Original Article

Prognostic value of tumor length in predicting survival for patients with esophageal cancer

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Background: To determine the prognostic value of tumor length in predicting overall survival (OS) for patients with esophageal cancer.

Methods: Patients who were diagnosed with esophageal cancer between 2010 and 2014 were identified from the Surveillance Epidemiology and End Results (SEER) data. We performed Kaplan-Meier survival analysis and developed a Cox regression proportional hazard model to explore the effect of tumor length on survival.

Results: A total of 6,897 esophageal cancer patients were identified. The patients were classified according to tumor length: 2,334 patients had a tumor length ≤3 cm, and 4,563 patients had a tumor length >3 cm. Patients with a tumor length >3 cm were more likely to have poorer histological grade (P<0.0001) and advanced T (P<0.0001), N (P<0.0001) or M (P<0.0001) stage compared to patients with a tumor length ≤3 cm. A greater risk of mortality was observed in patients with a tumor length >3 cm than in those with a tumor length ≤3 cm both in the Cox regression univariate analysis [hazard ratio (HR): 1.790; 95% CI: 1.667–1.922; P=0.000] and the multivariate analysis (HR: 1.447; 95% CI: 1.341–1.561; P=0.000). A stratified analysis based on different T stages showed that the HR for death was 1.84 (P=0.000) for T1 stage patients, 1.227 (P=0.046) for T2 stage patients, and 1.157 (P=0.012) for T3 stage patients; there was no difference in survival for T4 stage patients.

Conclusions: Tumor length significantly influences the OS of esophageal cancer patients, especially in early T stage patients. Further prospective trials are needed to validate the prognostic value of tumor length among esophageal cancer patients.

Keywords: Esophageal cancer; tumor length; overall survival (OS); Surveillance Epidemiology and End Results (SEER)

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Introduction

Esophageal cancer, which caused a total of 400,200 deaths in 2012, is the sixth leading cause of cancer death worldwide (1). Despite recent improvements in multimodal treatment, the 5-year relative survival rate was 41% for patients with localized stage, 23% for patients with regional stage, and only 5% for patients with distant stage esophageal cancer in the United States (2). Thus, an effective staging system is crucial for esophageal cancer patients in terms of determining the proper multidisciplinary therapy and

estimating prognosis. Currently the T classification of the 7th TNM staging system (3) depends only on the depth of the primary tumor; furthermore, the 8th edition (4), which was placed into effect in January 2018, still does not consider tumor length. Several authors have recently investigated the importance of tumor length on overall survival (OS) for esophageal cancer patients (5-10). However, almost all of these studies focused on patients with early or regional stage cancer; patients with distant stage cancer were not included. In addition, most conclusions were analyzed based on a small number of patients.

Our study was conducted to explore the prognostic value of tumor length using a population-based study cohort; patient information was retrieved from the Surveillance, Epidemiology, and End Results (SEER) database. As previous studies reported that 3 cm was an adequate separation (5,7,11-14), we used this length to evaluate survival time.

Methods

Patients

The SEER Program of the National Cancer Institute provides information in a cancer-related database. Last released in April 2017, SEER-18 includes 18 cancer registries and covers 9,675,661 cancer cases from the US population diagnosed between 1973 and 2014 (15). Patients with a diagnosis of esophageal cancer were identified from the SEER database, using the SEER*Stat software (version 8.3.4). The reference number obtained to access research data files was 12631-Nov2016. Given the lack of personal identifying information, informed consent was waived.

The inclusion criteria were as follows: (I) patients with Site recode ICD-O-3/WHO 2008 restricted to the "esophagus"; (II) exact tumor location (C15.0–C15.5); (III) diagnosed from 2010 or later. The exclusion criteria were as follows: unknown age, gender, race, tumor grade, tumor length, survival months, or TNM stage. Histology and tumor grade were coded based on the International Classification of Disease for Oncology, edition ICD-O-3. Tumor stage was coded according to the 7th edition of the TNM staging system.

