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Incidence and Prediction of Unrelated Mortality After Successful Endoscopic Eradication Therapy for Barrett's Neoplasia

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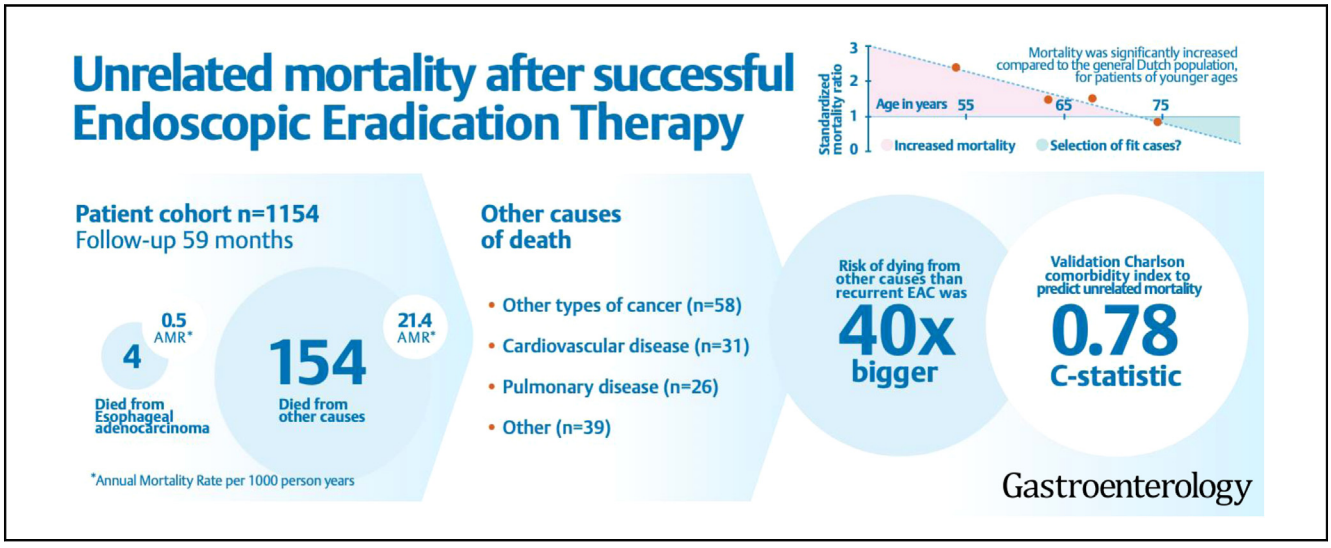

BACKGROUND & AIMS: Follow-up (FU) strategies after endoscopic eradication therapy (EET) for Barrett's neoplasia do not consider the risk of mortality from causes other than esophageal adenocarcinoma (EAC). We aimed to evaluate this risk during long-term FU, and to assess whether the Charlson Comorbidity Index (CCI) can predict mortality. **METHODS:** We included all patients with successful EET from the nationwide Barrett registry in the Netherlands. Data were merged with National Statistics for accurate mortality data. We evaluated annual mortality rates (AMRs, per 1000 person-years) and standardized mortality ratio for other-cause mortality. Performance of the CCI was evaluated by discrimination and calibration. **RESULTS:** We included 1154 patients with a mean age of 64 years (±9). During median 59 months (p25–p75 37–91; total 6375 person-years), 154 patients (13%) died from other causes than EAC (AMR, 24.1; 95% CI, 20.5–28.2), most commonly non-EAC cancers (n = 58), cardiovascular (n = 31), or pulmonary diseases (n = 26). Four patients died from recurrent EAC (AMR, 0.5; 95% CI, 0.1–1.4). Compared with the general Dutch population, mortality was significantly increased for patients in the lowest 3 age quartiles (ie, age <71 years). Validation of CCI in our population showed good discrimination

(Concordance statistic, 0.78; 95% CI, 0.72–0.84) and fair calibration. **CONCLUSION:** The other-cause mortality risk after successful EET was more than 40 times higher (48; 95% CI, 15–99) than the risk of EAC-related mortality. Our findings reveal that younger post-EET patients exhibit a significantly reduced life expectancy when compared with the general population. Furthermore, they emphasize the strong predictive ability of CCI for long-term mortality after EET. This straightforward scoring system can inform decisions regarding personalized FU, including appropriate cessation timing. (NL7039)

Keywords: Esophageal Cancer; Mortality; Charlson Comorbidity Index; Endoscopic Treatment.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Follow-up regimens after endoscopic eradication therapy for Barrett's neoplasia are rigorous, mostly based on expert opinion and do not consider the risk of mortality from causes other than recurrent esophageal cancer.

NEW FINDINGS

After successful treatment, the risk of mortality from unrelated causes was 40 times higher than the mortality risk from recurrent esophageal cancer, and this risk can accurately be predicted for an individual patient using the Charlson Comorbidity Index.

LIMITATIONS

We included only patients treated at expert centers in the Netherlands.

CLINICAL RESEARCH RELEVANCE

This study highlights the significance of considering unrelated mortality in post–endoscopic eradication therapy follow-up, while also showcasing the potential for mortality prediction through the utilization of the Charlson Comorbidity Index. These findings strongly advocate for the integration of these predictive measures into post–endoscopic eradication therapy protocols.

BASIC RESEARCH RELEVANCE

This study provides clinical evidence for shared risk factors for development of Barrett's cancer and other cancers and this may support further study.

