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Modified Charlson comorbidity index of long-term, non-gastric cancer mortality in patients with early gastric cancer: a multicenter retrospective study

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Abstract

Purpose In patients with early gastric cancer (EGC) who undergo endoscopic submucosal dissection (ESD) with endoscopic curability (eCura) C-2, the risk of non-gastric cancer mortality should be evaluated before receiving further gastrectomy. Charlson comorbidity index (CCI) is often used to estimate prognosis based on patient's background before treatment. We identified the long-term risk of mortality from other causes associated with comorbidities in CCI and applied it to the creation of EGC specific CCI (GCCI).

Methods A total of 1810 patients with EGC from 3 centers were included from January 2015 to February 2023. We used Cox proportional risk models to determine the risk of non-gastric cancer mortality related to comorbidities and used these hazard ratios to reweight the Charlson index to establish GCCI.

Results The Cox model suggested that moderate to severe liver disease, metastatic solid tumors, severe to very severe chronic obstructive pulmonary disease (COPD), and leukemia had the highest risk of non-gastric cancer mortality [hazard ratio (HR) > 5)]. Survival analysis showed that the 5-year non-gastric cancer mortality rates in low-risk group (GCCI score 0–1), medium-risk group (GCCI score 2–4), and high-risk group (GCCI score 5–13) were 3%, 10%, and 52%, respectively.

Conclusions GCCI could identify patients with EGC who have higher non-gastric cancer mortality. The GCCI could be used to help patients with EGC make medical decisions.

Keywords Early gastric cancer, Charlson comorbidity index, Early gastric cancer specific Charlson comorbidity index, Non-gastric cancer mortality

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Introduction

Early gastric cancer (EGC) is a definite gastric malignancy that is confined to the mucosa or submucosa, regardless of lymph node metastasis (LNM) [1]. Endoscopic submucosal dissection (ESD), now extensively regarded as a minimally invasive treatment for EGC, carries a negligible risk of LNM [2]. As the evidence accumulates, the indications for endoscopic resection and the criteria for curative resection continue to expand [3]. When the lesion does not meet the criteria for curative resection and post-ESD endoscopic cure is endoscopic curability (eCura) C-2, gastrectomy and lymphadenectomy are recommended as the standard of treatment [4, 5]. However, in clinical practice, it may be necessary to comprehensively evaluate the risk stratification of the eCura system for gastric cancer-specific mortality, non-gastric cancer-related mortality, and the risk of impaired quality of life [3]. Compared to ESD, surgery can be too invasive and does not necessarily have a better prognosis, especially for older people with poorer physical conditions [6]. In addition, a study of the natural history of EGC showed that the mean overall survival (OS) of EGC without intervention was 63 (47–78) months [7]. When the risk of non-gastric cancer death is significantly higher than the risk of gastric cancer specific death, patients recommended for further surgery may be at risk of being overtreated. However, to date, no studies have examined non-gastric cancer mortality in patients with EGC.

The Charlson Comorbidity Index (CCI) is the most extensively used comorbidity index to estimate life expectancy according to the presence of specific comorbidity [8]. Each comorbid disease was related to a weight based on its 1-year mortality risk, and the weights were added to an overall score proportional to the total mortality risk. The CCI is based on a 1985 study of 559 hospitalized patients [8]. Comorbidities are identified at the time of hospitalization, and the CCI has been found to be a strong predictor of OS and has been included in several nomograms predicting overall survival [9, 10].

Although the CCI is widely used, it may not be perfect for predicting long-term mortality in patients with EGC. The weights were established on basis of 1-year mortality rather than long-term mortality. These data are also based on outdated mortality estimates from the mid-1980s. In addition, empirical data from a large study on prostate and breast cancer shows that the risks related to comorbidities may be disease-specific [11].