Patients were categorized according to their ages (<65 and ≥65 years), gender (male and female), race (white, black and other), tumor grade [1–4], tumor location (cervical and upper third of esophagus; thoracic and middle third of the esophagus; abdominal and lower third of the esophagus), tumor length (≤3 and >3 cm), T stage [1–4], N stage [0–3] and M stage [0,1]. Histology was classified into three groups: esophageal adenocarcinoma (EAC, ICD-O-3 codes: 8140), esophageal squamous cell carcinoma (ESCC, ICD-O-3 codes: 8070) and others.

Statistical analysis

We divided the enrolled patients into two groups: a tumor length ≤3 cm group and a tumor length >3 cm group. Comparisons of the clinical characteristics between the two groups were performed using the chi-square test. OS of patients with different tumor lengths was evaluated using the Kaplan-Meier method and estimated by the log-rank test. Univariate and multivariate analyses were generated to examine the potential factors associated with OS. Hazard ratios (HRs) with 95% confidence intervals were used to quantify the strength of the association. Finally, a Cox proportional hazards analysis was performed to determine the association of tumor length with OS based on different T stages. A value of $P<0.05$ was defined as statistically significant. All analyses were performed using SPSS statistical software package (version 22.0).

Results

Patient characteristics

In total, 6,897 patients with esophageal cancer were identified, including 2,334 individuals with a tumor length ≤3 cm and 4,563 individuals with a tumor length >3 cm. The detailed clinical characteristics of the patients are shown in *Table 1*. The comparison between the two groups showed significant differences in all clinical characteristics (except tumor location). Patients with a tumor length ≤3 cm were more likely to have EAC (62.2% *vs.* 53.9%). Furthermore, with respect to tumor grade, patients with a tumor length ≤3 cm showed a better differentiation (10.8% *vs.* 4.6% in grade 1, 47.2% *vs.* 41.8% in grade 2). In addition, a significantly higher proportion of patients with a tumor length ≤3 cm was of earlier T stage (T1, T2), N stage (N0) and M stage (M0) ($P<0.001$).

Survival analysis

Kaplan-Meier analysis showed that patients with a tumor length ≤3 cm had a significantly better OS than those with a tumor length >3 cm ($\chi^2=275.850$, $P=0.0001$, *Figure 1*).

Table 1 Characteristics of 6,897 patients with esophageal cancer

Characteristics	Total (%)	Length ≤3 cm (%)	Length >3 cm (%)	P
Number	6,897 (100)	2,334 (33.8)	4,563 (66.2)	
Age (years)				0.0007
≤65	2,936 (42.6)	928 (39.8)	2,008 (44.0)	
>65	3,961 (57.4)	1,406 (60.2)	2,555 (56.0)	
Gender				0.0033
Male	5,475 (79.4)	1,806 (77.4)	3,669 (80.4)	
Female	1,422 (20.6)	528 (22.6)	894 (19.6)	
Race				0.0250
White	5,886 (85.3)	2,029 (86.9)	3,857 (84.5)	
Black	658 (9.5)	195 (8.4)	463 (10.1)	
Other	353 (5.1)	110 (4.7)	243 (5.3)	
Location				0.3061
Cervical/upper, third of esophagus	538 (7.8)	184 (7.9)	354 (7.8)	
Thoracic/middle, third of esophagus	1,519 (22.0)	489 (21.0)	1,030 (22.6)	
Abdomen/lower, third of esophagus	4,840 (70.2)	1,661 (71.1)	3,179 (69.7)	
Histology				<0.0001
EAC	3,912 (56.7)	1,451 (62.2)	2,461 (53.9)	
ESCC	1,976 (28.7)	601 (25.7)	1,375 (30.1)	
Other	1,009 (14.6)	282 (12.1)	727 (15.9)	
Tumor grade				<0.0001
Well differentiated	462 (6.7)	253 (10.8)	209 (4.6)	
Moderately differentiated	3,012 (43.7)	1,102 (47.2)	1,910 (41.8)	
Poorly differentiated	3,309 (48.0)	945 (40.5)	2,364 (51.8)	
Undifferentiated	114 (1.6)	34 (1.5)	80 (1.8)	
T stage				<0.0001
T1	2,042 (29.6)	1,054 (45.2)	988 (21.6)	
T2	916 (13.3)	415 (17.8)	501 (11.0)	
T3	3,065 (44.4)	743 (31.8)	2,322 (50.9)	
T4	874 (12.7)	122 (5.2)	752 (16.5)	
N stage				<0.0001
N0	2,900 (42.0)	1,381 (59.2)	1,519 (33.3)	
N1	2,922 (42.4)	739 (31.7)	2,183 (47.8)	
N2	812 (11.8)	169 (7.2)	643 (14.1)	
N3	263 (3.8)	45 (1.9)	218 (4.8)	
M stage				<0.0001
M0	5,405 (78.4)	2,036 (87.2)	3,369 (73.8)	
M1	1,492 (21.6)	298 (12.8)	1,194 (26.2)	