Guidelines recommend endoscopic eradication therapy (EET) for Barrett's esophagus (BE) with dysplasia or early cancer, and the combination of endoscopic resection (ER) of visible abnormalities followed by radiofrequency ablation (RFA) for flat BE is currently the standard of care.[1–3] Successful treatment results in complete eradication of BE (CE-BE) and re-epithelization of the esophagus with squamous epithelial cells and recent long-term follow-up (FU) studies have reported a low risk for recurrent dysplasia/cancer (1.0% to 2.8% per year).[4–7]

The purpose of endoscopic FU after EET is to identify recurrent dysplasia/cancer at an early stage, allowing for timely endoscopic retreatment to prevent progression to advanced esophageal adenocarcinoma (EAC) and related death. Current FU protocols, however, vary between guidelines, are largely based on expert opinion, and have barely changed since the first studies on efficacy of EET with RFA.[1–3] A single study, based on data from the US registry, developed evidence-based recommendations for post-EET FU intervals, which would result in a 37% decrease in the total number of endoscopies.[8]

However, neither this study nor other FU protocols, take into account the risk for mortality unrelated to EAC. Competing mortality is a key variable in decisions for endoscopic FU, because prior studies have shown that patients with nondysplastic BE (NDBE) undergoing endoscopic surveillance have a higher all-cause mortality risk than the general population.[9–11] If it is determined that the risk of mortality unrelated to EAC is also substantial after EET, it could potentially offset the advantages of FU for early disease detection in a subset of patients.

Thus, identification of patients at a high risk for unrelated mortality may help to identify patients in whom post-EET FU may not be opportune. The Charlson Comorbidity Index (CCI) is the most commonly used score to predict long-term mortality risk. This score, which is calculated by weighing 19 comorbid conditions and age, was developed in 1987 to predict 10-year mortality.[12,13] Since then, it has been externally validated in a wide variety of studies, consistently showing good predictive performance.[14–18] However, there are no data on the performance of CCI in a post-EET BE population.

In the current study, we aimed to (1) evaluate the risk for other-cause mortality during FU after successful EET; and (2) evaluate the performance of the CCI, using a high-quality registry of all patients with BE who underwent EET in a Barrett Expert Center (BEC) in the Netherlands. This information may help in developing individualized FU in the future.

Methods

This study used data from the nationwide BEC registry in the Netherlands. This registry has been described in detail in a previous study.[4] In short, in the Netherlands, EET for patients with BE-related neoplasia is centralized in 9 expert centers

*** Authors share co-first authorship.**

Abbreviations used in this paper: **AMR, annual mortality rate; BE, Barrett's esophagus; BEC, Barrett Expert Center; C-statistic, Concordance statistic; CBS, Centraal Bureau voor de Statistiek; CCI, Charlson Comorbidity Index; CE-BE, complete eradication of Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; EET, endoscopic eradication therapy; ER, endoscopic resection; FU, follow-up; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; RFA, radiofrequency ablation; SMR, standardized mortality ratio.**

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with dedicated, specifically trained endoscopists and pathologists who adhere to a joint treatment and FU protocol. All patients who received EET for BE-related neoplasia in the Netherlands since 2008 are included in the BEC registry. Treatment and FU protocols have been described in detail earlier.[4] In some patients, endoscopic FU was discontinued because of an expected limited life expectancy, as assessed by the treating physician and in consultation with the patient. There were no formal guidelines for discontinuing FU.

For the current study, the BEC registry data was matched with microdata from Centraal Bureau voor de Statistiek (CBS, ie, National Statistics) for date and cause of death, consulted in January 2022. The CBS database is a nationwide database that includes data on date and cause of death for all persons living in the Netherlands. All deceased persons registered in one of the districts of the Netherlands (mandatory registration when living more than 4 months in this nation) are included in the CBS database.

Study Population

We included all patients in the Netherlands who achieved CE-BE after EET between January 2008 and July 2019, with a minimal FU duration of 1 year.[4] This cohort is identical to the cohort published in prior publications, focusing on long-term endoscopic outcomes such as recurrence of dysplasia/cancer and risk factors for recurrence.[4,19]

CCI

We used the CCI score that includes age.[12,13] This score consists of age and several comorbidities with assigned weights, as shown in detail in Supplementary Table 1. We used definitions as described in the original publication and other validation studies.[12,15,17,18] EAC, before EET, was not scored as a solid tumor in our baseline assessment. Myocardial infarction was also scored for patients who underwent an (acute) intervention for clinical coronary heart disease, such as coronary artery bypass graft and percutaneous transluminal coronary angioplasty or percutaneous coronary intervention.

The CCI was scored retrospectively based on existing medical records, at the end of successful EET (ie, the moment FU was initiated). If comorbidities were not mentioned in the medical records, they were scored as nonexistent. Reliability of CCI data collection was scored according to predefined criteria (Supplementary Table 2). We considered reliability adequate if scored as moderate or good. Data collection was performed between July 2020 and December 2022.

Study Endpoints

The following were the primary endpoints:

1. Annual mortality rate (AMR, per 1000 patient-years) for other-cause mortality (ie, EAC-unrelated mortality).
2. Discrimination and calibration of the CCI for prediction of other-cause mortality.

A secondary endpoint was AMR for specific causes of death including EAC-related mortality. We also compared AMRs in our cohort with the general Dutch population adjusted for age and gender, reported as the standardized mortality ratio (SMR).

Statistical Analyses

Endoscopic FU was defined as time between first and last FU endoscopy. Vital FU was defined as the time period between first FU endoscopy (ie, the start point of FU) and either (1) date of death, or (2) date of confirmation that patient was alive (evaluated January 2022) in the CBS database (endpoint of FU). Patients who were alive at the endpoint of FU were censored. For analysis of unrelated mortality, patients with EAC-related death were censored. CBS is a nationwide database that evaluates mortality of all patients in the Netherlands, and all patients in our cohort were matched, so there were no patients lost to FU.

AMR was calculated by dividing the number of patients with other-cause mortality by the total person-years of vital FU and was reported per 1,000 person-years.

