# Mortality calculator as a possible prognostic predictor for overall survival after gastrectomy in elderly patients with gastric cancer

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**Research**

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# Abstract

Background The number of elderly patients with gastric cancer (elderGC) has been increasing. Most of elderly patients were associated with reduced physiological functions, which sometimes constitute an obstacle to safe surgical treatments. The risk calculator of National Clinical Database (NRC), a Japanese surgical big database, provides mortality and morbidity as surgical-related risks. The purpose of this study is to investigate clinical significance of operative mortality calculated by NRC (NRC-mortality) during long-term follow-up after gastrectomy for elderGC.

Methods We enrolled 73 patients aged 80 or over who underwent gastrectomy at our institution. Their surgical risk was evaluated based on the NRC-mortality. Several clinicopathological factors including NRC-mortality were selected and analyzed as possible prognostic factors for elderGC after gastrectomy. Statistical analysis was performing using the log-rank test and Cox proportional hazard model.

Results NRC-mortality ranged 0.5 to 10.6%, and median value was 1.7%. Dividing elderGC into high- (1.7% or more, n=38) and low- (less than 1.7%, n=35) mortality groups, high-mortality group showed a significantly poor prognosis in overall survival (OS) than the low-mortality group, whereas there was no difference between the two groups in disease specific survival (DSS). In the analysis of Cox proportional hazard model, multivariate analysis revealed that NRC-mortality was an independent prognostic factor as well as neutrophil-lymphocyte ratio and surgical procedure in OS. In contrast, PS and pStage were independent prognostic factors in DSS, but not NRC-mortality.

Conclusions The NRC-mortality might be clinical useful for not only predicting surgical mortality but also OS after gastrectomy in elderGC.


# Background

Japan has been one of the fastest aging society in the world [1], and surgical strategies for elderly patients have been emerging issue of geriatric medicine. Gastric cancer is the second most common of all cancers in Japan, against the background of the aging society, the number of elderly patients with gastric cancer (elderGC) has been increasing. [2] The most effective treatment for gastric cancer is radical gastrectomy with lymph node dissection. [3] Most of elderly patients, however, were associated with reduced physiological functions, which sometimes constitute an obstacle to safe surgical treatments. [4] Postoperative complications occur more frequently in such elderly patients, and result in occasionally fatal. [4, 5] Therefore, indication for surgical treatment should be evaluated comprehensively based on a balance between radicality, safety and appropriateness of the treatment for elderly patients. Various studies have been performed to predict the prognosis after gastrectomy for elderGC. However almost all of studies have reported prognostic factors mainly in terms of avoiding recurrences, in which reviewed clinicopathological factors in the same manner as in non-elderly patients. [6, 7]

Recently, some clinical database consisting of surgical big data provide surgery-related risk calculators for mortality and morbidities. [8, 9] In Japan, registration of web-based National Clinical Database (NCD)

began in 2011. Clinicopathological information, surgical results, postoperative complication, and surgery-related death have been registered via the web-based entry system, and over 4 billion cases from more than 4,100 facilities were registered over a 3-year period. [10] NCD data has been considered the most reliable baseline data that reflects common surgical practices in Japan. As a real-time feedback system on the web, the NCD Risk Calculator (NRC) provides predictive risks of mortality and several main morbidities by registering preoperative clinical data of each patients in eight major surgical procedures, including total gastrectomy [11] and distal gastrectomy [12].

The operative mortality calculated by the NRC (NRC-mortality) have been widely used to assess the safety of surgical treatment in clinical practice. In this study, we aimed to investigate clinical significance of NRC-mortality during long-term follow-up after gastrectomy for elderGC on the assumption that the NRC-mortality should reflect general condition of each patient.