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; other, other race includes American Indian/AK native, Asian/Pacific islander.

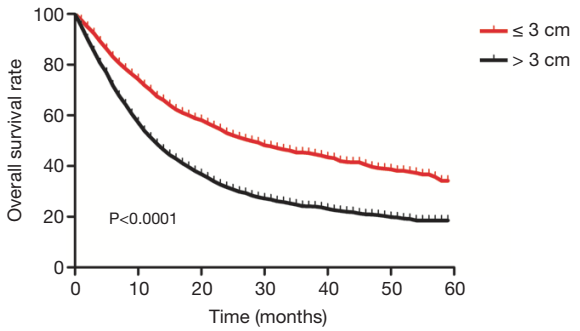

Figure 1 Kaplan-Meier survival curves for patients stratified by tumor length.

The median survival time in the two groups was 27 months (95% CI: 24.1–29.9) and 12 months (95% CI: 11.4–12.6), respectively.

The details of the univariate and multivariate analysis on OS are shown in *Table 2*. Univariate analysis showed that patients with a tumor length >3 cm had a significantly greater risk of mortality compared than those with a tumor length ≤3 cm (HR: 1.790; 95% CI: 1.667–1.922; P=0.000). However, analysis of the T stage revealed that when T1 stage was taken as the reference, patients with T2 stage had better prognosis (HR: 0.842; 95% CI: 0.753–0.942; P=0.003), and no significant difference in OS was observed between T1 and T3 stage patients (HR: 1.065; 95% CI: 0.987–1.150; P=0.105). Furthermore, multivariate analysis demonstrated that patients with a tumor length >3 cm presented with poorer prognosis (HR: 1.447; 95% CI: 1.341-1.561; P=0.000) and T2 stage patients showed a lower risk of mortality (HR: 0.863; 95% CI: 0.771–0.967; P=0.011). Age, race, histology, tumor grade, N stage and M stage were also evaluated as independent prognostic factors for OS in the multivariate analysis (P<0.05).

Finally, stratified analysis based on different T stages was performed to identify the prognostic importance of tumor length, and the details are shown in *Table 3*. Characteristics of esophageal cancer patients with T1 and T2 stage are shown in *Tables 4* and *5* separately.

Univariate analysis indicated that compared with the tumor length ≤3 cm group, tumor length >3 cm group had poorer OS among T1 (HR: 2.869; 95% CI: 2.528–3.257; P=0.000), T2 (HR: 1.430; 95% CI: 1.180–1.732; P=0.000) and T3 (HR: 1.207; 95% CI: 1.079–1.350; P=0.001) stage patients but not among T4 stage patients (HR: 1.057; 95% CI: 0.851–1.312; P=0.617). When adjusted for age, gender, race, tumor location, tumor grade, histology, N stage and M stage, similar results were observed for T1 (HR: 1.844; 95% CI: 1.606–2.116; P=0.000), T2 (HR: 1.227; 95% CI: 1.003–1.501; P=0.046) and T3 (HR: 1.157; 95% CI: 1.033–1.295; P=0.012) stage patients by the multivariate Cox regression model. Survival curves of the tumor length groups based on different T stages are shown in *Figure 2*.