SMR was calculated as ratio between the AMR in our population and in the general Dutch population, matched for age and gender. Statistical significance was evaluated using the 1-sample log rank test.[20] The null hypothesis was defined as there is no difference in all-cause mortality between our study population and the general population. For each year of FU duration, the expected number of deaths in the Dutch population was calculated and compared with the number of deaths in the study sample. Mortality rates in the general population were obtained through the National Statistics Statline CBS Database (open access).[21] In a subanalysis, we stratified SMR by baseline age divided into quartiles (ie, 4 equal groups each containing 25% of the patients in the cohort).

Performance of CCI was evaluated by discrimination (ie, the ability of CCI to differentiate between patients who were alive vs those who were deceased) using the Concordance statistic (C-statistic) based on Cox models. A 95% confidence interval (CI) was provided using 500 bootstrap samples based on the percentile method. Calibration (ie, agreement between observed mortality risks and predicted mortality risks over 10 years) was evaluated using calibration plots. Observed 10-year survival rates were obtained from life tables using Kaplan-Meier estimates.

We also evaluated the performance of age (without other comorbidities) to predict other-cause mortality. Discrimination of this model vs the full CCI was compared based on the DeLong method.[22]

We performed several sensitivity analyses to evaluate the robustness of our findings: (1) performance of the CCI in a larger cohort including all patients in whom we initiated endoscopic therapy. This included patients with RFA failure, patients with ER monotherapy, and surveillance of the remaining BE due to expected short life expectancy, and patients in whom we decided to discontinue EET early because of development of new comorbidities with expected short life expectancy; (2) prediction of 3- and 5-year mortality instead of 10-year mortality; (3) development of a new predictive model including all parameters from the CCI (Cox regression model); and (4) analysis of patients with baseline EAC scored as having a solid tumor.

Analyses were performed using R version 3.6.2. All P values were 2-sided and $P < .05$ was considered statistically significant. Results from the study are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement on guidelines for reporting observational studies.[23]

Results

A total of 1154 patients with CE-BE were included and all patients were successfully matched with the CBS database for evaluation of vital status (ie, dead or alive) (Supplementary Figure 1). Clinical and demographic features are presented in Table 1. The median vital FU after CE-BE was 59 months (p25–p75 37–91), corresponding to a total of 6375 person-years of vital FU. Vital FU from start of EET was median 70 months (p25–p75 47–102).

Other-Cause Mortality

A total of 154 patients died from causes unrelated to EAC (13%), corresponding to an AMR of 24.1 per 1000 person-years (95% CI, 20.5–28.2). Death occurred a median 47 months (p25–p75 26–80) after CE-BE and at a mean age of 73 years (standard deviation ±10). The cumulative incidence curves in Figure 1 show that unrelated mortality substantially surpasses the risk for recurrent neoplasia and risk for EAC-related mortality during FU. As expected,

Table 1. Baseline Characteristics of 1154 Patients With Successful CE-BE, Stratified for Unrelated Mortality During Long-Term FU

	Total N = 1154	No unrelated mortality n = 1000	Unrelated mortality n = 154	*P* value
Demographics				
Male gender, n (%)	947 (82)	823 (82)	124 (81)	.67
Age, *y*, median (p25-p75)	65 (58–71)	64 (58–70)	70 (62–76)	<.01
BMI, kg/m^2 , median (p25–p75)	27 (25–30)	27 (25–30)	26 (24–29)	<.01
Smoking (former or current), n (%)	535 (46)	457 (46)	78 (51)	<.01
BE at baseline				
Circumferential extent, median (p25–p75)	2 (0–5)	2 (0–5)	2 (0–5)	.62
Maximum extent, median (p25–p75)	4 (3–7)	5 (3–7)	4 (3–7)	.76
Worst overall histology, n (%)				<.01
LGD	306 (27)	289 (29)	17 (11)	
HGD	363 (31)	317 (32)	46 (30)	
Low-risk cancer	486 (42)	394 (39)	91 (59)	
Charlson Comorbidity Index				
Charlson score, median (p25–p75)	3 (2–4)	3 (2–4)	4 (3–5)	<.01
Comorbidities, n (%)				
AIDS (or HIV)	3 (0.3)	3 (0.3)	0 (0)	1.00
Cancer				.67
Solid tumor	75 (6)	64 (6)	11 (7)	
Metastatic tumor	6 (1)	5 (1)	1 (1)	
Congestive heart failure	22 (2)	14 (1)	8 (5)	<.01
Connective tissue disease	46 (4)	36 (4)	10 (6)	.56
COPD	155 (13)	121 (12)	34 (22)	<.01
CVA or TIA	100 (9)	79 (8)	21 (14)	.03
Dementia	3 (0.3)	1 (0.1)	2 (1)	.06
Diabetes mellitus				<.01
Uncomplicated	149 (13)	114 (11)	35 (23)	
End-organ damage	9 (1)	8 (1)	1 (1)	
Hemiplegia	8 (1)	8 (1)	0 (0)	.56
Leukemia	5 (0.4)	3 (0.3)	2 (1)	.27
Liver disease				.10
Mild	8 (1)	6 (1)	2 (1)	
Moderate to severe	6 (1)	4 (0.4)	2 (1)	
Lymphoma	7 (1)	3 (0.3)	4 (3)	<.01
Moderate to severe kidney disease	14 (1)	7 (1)	7 (5)	<.01
Myocardial infarction	165 (14)	128 (13)	37 (24)	<.01
Peripheral vascular disease	61 (5)	50 (5)	11 (7)	.36
Peptic ulcer disease	20 (2)	17 (2)	3 (2)	1.00
Vital FU				
Vital FU, *mo*, median (p25–p75)	59 (37–91)	64 (42–93)	47 (26–80)	<.01
Endoscopic FU, *mo*, median (p25–p75)	43 (22–69)	46 (22–74)	38 (20–62)	<.01
Unrelated death, n (%)	154 (13)	0 (0)	154 (13)	
EAC-related death, n (%)	4 (0.3)	4 (0.3)	0 (0)	

AIDS, acquired immunodeficiency syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HIV, human immunodeficiency virus; TIA, transient ischemic attack.