In this present study, we identified the long-term risk of non-gastric cancer mortality related to specific comorbidities by reviewing samples from 1,810 patients with EGC at 3 centers. We wanted to replicate Charlson's initial research design to determine whether the risk of comorbidities would be different among a contemporary population of EGC with long-term follow-up. We then determined whether the CCI could be reweighted to improve predictions of long-term non-gastric cancer mortality.

Methods

Setting and participants

This was a multicenter retrospective observational study from the First Affiliated Hospital of Dalian Medical University, the Second Affiliated Hospital of Dalian Medical University, and the Second People's Hospital of Liaocheng. The ethics committee of the First Affiliated Hospital of Dalian Medical University granted approval for this study (Approval Number: PJ-KS-KY-2024-599(X)). After excluding 4 patients who died due to postoperative complications and 35 patients who were lost to follow-up, a total of 1810 patients with EGC admitted to these three centers from January 2015 to February 2023 were included in our study (Supplementary flow chart). Medical records were reviewed to determine age, sex, tumor features, major type of treatment, and comorbidities at diagnosis. Informed consent from all study participants was obtained by contacting the patients themselves or their families by phone. Authors had no access to information that could identify individual participants after data collection.

Comorbidities

Comorbidities at the time of diagnosis were determined by reviewing the electronic medical record. The evaluation was conducted independently by two investigators. Comorbidities must exist at the time of making treatment decisions. We classified comorbidities following the method used by Charlson. Since all patients had EGC, EGC was not included in the comorbidity of each subject.

Mortality rate

Survival was measured from the date of treatment to the date of death. Patients treated with ESD or surgical procedures for EGC were regularly reviewed according to previous guidelines, and patients who were not treated were reviewed for their last hospital stay to determine survival. We used medical records to determine the date of death. Deaths from gastric cancer itself or from causes related to metastasis of gastric cancer are considered gastric cancer-related deaths. Non-gastric cancer mortality was defined as death from other causes.

Statistical analysis

Cox proportional regression model was used to determine the weight for each comorbidity. We applied the identical weighting method utilized by Charlson to predict mortality from other causes of EGC, the weight of hazard ratio (HR) 1.2 and below is 0, the weight of HR 1.3 to less than 1.5 is 1, the weight of HR 1.5 to less than

2.5 is 2, the weight of HR 2.5 to less than 3.5 is 3, and the weight of HR 3.5 and above is 6. Just like Charlson did, we assign weights to comorbidities according to hazard ratios, regardless of their statistical significance in the final model [12]. We then calculated comorbidity scores for the study population using the original CCI and GCCI weights. The Receiver Operating Characteristic (ROC) curve was used to compare the ability of CCI and GCCI to predict 5-year survival. And next, we performed multivariate risk regression analyses for GCCI to calculate the sub-risk of non-gastric cancer mortality from the GCCI score across the cohort. We then divided GCCI scores into three groups using X-tile software [13, 14] and calculated the cumulative incidence of non-gastric cancer deaths in each group. Finally, we plotted the survival curve.

Results

A total of 1810 new cases of EGC were reviewed. And 185 (10.2%) patients died from non-gastric cancer-related causes (Table 1). The median follow-up time for the entire cohort was 44 months (range 2 to 117), the mean follow-up time for those alive at the end of follow-up was 48 months (range 2 to 117), and the mean follow-up time for those who died was 37 months (range 2 to 113).

The Table 2 below presents the results of the Cox proportional risk regression analysis, which predicted the risk of non-gastric cancer mortality related to individual Charlson comorbidity after adjusting for age, sex, treatment method, and other Charlson comorbidities. The results showed that the highest risk of long-term non-gastric cancer mortality (HR greater than 5) was associated with moderate to severe liver disease, metastatic solid tumors, severe to very severe chronic obstructive pulmonary disease (COPD), and leukemia. Lower but still higher risk comorbidities (HR 2.5 - less than 3.5) include lymphoma, moderate to severe kidney disease, and congestive heart failure in New York Heart Association (NYHA) III. The comorbidities with the lowest risk that did not warrant inclusion in the model (HR less than 1.3) were Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome (HIV/AIDS) and peptic