Discussion

Esophageal tumor length was used as a staging factor for the 1983 version of the AJCC TNM staging system (16). However, esophageal tumor length was replaced by depth of esophageal wall invasion in the 1987 version (17) because some studies demonstrated that the depth of tumor invasion more accurately correlated with survival than tumor length (18). From 1987 to the present, only the depth of tumor invasion has been used in the T classification. The current 7th edition of the UICC-AJCC TNM staging system includes the depth of tumor invasion, the number of positive lymph nodes, histology (adenocarcinoma and squamous cell carcinoma are staged separately), tumor grade and primary tumor location. However, tumor length is not included.

Some researchers have reported that tumor length is closely related to esophageal cancer outcome. Hollis et al retrospectively analyzed 389 esophageal cancer patients and demonstrated that tumor length on pathology was significantly related to OS, although no significant independent association was detected after adjusting for tumor-related factors (19). A similar finding was reported in a German study (20). However, other reports showed that tumor length may provide additional prognostic information beyond the TNM staging system, especially among esophageal cancer patients with early stages (7,18). Eloubeidi *et al.* conducted a population-based study, and they proposed tumor length as an independent prognostic factor in patients with localized disease; thus, they suggested a revised T-category of the esophageal TNM staging system to incorporate tumor length (9). Although this study provided some important evidence and was the largest study cohort, there were still some limitations. First, patients in their study were diagnosed in 1988 or later. However, clinical treatments and outcomes of esophageal cancer have recently improved, thereby compromising the strength of the evidence. Second, patients were staged using the 6th TNM edition, and thus, their results could not differentiate as to whether tumor length supplies additional prognostic information beyond the current 7th edition.

In the present study, we attempted to predict the

Table 2 Univariate and multivariate Cox regression analysis of overall survival

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
≤65	1		1	
>65	1.195 (1.121–1.274)	0.000	1.339 (1.255–1.429)	0.000
Gender				
Male	1		1	
Female	0.955 (0.882–1.033)	0.251	0.929 (0.855–1.010)	0.086
Race				
White	1		1	
Black	1.415 (1.283–1.562)	0.000	1.315 (1.182–1.462)	0.000
Other	1.094 (0.948–1.262)	0.217	1.020 (0.882–1.179)	0.792
Location				
Cervical/upper, third of esophagus	1		1	
Thoracic/middle, third of esophagus	0.937 (0.826–1.062)	0.308	0.938 (0.826–1.066)	0.326
Abdomen/lower, third of esophagus	0.807 (0.720–0.904)	0.000	0.859 (0.755–0.978)	0.861
Histology				
EAC	1		1	
ESCC	1.254 (1.168–1.346)	0.000	1.123 (1.023–1.232)	0.015
Other	1.268 (1.158–1.387)	0.000	1.139 (1.037–1.251)	0.007
Tumor grade				
Well differentiated	1		1	
Moderately differentiated	1.621 (1.383–1.900)	0.000	1.418 (1.209–1.663)	0.000
Poorly differentiated	2.187 (1.870–2.559)	0.000	1.725 (1.472–2.021)	0.000
Undifferentiated	2.487 (1.910–3.238)	0.000	2.131 (1.633–2.780)	0.000
T classification				
T1	1		1	
T2	0.842 (0.753–0.942)	0.003	0.863 (0.771–0.967)	0.011
T3	1.065 (0.987–1.150)	0.105	0.920 (0.847–1.001)	0.052
T4	2.195 (1.992–2.418)	0.000	1.438 (1.296–1.596)	0.000
N classification				
N0	1		1	
N1	1.458 (1.360–1.564)	0.000	1.085 (1.005–1.171)	0.037
N2	1.470 (1.326–1.630)	0.000	1.201 (1.076–1.340)	0.001
N3	2.084 (1.789–2.427)	0.000	1.339 (1.141–1.571)	0.000
M classification				
M0	1		1	
M1	2.970 (2.772–3.183)	0.000	1.566 (1.451–1.691)	0.004
Tumor length (cm)				
≤3	1		1	
>3	1.790 (1.667–1.922)	0.000	1.447 (1.341–1.561)	0.000