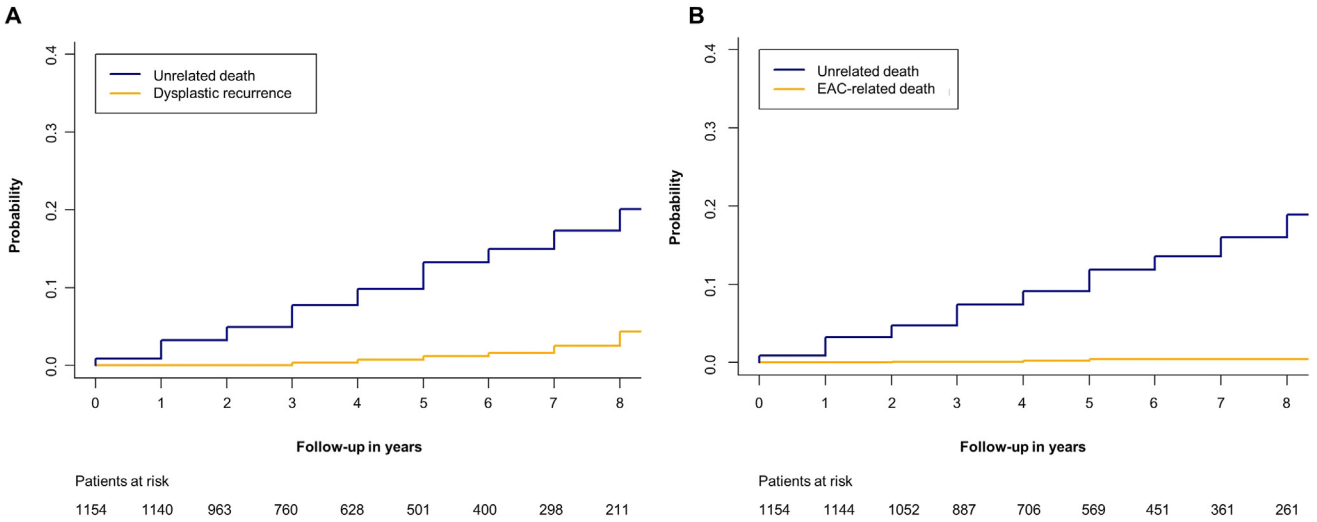

Figure 1. Cumulative incidence of unrelated mortality against recurrent dysplasia and against EAC-related death. Shown are the cumulative incidence curves of patients dying from other causes than esophageal cancer after successful EET against the risk for recurrent dysplasia after successful EET during FU (*A*) and against the risk for EAC-related death (*B*).

mortality increased along with increasing age at baseline (Supplementary Figure 2*A–D*). The most common causes of death were non-EAC cancers (n = 58; AMR, 8.4; 95% CI, 6.0–10.8); most commonly pulmonary (n = 22), hematological (n = 9), and bladder malignancies (n = 7), cardiovascular disease (n = 31; AMR, 4.2; 95% CI, 3.3–7.0), and respiratory disease (n = 26; AMR, 3.1; 95% CI 2.0–4.7) (Table 2).

EAC-related Mortality

A total of 4 patients died of new EAC during FU, corresponding to an AMR of 0.5 per 1000 person-years (95% CI, 0.1–1.4)]. These patients were described in detail in a prior study.[4] In short, 3 of 4 patients had long-segment BE at baseline (mean C8M10) and all 4 had (multifocal) high-grade dysplasia (HGD) or early EAC. Patients initially achieved CE-BE but were diagnosed with advanced EAC during endoscopic FU. All patients were still under endoscopic FU when progression occurred.

No patients died from complications related to EET.

FU Endoscopies

At the end of vital FU, 970 of 1154 (84%) patients were under endoscopic FU, and in the remaining 167 of 1154 (15%) endoscopic FU was prematurely discontinued because of expected limited life expectancy. This was a subjective assessment of the treating endoscopist. The other 17 of 1154 (1%) patients were lost to FU after median 34 months (interquartile range 20–83) of endoscopic FU.

The proportion of patients in whom endoscopic FU was stopped prematurely was significantly higher among those who died (31%) vs those who were still alive (12%, $P < .01$) (Supplementary Table 3).

Median duration between the last FU endoscopy and death was 14 months (p25–p75 7–24). In 34 patients (22% of the patients that died), an FU endoscopy was performed within 6 months before unrelated death occurred and in 16 of these, this FU endoscopy was performed within 3 months of death.

Table 2. Causes of Death for All 158 Patients Who Died

Main classification	Sub classification	Total, n (%)
Overall		158 (100)
Neoplasms		62 (39)
	Pulmonary	22 (14)
	Hematologic	9 (6)
	Bladder	7 (4)
	Prostate	4 (3)
	Colon	4 (3)
	Esophagus (EAC)	4 (3)
	Pancreas/liver	3 (2)
	Other	9 (6)
Cardiovascular disease		31 (20)
	Stroke	19 (12)
	Cardiac failure	11 (7)
	Other	1 (1)
Respiratory diseases		26 (17)
	COPD	13 (8)
	Pneumonia	7 (4)
	Other	3 (2)
Neurologic diseases		8 (5)
Diseases of the digestive tract		7 (4)
Diseases of the urogenital system		4 (3)
Infectious diseases		3 (2)
Diseases of the endocrine system		2 (2)
Other		15 (10)

COPD, chronic obstructive pulmonary disease.