Table 1 Clinical characteristics of 1810 patients with early gastric cancer under different treatment methods

	ESD (*n* = 707)	Surgery (*n* = 1060)	Watchful waiting (*n* = 43)
Age, median (range)	66 (50–88)	65 (50–89)	72 (53–89)
Sex, Male (n, %)	495 (70.0)	735 (69.3)	35 (81.3)
Comorbidity			
Mild liver disease	22 (3.1)	26 (2.4)	0 (0.0)
Moderate-severe liver disease	7 (0.9)	7 (0.6)	3 (6.9)
Any tumor	120 (16.9)	113 (10.6)	11 (25.5)
Metastatic solid tumor	19 (2.6)	30 (2.8)	7 (16.2)
Mild-moderate COPD	33 (4.6)	41 (3.8)	4 (9.3)
Severe-very severe COPD	9 (1.2)	34 (3.2)	3 (6.9)
Lymphoma	2 (0.2)	3 (0.2)	2 (4.6)
Leukemia	2 (0.2)	7 (0.6)	0 (0.0)
Congestive heart failure II	14 (1.9)	20 (1.8)	5 (11.6)
Congestive heart failure III	25 (3.5)	29 (2.7)	2 (4.6)
Mild renal disease	12 (1.6)	12 (1.1)	2 (4.6)
Moderate-severe renal disease	37 (5.2)	59 (5.5)	2 (4.6)
Diabetes	124 (17.5)	157 (14.8)	11 (25.5)
Diabetes with end organ damage	24 (3.3)	37 (3.4)	1 (2.3)
Arrhythmia	52 (7.3)	57 (5.3)	5 (11.6)
Myocardial infarction	66 (9.3)	82 (7.7)	7 (16.2)
Cerebrovascular disease	38 (5.3)	46 (4.3)	6 (13.9)
Dementia	1 (0.1)	3 (0.2)	0 (0.0)
Hemiplegia	15 (2.1)	102 (9.6)	0 (0.0)
Connective tissue disease	27 (3.8)	16 (1.5)	2 (4.6)
Peripheral vascular disease	43 (6.0)	47 (4.4)	5 (11.6)
Peptic ulcer disease	28 (3.9)	78 (7.3)	7 (16.2)
HIV/AIDS	8 (1.1)	7 (0.6)	0 (0.0)
Death			
Non-gastric cancer-related deaths	63 (8.9)	118 (11.1)	4 (9.3)

ESD Endoscopic submucosal dissection, *COPD* chronic obstructive pulmonary disease, *HIV/AIDS* Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome. Comorbidities in bold were included in the original Charlson index, whereas others were not. The bold plus slant shows a further distinction in the severity of the disease in Charlson comorbidity index

Table 2 Cox proportional hazards analysis for non-gastric cancer mortality among Charlson comorbidities

