data is underscored by the large variability in the incidence rates of colorectal cancer worldwide, an increase in its incidence in Saudi Arabia, and the well-documented role of ethnicity in the susceptibility to this type of cancer.^{39–41}

The major findings of this study include the demonstration that colon cancer patients who underwent chemotherapy had a significantly lower risk of mortality controlling for surgery and radiotherapy as well as a multitude of other variables (age, gender, stage of cancer, and family history of colorectal cancer). This finding is consistent with previously published research that demonstrated a favorable effect of chemotherapy among colorectal cancer patients.^{34–37} Colon cancer patients who underwent systemic chemotherapy as an adjuvant therapy after surgical resection of lymph nodes had significantly better survival rates compared to their counterparts who only underwent surgical resection of lymph nodes.³⁴ Moreover, in a meta-analysis that compared the survival rates among patients with stage IV colorectal cancer with or without primary tumor resection using mostly retrospective data, patients who underwent primary tumor resection in addition to chemotherapy and radiotherapy had higher survival rates compared to those who did not receive chemotherapy.³⁵ However, this finding was only shown among colon cancer patients in the multiple Cox

Table 3 Kaplan–Meier Estimated Survival Probabilities Across Colon and Rectal Cancer Patients

Variable	KM Survival Estimate
Rectal Cancer	
Stage I	–
Stage II	–
Stage III	0.751
Stage IV	0.540
Colon Cancer	
Stage I	0.583
Stage II	0.375
Stage III	0.366
Stage IV	0.120

Abbreviation: KM, Kaplan–Meier.

Table 4 The Hazard Ratios of Bivariate Cox Regression of Different Variables for 36-Month Mortality Among Rectal Cancer Patients

Variable	Hazard Ratio (95% Confidence Interval)	P-value
Surgery	0.48 (0.11–2.2)	0.35
Chemotherapy	0.39 (0.08–1.74)	0.22
Radiotherapy	1.00 (0.01–1.2)	0.99
Female gender	0.38 (0.04–3.18)	0.37
Family history of colorectal cancer	16.44 (0.05–20)	0.99
Age	1.04 (0.97–1.12)	0.21
Stage of cancer	0.68 (0.29–1.61)	0.38

Table 5 The Hazard Ratios of Bivariate Cox Regression of Different Variables for 36-Month Mortality Among Colon Cancer Patients

Variable	Hazard Ratio (95% Confidence Interval)	P-value
Surgery	0.48 (0.21–1.09)	0.08
Chemotherapy	0.66 (0.29–1.49)	0.32
Radiotherapy	1.49 (0.35–6.39)	0.59
Female gender	0.68 (0.28–1.64)	0.39
Family history of colorectal cancer	3.14 (1.21–8.13)	0.02*
Age	0.97 (0.97–1.03)	0.86
Stage of cancer	1.49 (0.98–2.29)	0.07

Note: *Indicates statistically significant difference.

Table 6 Multiple Cox-Proportional Hazard Model for 36-Month Mortality Among Colon Cancer Patients

Variable	Hazard Ratio (95% Confidence Interval)	P-value
Surgery	0.44 (0.14–1.41)	0.17
Chemotherapy	0.33 (0.11–0.91)	0.03*
Radiotherapy	1.03 (0.12–9.09)	0.98
Female Gender	0.99 (0.38–2.59)	0.97
Family history of colorectal cancer	3.40 (1.20–9.61)	0.02*
Age	1.01 (0.97–1.04)	0.75
Stage	1.51 (0.90–2.53)	0.11

Note: *Indicates statistically significant difference.

proportional-hazards model and not among rectal cancer patients due to the small number of rectal cancer patients in the study sample. Additionally, it was found that colon cancer patients with a family history of colorectal cancer had a higher risk of mortality controlling for previously mentioned variables.

The proportion of male colorectal cancer patients in the studied sample was 57.34%, a percentage consistent with the results of a previous investigation utilizing the National Saudi Cancer Registry data.⁹ A similar tendency is also observed worldwide regardless of the incidence rate of the disease. Approximately, 60% of the reported cases in central Africa were among males, where the incidence of colorectal cancer is the lowest, and 58% in Australia and New Zealand, where the incidence is the highest.^{42,43} A previous analysis has determined that during the period from 1990 to 1998,³³ the mean age of Saudi patients at the time of colorectal cancer diagnosis was 55.6 years for men and 52.8 for women, somewhat lower than the mean age of 59.41 ± 12.84 that was found in this study. It should be noted that in both the prior and the present investigations,³³ the age of patients at the time of diagnosis was markedly lower than that reported in the western countries, where it averages 70 years.^{43,44} In addition to male sex and older age, family history of the disease,^{45,46} diabetes,⁴⁷ hypertension,⁴⁸ inflammatory bowel disease,^{49,50} smoking,⁵¹ and alcohol abuse,⁵² are often considered risk factors for colorectal cancer. In the population under study, the incidence of colorectal cancer was highest in subjects suffering from hypertension (33.33%) and diabetes (31.48%), reflecting the worldwide trends.^{30,43} Markedly, lower proportion of patients had a family history of colorectal cancer (14.69%) and inflammatory bowel disease (2.79%). However, due to the relatively small sample size, it cannot be definitely determined whether the lower incidence of these conditions is generalizable to the overall Saudi population of colorectal cancer patients.

The mean 36-month survival was not affected by the patient gender. However, a significant difference in survival was seen between diabetic and non-diabetic patients as well as between patients with a family history of colorectal cancer and those without. Moreover, it should be recognized that a lower likelihood of survival among the colorectal cancer that was reported in this study in comparison to previously published studies may be related to the fact that a larger percentage of patients (62.24%) were presenting with advanced stage of cancer (stages III and IV).⁸

Surgery is generally considered to be the principal treatment for colorectal cancer, particularly in the absence of metastasis.³⁰ However, surgery was not found to have a positive impact on survival in this study among either rectal or colon cancer patients, which might be due to the larger proportion of patients with advanced stages of cancer as well as the smaller sample size compared to previously published studies.^{30,32} The present study

demonstrated unequivocally the benefit of chemotherapy in the management of colorectal cancer, either alone or in combination with surgery and radiotherapy. Furthermore, the results of the current analysis indicate that the prevention and management of diabetes should be incorporated as part of the efforts to decrease the negative impact of colorectal cancer on the patient survival and quality of life.

Finally, the current investigation represents the first effort in Saudi Arabia to determine the risk of mortality among colorectal cancer patients undergoing distinct treatments, controlling for multiple variables. However, some limitations of this study have to be acknowledged. First, the study had a relatively short follow-up period. In addition, the ultimate outcomes of different therapies cannot be ascertained after 36 months of follow-up. Furthermore, the analysis did not control for the tumor location due to missing data.

Conclusion

The incidence of colorectal cancer is increasing especially in low incidence areas such as Saudi Arabia. Despite the shortcomings of this study, it presents valuable information regarding the efficacy of different therapeutic protocols for colorectal cancer in this part of the world, highlighting the necessity to conduct studies with more robust designs, larger sample sizes, and longer follow-up periods to determine the clinical outcomes in patients undergoing different treatment modalities.

Abbreviations

HR, Hazard Ratio; KM, Kaplan–Meier.

Data Sharing Statement

Study data are available from the authors upon request.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval for the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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