Table 3 Univariate and multivariate Cox regression analysis based on T stage

Factor (cm)	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
T1				
≤3	1		1	
>3	2.869 (2.528–3.257)	0.000	1.844 (1.606–2.116)	0.000
T2				
≤3	1		1	
>3	1.430 (1.180–1.732)	0.000	1.227 (1.003–1.501)	0.046
T3				
≤3	1		1	
>3	1.207 (1.079–1.350)	0.001	1.157 (1.033–1.295)	0.012
T4				
≤3	1		–	
>3	1.057 (0.851–1.312)	0.617	–	–

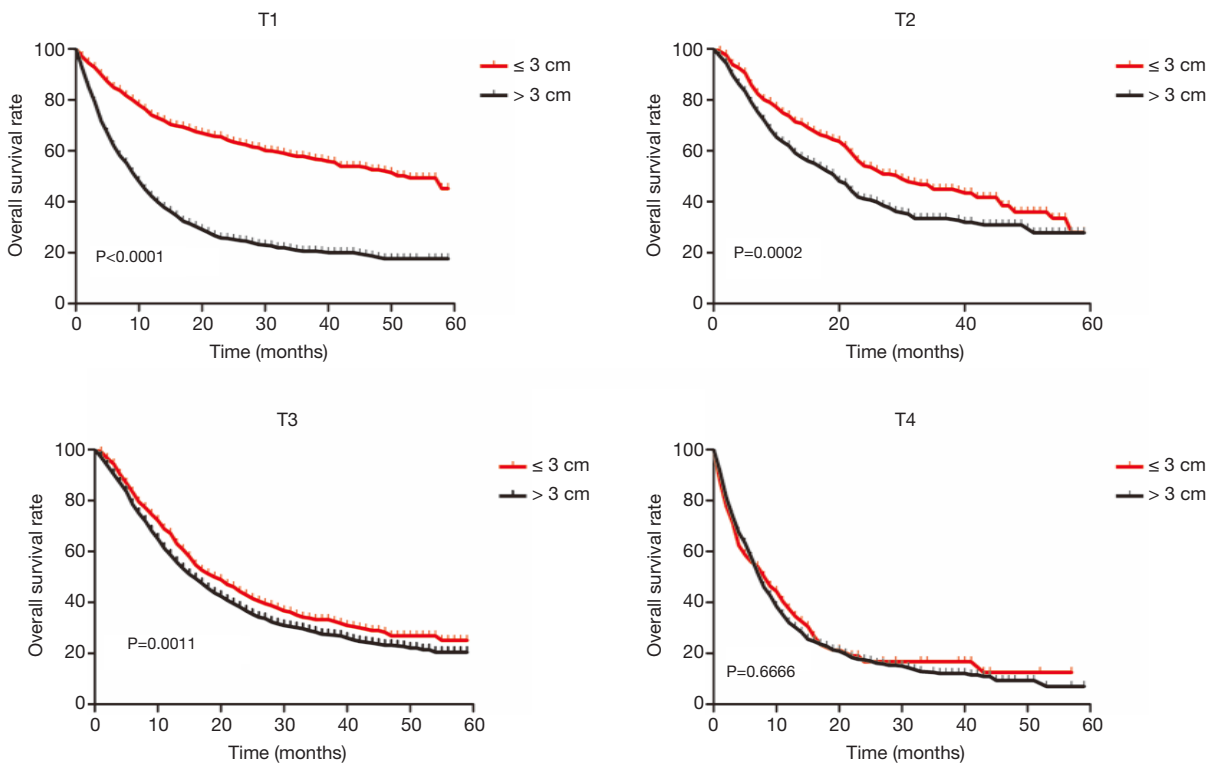

Figure 2 Kaplan-Meier survival curves of tumor length based on different T stages.

Table 4 Characteristics of esophageal cancer patients with T1 stage

Characteristics	Length ≤3 cm	Length > 3 cm	P
Age (years)			0.9148
≤65	395	368	
>65	659	620	
Race			0.073
White	914	825	
Black	91	115	
Other	49	48	
Gender			0.8942
Male	821	772	
Female	233	216	
Location			0.0424
Cervical/upper, third of esophagus	72	74	
Thoracic/middle, third of esophagus	235	264	
Abdomen/lower, third of esophagus	747	650	
Histology			<0.0001
EAC	696	520	
ESCC	241	318	
Other	117	150	
Tumor grade			<0.0001
Well differentiated	158	41	
Moderately differentiated	548	415	
Poorly differentiated	334	507	
Undifferentiated	14	25	
N stage			<0.0001
N0	842	520	
N1	187	392	
N2	19	59	
N3	6	17	
M stage			<0.0001
M0	937	599	
M1	117	389	

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; other, other race includes American Indian/AK native, Asian/Pacific islander.