Comparison With the General Dutch Population

After adjustment for age and gender, overall mortality in our cohort did not exhibit a statistically significant difference compared with mortality in the general Dutch population (SMR, 1.14; 95% CI, 0.96–1.37) (Supplementary Figure 3 and Table 3). AMR in our study cohort was 24.1 (95% CI, 20.5–28.2), AMR in the general Dutch population matched cohort was 21.2 (95% CI, 17.8–25.0).

However, the SMR differed by age. Stratified for age in quartiles, mortality in the lowest 3 age quartiles was significantly higher than that of the general population, and mortality in the highest age group was significantly lower. The SMR was 2.38 (95% CI, 1.81–3.14) for patients in the lowest age quartile (ie, <58 years) and 0.86 (95% CI, 0.76–0.98) in the highest age quartile (ie, >71 years) (Figure 2, Table 3, and Supplementary Figure 4*A*–*D*).

The risk of dying from neoplasms other than EAC was significantly increased in comparison with the general population for the younger age groups (Table 3). Patients aged <58 years had the highest SMR, with 3.25-fold (95% CI, 2.29–4.62) increase in the risk of dying from other neoplasms as compared with the general population. The risk of dying from cardiovascular or respiratory disease was not increased in either of the age categories (Table 3).

Performance of CCI for Prediction of Mortality

CCI was calculated for all 1154 patients and reliability of CCI data collection was evaluated according to definitions shown in Supplementary Table 2. Data collection was reliable in 94% (n = 1090) of patients. In only 5% of patients, the reliability of CCI was rated as poor (n = 39; 3%) or unreliable (n = 25; 2%). The CCI score for the latter 25 patients was derived solely from their age, under the assumption that no relevant comorbidities were present, as none were documented in their medical records.

The probability of dying increased along with an increasing CCI (Figure 3). Among the 48 patients with a CCI of 0, EAC-unrelated mortality was 2% (1 of 48) after a median FU of 6.0 years (p25–p75 4.0–8.6). Cumulative EAC-unrelated mortality during median 6.0 years of FU increased for a CCI of 1 (4%; 6 of 152); CCI of 2 (8%; 22 of 284); CCI of 3 (10%; 27 of 261); CCI of 4 (21%; 42 of 202); and a CCI of 5 (24%; 29 of 123) ($P < .01$). Given the low number of patients with a CCI of 6 and higher, we combined these categories into 1 group of total 84 patients with a mortality risk of 32% (27 of 84) (Supplementary Table 4).

The C-statistic was 0.78 (95% CI, 0.72–0.84) (Figure 4). We compared the C-statistic of the CCI with the C-statistic of age alone (C-statistic, 0.65; 95% CI, 0.64–0.77), because the

Table 3. Standardized Mortality Ratios Compared With the General Population

		Annual mortality rate in study cohort (95% CI)	Annual mortality rate in matched Dutch population cohort (95% CI)	Standardized mortality ratio (95% CI)	*P* value
			Other-cause mortality		
Overall population		24.1 (20.5–28.2)	21.2 (18.8–25.0)	1.14 (0.96–1.37)	.09
Quantile 1	<58 y	7.92 (5.27–11.40)	3.33 (1.93–5.87)	2.38 (1.81–3.14)	<.01
Quantile 2	58–65 y	20.71 (14.71–28.12)	13.54 (9.18–20.32)	1.53 (1.24–1.89)	<.01
Quantile 3	65–71 y	28.22 (22.64–34.60)	19.46 (15.02–25.52)	1.45 (1.23–1.72)	.02
Quantile 4	>71 y	44.49 (37.49–52.72)	51.73 (44–60.32)	0.86 (0.76–0.98)	.01
			Neoplasms		
Overall population		6.12 (4.68–7.82)	4.93 (3.65–6.69)	1.24 (0.93–1.64)	.09
Quantile 1	<58 y	4.52 (3.01–6.00)	1.39 (0.56–2.89)	3.25 (2.29–4.62)	<.01
Quantile 2	58–65 y	4.60 (3.15–6.69)	2.63 (1.40–4.01)	1.75 (1.28–2.38)	<.01
Quantile 3	65–71 y	6.19 (1.53–4.09)	4.27 (2.79–6.34)	1.45 (1.12–1.89)	.01
Quantile 4	>71 y	9.89 (7.48–12.82)	11.91 (9.18–14.99)	0.83 (0.65–1.04)	.83
			Cardiovascular disease		
Overall population		3.76 (2.41–5.59)	4.14 (2.67–5.97)	0.91 (0.61–1.35)	.91
Quantile 1	<58 y	2.26 (1.17–4.14)	2.26 (1.17–4.14)	1.00 (0.58–1.70)	1.00
Quantile 2	58–65 y	2.30 (1.19–4.01)	1.97 (0.92–3.52)	1.17 (0.54–2.54)	.66
Quantile 3	65–71 y	4.13 (2.45–6.51)	2.56 (1.26–4.51)	1.61 (0.99–2.51)	.07
Quantile 4	>71 y	7.06 (4.77–10.11)	10.09 (7.34–13.61)	0.70 (0.48–1.02)	.03

CI, confidence interval.