## Methods

# Patients

Ninety-eight patients aged 80 or over with gastric cancer were underwent gastrectomy at University of Yamanashi hospital between 2001 and 2014. Seven patients with remnant gastric cancer, 14 patients with R1 or R2 resection, and 4 patients who lost during follow-up were excluded from this study. Finally, these 73 elderGC after gastrectomy were enrolled, and reviewed clinicopathologically from their medical records in this study. Their surgical risk was evaluated based on the NRC-mortality

Several clinicopathological factors were selected and analyzed as possible prognostic factors for elderGC after gastrectomy. The factors included patient-related one such as gender, performance status of Eastern Cooperative Oncology Group (PS), Glasgow prognostic score (GPS), Onodera's Prognostic nutritional index (PNI) [13], neutrophil-lymphocyte ratio (NLR) and NRC-mortality. All these factors were calculated at the time of admission for surgery

On the other hand, tumor-related factor was pathological stage of gastric cancer (pStage) and surgery-related were surgical procedure, lymph node dissection, operative time, blood loss, and post-operative complications defined by Clavien-Dindo grade 2 or more.

The clinicopathological findings was classified based on the UICC TNM classification 8th edition [14]. Lymph node dissection was performed in principal according to the gastric cancer treatment guidelines of Japanese Gastric Cancer Association [15]. Patient prognosis was assessed for each factor by overall survival (OS) and disease-specific survival (DSS) from the date of surgery. The observation period for this study was up to 5 years after surgery.

All procedures carried out in this study were in accordance with the ethical standards of the institutional and national responsible committee on human experimentation, and the Helsinki Declaration of 1964 and

its later amendments or equivalents. This study was approved by the University of Yamanashi faculty of Medicine Ethics Committee.

# Statistical analysis

All statistical analysis was carried out using the statistical computing software R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Survival curves were estimated using the Kaplan-Meier method and statistical analysis was performing using the log-rank test. The Cox proportional hazard model was used to calculate hazard ratios for OS and DSS, respectively. Statistically significant was set at $p < 0.05$.

# Results

The patient's characteristics was shown in Table 1. Total gastrectomy was performed in 28 patients and distal gastrectomy was performed in 45 patients. Laparoscopic surgery was performed in 11 patients. Twenty-two patients developed postoperative complications. Of these, pneumonia was the most common in 5 patients, followed by anastomotic leakage in 4 patients. Recurrences were observed in 15 patients, of which 7 developed liver metastasis. Thirty-three patients died during follow-up period of 5 years after surgery, of which 13 from gastric cancer and 20 from other diseases. There were two surgery-related deaths within 90 days after surgery.

Table 1 Patients characteristics

| | n=73 |
|---|---|
| Age (years) | 82 (80-95) |
| Gender (male/female) | 45/28 |
| ECOG PS (0/1/2/3) | 16/39/17/1 |
| Glasgow prognostic score (0/1/2) | 51/16/6 |
| Prognostic nutritional index | 44.2 (31.0-59.0) |
| Neutrophil lymphocyte rate (%) | 2.15 (0.70-13.35) |
| NRC-mortality (%) | 1.7 (0.5-10.6) |
| pT (1a/1b/2/3/4a/4b) | 13/29/9/8/12/2 |
| pN (0/1/2/3a) | 40/17/12/4 |
| pStage (IA/IB/IIA/IIB/IIIA/IIIB) | 32/15/5/3/12/6 |
| Surgical procedure (total gastrectomy/distal gastrectomy) | 28/45 |
| Surgical approach (open/laparoscopic) | 62/11 |
| Lymphadenectomy (<D2/D2) | 49/24 |
| Operative time (min) | 241 (88-800) |
| Blood loss (ml) | 351 (28-3257) |
| Post-operative complications* (presence/absence) | 22/51 |
| ECOG PS: Eastern Cooperative Oncology Group Performance Status, NRC-mortality : The operative mortality calculated by the National Clinical Database risk calculator, *Clavien-Dindo grade 2 or more | |

NRC-mortality ranged 0.5 to 10.6%, and median value was 1.7%. 38 patients above median NRC-mortality were classified as high-mortality group, whereas 35 patients were classified as low-mortality group. Figure 1 shows survival curves of each groups classified by the median NRC-mortality. The high-mortality group had a significantly poor prognosis in OS, but there was no difference between the two groups in DSS.