	No.	Original Wt	HR*	*p* Value	New Wt	Difference
Moderate-severe liver disease	17	3	5.1(2.2–11.8)	< 0.01	6	+ 3
Metastatic solid tumor	56	6	7.4(4.4–12.2)	< 0.01	6	0
Severe-very severe COPD	46	1	7.1(4.4–11.6)	< 0.01	6	+ 5
Leukemia	9	2	5.6(2.6–12.0)	< 0.01	6	+ 4
Congestive heart failure III	56	1	3.1(1.7–5.7)	< 0.01	3	+ 2
Lymphoma	7	2	3.4(1.3–8.9)	0.01	3	+ 1
Moderate-severe renal disease	98	2	2.9(1.9–4.4)	< 0.01	3	+ 1
Congestive heart failure II	39	1	2.3(1.2–4.6)	0.02	2	+ 1
Mild liver disease	48	1	2.2(1.1–4.4)	0.04	2	+ 1
Diabetes with end organ damage	62	2	2.1(1.3–3.6)	< 0.01	2	0
Arrhythmia	114	0	2.1(1.3–3.7)	0.01	2	+ 2
Myocardial infarction	155	1	2.0(1.3–3.1)	< 0.01	2	+ 1
Mild-moderate COPD	78	1	1.9(1.0-3.7)	0.06	2	+ 1
Mild renal disease	26	0	1.9(0.8–4.2)	0.14	2	+ 2
Cerebrovascular disease	90	1	1.8(1.1-3.0)	0.03	2	+ 1
Dementia	4	1	1.8(0.2–14.1)	0.57	2	+ 1
Any tumor	244	2	1.7(1.1–2.6)	0.01	2	0
Diabetes	292	1	1.5(1.0-2.2)	0.03	1	0
Hemiplegia	117	2	1.4(0.8–2.5)	0.25	1	-1
Connective tissue disease	45	1	1.4(0.7-3.0)	0.36	1	0
Peripheral vascular disease	95	1	1.3(0.8–2.1)	0.27	1	0
Peptic ulcer disease	113	1	1.0(0.6–1.7)	0.94	0	-1
HIV/AIDS	15	6	0.3(0.1–2.4)	0.27	0	-6

Wt weight, *HR* hazard ratio, *COPD* chronic obstructive pulmonary disease, *HIV/AIDS* Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome. Comorbidities in bold were included in the original Charlson index, whereas others were not. The bold plus slant shows a further distinction in the severity of the disease in Charlson comorbidity index. * Corrected for age, sex, type of primary treatment and other comorbidities

Table 3 Individual and grouped sub-hazard ratios of non-gastric cancer mortality by GCCI score

GCCI Score	No. Pts	SHR (95% CI)
Individual		
0	757	Referent
1	169	2.6(1.2–5.6)
2	365	3.6(1.9–6.5)
3	176	4.8(2.5–9.1)
4	105	7.3(3.8–14.1)
5	61	11.7(5.8–23.5)
6	66	18.9(9.9–36.2)
7	29	25.5(12.2–53.6)
8	28	23.0(10.6–49.9)
9+	54	47.4(27.0-83.3)
Grouped		
0–1	926	Referent
2–4	646	3.5(2.3–5.5)
5–13	238	18.2(11.9–27.6)

GCCI early gastric specific Charlson comorbidity index, *SHR* sub-hazard ratio

ulcers. The table gives a revised weight for each comorbidity according to the HR and it also gives a comparison to the original CCI.

A comparison of the overall concordance index (c index) of GCCI and CCI showed that GCCI had a modest improvement in predicting non-gastric cancer mortality. When comparing actual and predicted 5-year non-gastric cancer mortality, the GCCI had a c index of 0.820 versus 0.772 for CCI (Supplementary Fig. 1).

Multivariate Cox regression analysis of the GCCI score for non-gastric cancer deaths showed that the sub-risk of death increased with the score (Table 3). The two cut-off points of GCCI identified by the X-tile software were 1 and 4 (Supplementary Fig. 2). We used these two cut-off points to divide the risk of non-gastric cancer deaths into three groups: low-risk group (GCCI score 0–1), medium-risk group (GCCI score 2–4), and high-risk group (GCCI score 5–13). The sub-hazard ratios of GCCI 2–4 and 5–13 were 3.5 [95% confidence interval(CI), 2.3–5.5)], 18.2 (95% CI, 11.9–27.6), respectively (Table 3). Survival analysis showed that 5-year non-gastric cancer mortality was 3%, 10%, and 52% in the low-risk, medium-risk, and high-risk groups, respectively (Fig. 1; Table 4).