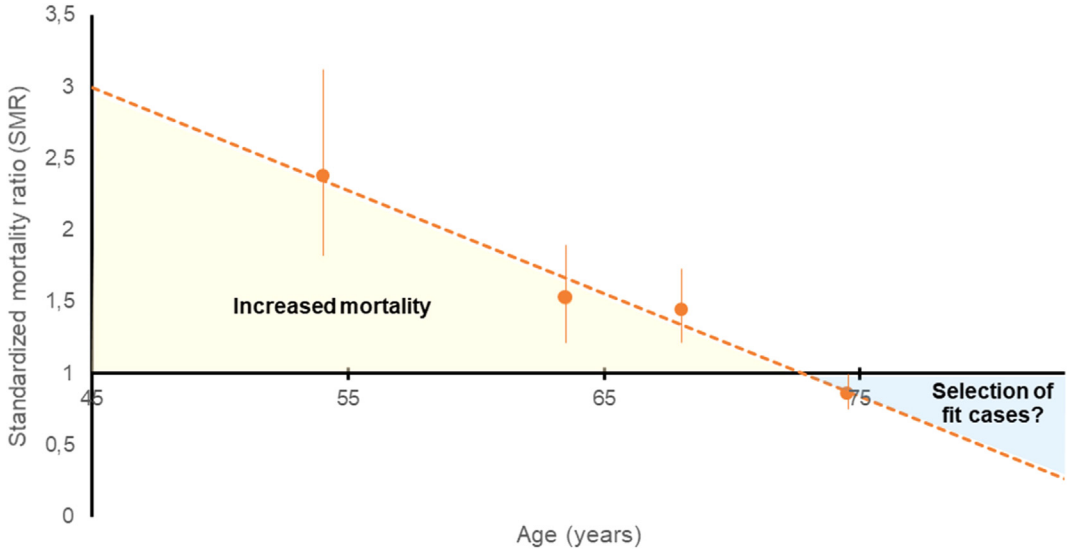

Figure 2. SMR stratified against age. The SMR (ie, the mortality observed in our cohort compared with the general population) is shown on the y-axis. The x-axis is age in years. An SMR of 1 indicates comparable risk for mortality; SMR <1 indicates a lower risk for mortality; and SMR >1 indicates an increased risk for mortality. The SMR was stratified in age quartiles. The *dotted line* represents the trend line. For patients younger than 72 years, mortality in patients after endoscopic treatment for BE was increased when compared with the general population.

latter is easier to use in daily practice. Our findings revealed a statistically significant improvement in discrimination when comparing CCI with age alone ($P < .01$).

Calibration is shown in Figure 4 and Supplementary Table 4. The plot indicates overall fair calibration, with slight underestimation of the actual mortality risk for lower CCI scores and slight overestimation of the actual mortality risk for higher CCI scores.

Sensitivity Analysis

CCI performed comparably for shorter-term mortality predictions of 3 years (C-statistic, 0.69; 95% CI, 0.61–0.75) and 5 years (C-statistic, 0.70; 95% CI, 0.64–0.74). Second, performance of CCI was evaluated in all patients who underwent at least 1 endoscopic treatment session (n = 1479). This cohort includes patients with RFA failure, patients with ER monotherapy and surveillance of the remaining BE due to expected limited life expectancy, and patients in whom we decided to discontinue EET early because of development of new comorbidities. Baseline characteristics of this cohort of 1479 patients are shown in Supplementary Table 5. The C-statistic was comparable to the C-statistic of the post-EET population (0.77, 95% CI, 0.73–0.81) and calibration was fair (Supplementary Figure 5). In addition,

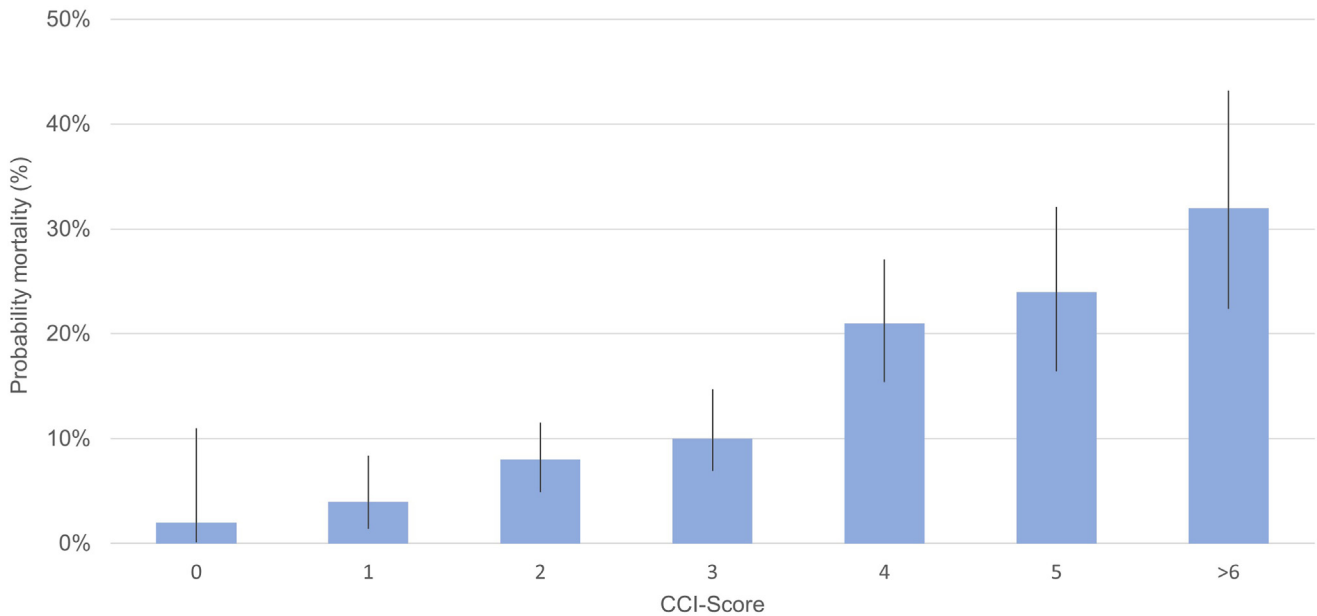

Figure 3. Probability of mortality per CCI score in the entire cohort. This histogram shows the probability of death per CCI score.