Table 5 Characteristics of esophageal cancer patients with T2 stage

Characteristics	Length ≤3 cm	Length >3 cm	P
Age (years)			0.0868
≤65	159	220	
>65	256	281	
Race			0.7187
White	365	449	
Black	32	34	
Other	18	18	
Gender			0.0338
Male	315	409	
Female	100	92	
Location			0.1866
Cervical/upper, third of esophagus	33	25	
Thoracic/middle, third of esophagus	86	107	
Abdomen/lower, third of esophagus	296	369	
Histology			0.7723
EAC	240	284	
ESCC	119	141	
Other	56	76	
Tumor grade			0.0052
Well differentiated	41	20	
Moderately differentiated	196	248	
Poorly differentiated	171	223	
Undifferentiated	7	10	
N stage			<0.0001
N0	223	214	
N1	159	197	
N2	28	74	
N3	5	16	
M stage			0.0001
M0	387	427	
M1	28	74	

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; other, other race includes American Indian/AK native, Asian/Pacific islander.

outcomes of 6897 esophageal cancer patients diagnosed in 2010–2014 with known tumor length from the SEER database. All patients were staged according to the 7th edition. We found that patient age, race, histology, tumor grade, T stage, N stage, M stage and tumor length were all independent prognostic factors for OS. Patients with a tumor length ≤3 cm were more likely to be T1–2 (63%), N0 (59.2%) and M0 (87.2%) stage. The results of the multivariate Cox regression analysis also showed that tumor length >3 cm was associated with a worse OS among all 6,897 patients (HR: 1.447; 95% CI: 1.341–1.561; P=0.000).

The number of positive regional lymph nodes has been established as an independent predictor for esophageal cancers (21,22). Analysis of N classification in our study showed that mortality increased with progression of the N stage, consistent with the above reports. The depth of tumor invasion is another definite predictor for esophageal cancer. However, our results showed that T2 (HR: 0.863; 95% CI: 0.771–0.967; P=0.011) was associated with a lower risk of mortality compared with the T1 group, similar to the outcomes of Eloubeidi *et al.* (9). Interestingly, Wang *et al.* reported that there was no significant survival difference between T3 and T4 stages (21). These findings indicate that the current T stage, which is only based on depth of tumor invasion, may not be a good predictor for survival. In our stratified analysis, we classified all patients into T1, T2, T3 or T4 groups. The results reflected that the prognostic value of tumor length on OS was greatest among T1 stage patients (HR: 1.844; P=0.000) and weaker among T2 (HR: 1.227; P=0.046) and T3 (HR: 1.157; P=0.012) stage patients compared with T4 stage patients (HR: 1.057; P=0.617). Thus, the discriminatory power of tumor length was lost. We conclude that a tumor length >3 cm is closely related to an increased risk of mortality, especially when the tumor is localized within the lamina propria, the muscularis propria or the submucosa of the esophageal wall. When the primary tumor has developed over the esophageal wall, other factors determine the outcome.

Strengths of our study include the large number of patients from different institutions across the country and that all patients were staged according to the 7th edition of the AJCC-TNM staging system. However, there are still some limitations of our investigation. First, this is a retrospective study. Second, tumor length can be measured using various methods, including endoscopy (23,24), measurements by the pathologist, contrast esophagography, and CT scans. Thus, there may have been a lack of uniformity in measurement methods. Third, there were no details on treatment modalities, including techniques of surgical management, type of chemotherapy or radiotherapy. Each of these limitations may compromise the strength of the evidence.

In conclusion, our study suggests that esophageal tumor length is of great prognostic value in predicting OS, especially in early T stage patients. We propose that further prospective trials are needed to validate the prognostic value of tumor length among esophageal cancer patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.05.07). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional ethical approval and informed consent were waived.

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