Discussion

In this present study, we defined the long-term risk of non-gastric cancer mortality related to common comorbidities in the CCI to establish GCCI. Our study showed that these risks changed significantly in comparison to the original CCI. These findings support earlier work that the risk of death related to a particular comorbidity may vary among people with different disease types, due to the specific incidence of the disease or the risks related

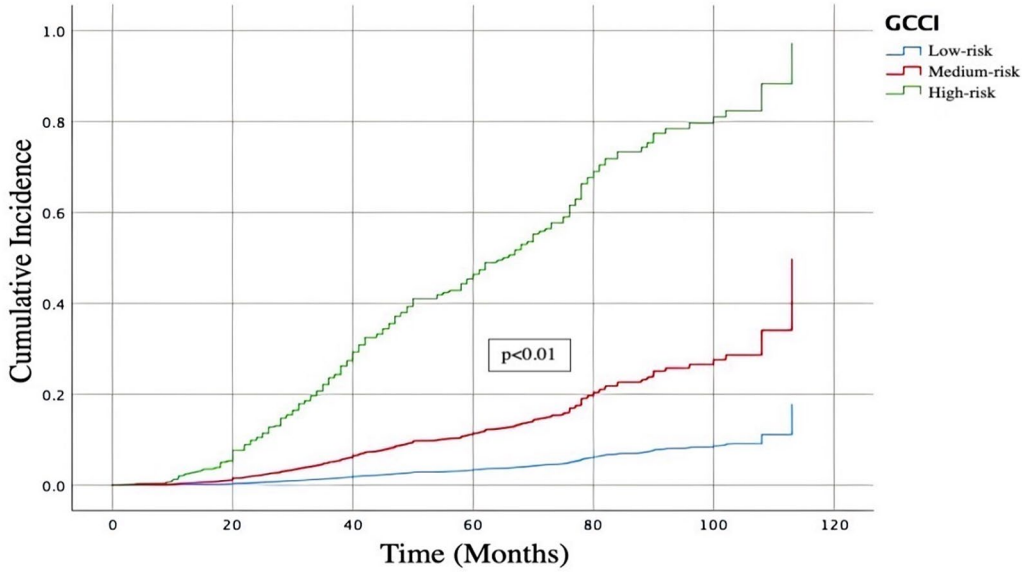

Fig. 1 Cumulative event incidence of non-gastric cancer mortality in 3 risk groups. *GCCI* early gastric specific Charlson comorbidity index

Table 4 Cumulative incidence of non-gastric cancer mortality in 3 risk groups

GCCI	% 1 Yrs	% 3 Yrs	% 5 Yrs	% 8 Yrs
Low-risk	0	2	3	10
Medium-risk	1	5	10	29
High-risk	2	25	52	75

GCCI early gastric specific Charlson comorbidity index, *Yrs* years

to the treatment [11]. Different from the original CCI, the risk defined in our study was based on long-term rather than 1-year mortality. This is of clinical significance for patients with eCura C-2 after ESD for EGC.

There have been many studies on whether patients who have eCura C-2 after ESD for EGC need additional surgical intervention. This is because surgical treatment is more traumatic than ESD [6], and it significantly reduces patient's quality of life after gastrectomy [3]. Besides, LNM is found in only 5-10% of patients who undergo additional surgical treatment [15, 16]. In addition, EGC is a slow-progressing disease with a long natural course of disease, which is about 63 (47–78) months without intervention [7]. Tomohiro Shimada's study showed that severe comorbidities with a high CCI score (≥3) were independent predictors of short-term survival for EGC. Because the cause of death in most patients is not gastric cancer, observational follow-up without further gastrectomy may be an alternative strategy for patients in poor general condition (CCI ≥ 3) [17]. However, this is only a rough estimate. As far as we know, no studies to date have accurately predicted the likelihood of a patient with EGC dying from non-gastric cancer causes. Naoto Iwai's study suggested that high-risk comorbidities were a major factor affecting the prognosis of EGC patients with non-curable ESD. For patients with non-curable ESD, CCI should be considered as a prognostic factor [18]. A review from Japan suggested that non-gastric cancer-related mortality risk as well as gastric cancer-specific mortality risk should be considered when patients with non-curative ESD require additional surgery. In addition, the International Society of Oncology recently encouraged greater attention to the quality of life of cancer patients [3]. Therefore, only patients who survive long enough will benefit from aggressive additional surgical treatment. That said, identifying patients who are most likely to die from non-gastric cancer causes is of great value in determining whether additional gastrectomy is necessary.