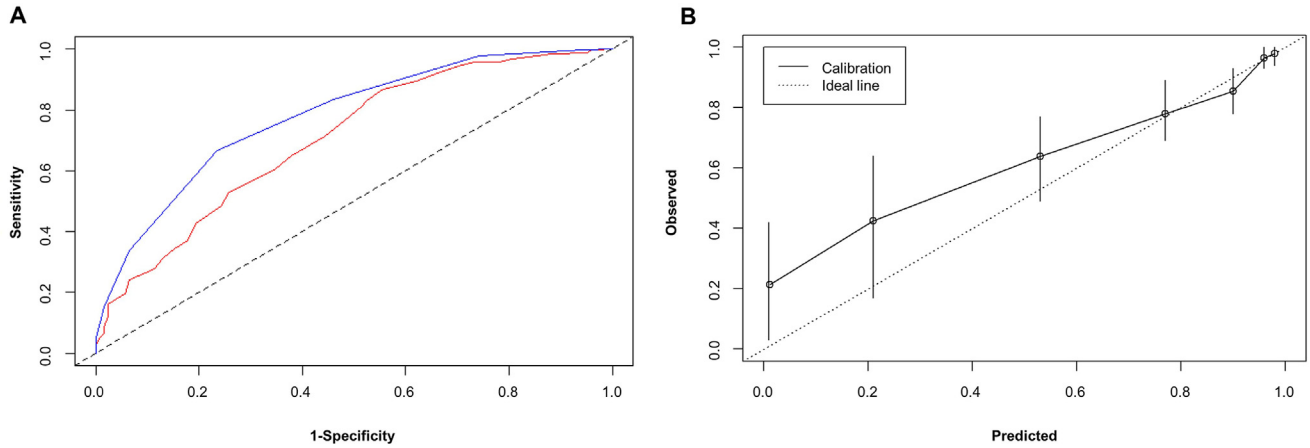

Figure 4. Area under the curve (AUC) plot of the prediction for other-cause mortality using the CCI or age alone and calibration plot. (A) Shown is the AUC of the prediction for other-cause mortality of the CCI-model (in *blue*) and the model of age alone (in *red*). The AUC of the CCI was 0.78 (0.72–0.84) and of age alone 0.65 (0.64–0.77). A higher score between 0 and 1 indicates better discrimination (ie, the distinctive ability of the model between patients who died and patients still alive). (*B*) Shown is the calibration plot of the CCI in the post-EET population. The *plot* shows the predicted (x-axis) against the observed survival of patients corrected for 10 years (y-axis). The *dotted line* indicates optimal calibration. The *plot* shows fair calibration.

CCI also performed comparably if EAC at baseline, before EET, was scored as a solid tumor in the CCI score (C-statistic, 0.71; 95% CI, 0.65–0.77; Supplementary Figure 6).

First, we evaluated discrimination of the existing CCI, with reweight of the variables in our population. This resulted in a C-statistic of 0.77 (0.73–0.81). Addition of an interaction term for age did not improve the model ($P = .17$; C-statistic, 0.70; 95% CI, 0.65–0.75).

Individual components of the CCI that had the highest predictive value in a newly developed multivariate model were (highest to lowest): lymphoma, dementia, chronic kidney disease, congestive heart failure, diabetes mellitus, increasing age, chronic obstructive pulmonary disease, and myocardial infarction (Supplementary Table 6). Of note, age was calculated per 10-year increase in this model. Evaluation of model performance of this newly created model, in internal validation, resulted in fair discrimination (C-statistic, 0.75; 95% CI, 0.67–0.83) and good calibration (Supplementary Figure 7). Finally, calibration for varying age groups appeared comparable (Supplementary Figure 8).

Baseline Histology

In univariable Cox regression analysis, we found an association between baseline histology and other-cause mortality ($P < .01$; hazard ratio for cancer vs LGD, 2.67; 95% CI, 1.58–4.47). This association remained significant in multivariable analyses adjusted for CCI ($P < .01$).

SMR stratified for baseline histology for LGD, HGD, and cancer was 0.87 (0.51–1.49); 1.41 (0.82–1.59); and 1.69 (1.34–2.14), respectively. Detailed analyses are shown in the Supplementary Results Section 1.

Discussion

This study shows that unrelated mortality in a patient population successfully treated with EET for BE is more than 40 times higher (48; 95% CI, 15–99) than EAC-related mortality. The risk for unrelated mortality was higher than the general population, especially in younger patients. Patients treated with RFA for BE-related neoplasia were far more likely to die from other diseases, especially from other types of cancer, than from EAC. Moreover, the risk for unrelated mortality can be predicted using the CCI, a well-characterized, easily calculable clinical scoring system.

To better understand the absolute AMRs found in our BE population, we compared mortality in our cohort with that of the general Dutch population matched for age and gender. We found that this comparison differed with age. Patients in the youngest age quartile (ie, younger than 58 years) had a 2.4 times higher risk of other-cause mortality when compared with the general population. In contrast, patients in the highest age quartile (ie, older than 71 years) had a lower mortality risk when compared with the general Dutch population. One possible explanation for this last finding includes the "healthy patient effect," in which, at older ages only relatively fit patients may have been selected to undergo endoscopic treatment of their neoplastic BE. However, this hypothesis could not be confirmed by our data.

The increased mortality in patients with BE post-EET is largely based on an increased risk of death from other types of cancer than EAC. Shared risk factors for developing cancers may have played a role, such as genetic risk factors or lifestyle factors. Aiming to improve overall survival, we may need to focus our attention on diseases that are causing the increased mortality in our population. Speculatively, improving overall health of patients may be more beneficial in reducing mortality than screening for recurrent EAC.

Only a single study, from the US RFA Registry, evaluated all-cause mortality after RFA for Barrett's neoplasia among 4982 patients.[24] This study reported a much lower mortality rate, namely 3% during an average 2.7 years of FU, whereas the risk for EAC-related death was 0.2%. As also reported in our study, the risk for unrelated mortality significantly surpassed the risk of dying from EAC. However,

this US study included all patients initially selected for EET, being a mixture of treatment indications (ie, approximately 50% had NDBE), treatment failures, patients with progression during treatment, and patients with CE-BE. Furthermore, mortality data were provided by the medical centers and not matched with a National Statistics database, such as in our study, which is a risk for missing data and an underestimation of the true unrelated mortality risk. Furthermore, FU duration was shorter.

In general, mortality has been studied predominantly in the NDBE-populations under endoscopic surveillance. Most studies reported that patients undergoing surveillance for NDBE have a higher mortality risk compared with the general population, mainly due to other causes than EAC, such as other cancers and diseases of the circulatory system.[9–11,25] However, this increased risk in the NDBE population is not supported by all studies.[26,27] In our study, an association was found between higher baseline histology and a higher risk for mortality. In our opinion, it seems unlikely that this is a *causal* relationship. There is no biological foundation that supports an association between histology and unrelated mortality. In daily practice, we only initiate EET for LGD in patients with significant life expectancy, whereas EET for HGD or cancer may also be initiated in patients with shorter life expectancy (ie, confounding by indication). Apparently, CCI cannot eliminate the observed association between histology and mortality, indicating residual confounding from unidentified factors.

This study has important strengths. This is the first study to evaluate other-cause mortality in a BE population after successful EET. High-quality data were collected from all patients with BE in the Netherlands after treatment in specific expert centers. Information on date and cause of death was obtained from the Dutch CBS database, a nationwide database with complete mortality data of the Dutch population. The use of a validated, widely used, easily applied morbidity index, the CCI, will facilitate the insertion of comorbidity into future models studying post-EET surveillance.

This study has some limitations as well. We included only patients treated in the Netherlands and mortality outcomes may be different in other countries, which would impair the generalizability of our results. However, given that levels of body mass index, diabetes, and metabolic syndrome are lower in the Netherlands than, for example, in the United States and some other Western countries, and given that the Netherlands has one of the highest life expectancies in the world, we might expect that non–EAC-related mortality is even more pronounced in other countries.[28] Second, CCI requires evaluation of multiple comorbidities and data were scored retrospectively with a risk for missing information. However, CCI data collection was considered reliable in 94% of patients. Evaluation of multiple comorbidities for calculation of CCI may be challenging in routine clinical practice. Still, CCI requires evaluation of major comorbidities only, and there are multiple online calculators available. All patients in the current study were treated in expert centers, and outcomes such as recurrence risk and EAC-related mortality risk may be different in community centers, and this may impair generalizability of our results. The risk for EAC-related mortality is logically influenced by early detection and treatment of recurrent dysplasia, as was the case in 34 patients in this cohort. We were unable to compare the risk for EAC-related mortality in our population to its risk in the general Dutch population because of low numbers. This comparison may be interesting to evaluate in future studies because if the risk for EAC-related mortality after successful EET is comparable to this risk in the general population, one may argue that these patients do not need to undergo FU after EET at all. We performed multiple statistical tests without adjusting for multiple testing and this has increased the risk for a type I error. Finally, in cases in which patients relocated abroad, mortality data were not available from CBS.

Currently, there is no consensus about the optimal post-EET FU protocol. Recommendations vary between guidelines and most are based on expert opinion.[1–3] Even though the strict FU in the first year after treatment is attenuated in some recent guidelines, the proposed protocols still have in common that FU endoscopies are performed frequently with the goal to detect recurrent disease at an early stage, amenable to endoscopic retreatment. Cotton and colleagues[8] provided evidence-based guidance for FU intervals by using model projections to estimate optimal intervals based on the risk of recurrent invasive EAC. However, this model did not account for other-cause mortality, nor did it suggest an age to stop surveillance.

The real outcome of interest for patients with BE after treatment may not be prevention of early, asymptomatic recurrence, but prevention of symptomatic EAC and/or EAC-related death. Dysplasia itself is asymptomatic and, as long as it does not progress, is harmless. Surveillance is only useful if progression to clinically relevant EAC is prevented. In a prior publication, our group developed a prediction model for recurrent dysplasia, reasoning that patients with a high risk may be surveilled more frequently than patients with a low risk for recurrence.[19] However, to create optimal surveillance intervals after successful EET, a better understanding of competing mortality pressures on this patient population is still required. This report is the first comprehensive attempt to understand these competing pressures. It will inform further model-building exercises and allows more precise and personalized guidance for the individual patient after successful EET. Apart from FU after EET, the same reasoning holds for *initiation* of EET as well as for initiation of endoscopic surveillance for nondysplastic BE, and this is an important topic for further study.

In conclusion, after successful EET of BE with dysplasia or early cancer, the risk for unrelated mortality is more than 40 times higher (48; 95% CI, 15–99) than the risk for EAC-related mortality. The 10-year mortality risk for an individual patient after EET can reliably be predicted using the well-known and easy-to-calculate CCI. Based on our study, the risk for unrelated mortality competes with the benefits of endoscopic FU after EET and should therefore be taken into account in post-EET FU protocols. The results of this study may contribute to more patient-tailored management and FU of patients with BE-related dysplasia/cancer.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.02.033.

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Data Availability
Data, analytic methods, and study materials will not be made available online for others.