Compared with the original CCI, the GCCI was better able to identify patients with EGC who had a high mortality rate from other causes. When we included death from other causes within 5 years as the study endpoint, the GCCI showed better differentiation than CCI (c-index 0.820 vs. 0.772). We think this is a more clinically relevant result in EGC treatment decisions. Because the mean survival of EGC without any intervention is about 5 years (63 months) [7]. Patients who are significantly less likely to benefit from active treatment after ESD [i.e., high-risk group (GCCI score 5–13), 52% of deaths from other causes over 5 years] need to make a decision after weighing the benefits and risks, while patients with mild-to-moderate comorbidities may be considered for more aggressive treatment. Thus, the index's ability to identify patients at low to moderate risk of death (i.e., patients with mild or moderate comorbidities) may be of less clinical relevance than its ability to identify patients at highest risk (i.e., patients with severe comorbidities).

Differences in risk of mortality from other causes related to specific comorbidity in our study compared with the original CCI may reflect changes in treatment and features of diseases over recent years (e.g., HIV/AIDS) and the cumulative impact of chronic diseases (e.g., COPD, heart failure) on long-term survival. The prevalence of novel coronavirus pneumonia may be an important factor in the increased weight of patients with COPD and heart failure. And we found that EGC patients with peptic ulcerative disease did not have an increased risk of death. This finding may be due to the development of digestive endoscopy, which allows such patients to be treated in a timely manner.

Of course, there are some limitations to our study. First, because our index had no validation on external data sets, these findings should be considered only preliminary. Multicenter, prospective studies are needed in the future to continue optimizing our index. Secondly, because of the large sample size required for this study and some diseases have a lower incidence, the data collection period was long, during which some improvements in the level of care may have occurred, which may have had a certain impact on our findings. Finally, previous studies have used age-adjusted CCI, and our index GCCI lacks age adjustment. In the future, we will continue to deepen this research and build an age-adjusted GCCI score.

Conclusions

Accurate comorbidities assessment is critical when considering the need for additional surgical treatment for patients with eCura C-2 after ESD for EGC. Our findings shown that the long-term risk of non-gastric cancer mortality related to common comorbidities in the GCCI was significantly different from that in the original CCI. After the use of the contemporary GCCI, we can accurately identify patients with the highest non-gastric cancer mortality. Further research in this field will enable patients with EGC with severe comorbidities to make a more sensible decision regarding whether to pursue aggressive treatment.

Abbreviations

AUC	Area under the curve
CCI	Charlson comorbidity index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
eCura C-2	Endoscopic curability C-2
EGC	Early gastric cancer
ESD	Endoscopic submucosal dissection
GCCI	Early gastric cancer specific CCI
HIV/AIDS	Human immunodeficiency virus/ acquired immunodeficiency syndrome
HR	Hazard ratio
LNM	Lymph node metastasis
NYHA	New york heart association
ROC	Receiver-operating characteristic
Wt	Weight

Supplementary Information

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Supplementary Material 1

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Author contributions

(I) Conception and design: AG and XS; (II) Collection and assembly of data: SX and YY; (III) Data analysis and interpretation: XS and YY; (IV) Manuscript writing: XS wrote the article. AG reviewed the article. All authors have endorsed the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (Approval Number: PJ-KS-KY-2024-599(X)). Informed consent from all study participants was obtained by contacting the patients themselves or their families by phone.

Consent for publication

All authors have read and agreed to the publication of this study.

Competing interests

The authors declare no competing interests.

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