In the analysis of Cox proportional hazard model, univariate analysis showed that PS, PNI, NLR, surgical procedure and post-operative complication were significantly correlated with OS as well as NRC-mortality. Multivariate analysis showed that NLR, NRC-mortality and surgical procedure were independent prognostic factors in OS (Table 2). In contrast, PS, NRC-mortality and pStage were significantly correlated with DSS in the univariate analysis. Multivariate analysis, however, showed that PS and pStage were independent prognostic factors in DSS, but not NRC-mortality (Table 3).

Table 2 Survival analysis of variables predicting prognostic factors for overall survival in elderly patients with gastric cancer after gastrectomy

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Variable | HR | 95%CI | p-value | HR | 95%CI | p-value |
| Gender (male) | 1.613 | 0.768-3.391 | 0.207 | | | |
| ECOG PS (≧2) | 4.727 | 2.356-9.485 | <0.001 | 1.922 | 0.747-4.945 | 0.176 |
| Glasgow prognostic score (≧1) | 1.599 | 0.786-3.255 | 0.195 | | | |
| Prognostic nutritional index | 0.938 | 0.888-0.991 | 0.023 | 1.003 | 0.936-1.075 | 0.926 |
| Neutrophil lymphocyte rate | 1.253 | 1.064-1.475 | 0.007 | 1.292 | 1.025-1.628 | 0.03 |
| NRC-mortality | 1.336 | 1.195-1.494 | <0.001 | 1.266 | 1.093-1.466 | 0.002 |
| pStage (≧II) | 1.976 | 0.994-3.926 | 0.052 | | | |
| Surgical procedure (total gastrectomy) | 2.509 | 1.259-4.997 | 0.009 | 2.545 | 1.222-5.303 | 0.013 |
| Lymphadenectomy (<D2) | 1.414 | 0.657-3.043 | 0.376 | | | |
| Operative time | 1 | 0.996-1.003 | 0.734 | | | |
| Blood loss | 1 | 0.999-1.001 | 0.997 | | | |
| Post-operative complications* (presence) | 2.034 | 1.010-4.093 | 0.047 | 1.224 | 0.555-2.699 | 0.617 |

ECOG PS: Eastern Cooperative Oncology Group Performance Status, NRC-mortality: The operative mortality calculated by the National Clinical Database risk calculator, *Clavien-Dindo grade 2 or more, HR: Hazard ratio

Table 3 Survival analysis of variables predicting prognostic factors for disease specific survival in elderly patients with gastric cancer after gastrectomy

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Variable | HR | 95%CI | p-value | HR | 95%CI | p-value |
| Gender (male) | 0.831 | 0.279-2.473 | 0.739 | | | |
| ECOG PS (≧2) | 3.73 | 1.203-11.57 | 0.023 | 7.978 | 1.633-38.97 | 0.01 |
| Glasgow prognostic score (≧1) | 2.428 | 0.815-7.24 | 0.111 | | | |
| Prognostic nutritional index | 0.927 | 0.850-1.012 | 0.089 | | | |
| Neutrophil lymphocyte rate | 1.285 | 0.977-1.69 | 0.073 | | | |
| NRC-mortality | 1.272 | 1.039-1.558 | 0.02 | 1.038 | 0.794-1.357 | 0.785 |
| pStage (≧II) | 5.464 | 1.679-17.78 | 0.005 | 9.375 | 2.202-39.92 | 0.002 |
| Surgical procedure (total gastrectomy) | 1.865 | 0.623-5.583 | 0.265 | | | |
| Lymphadenectomy (<D2) | 0.623 | 0.209-1.854 | 0.395 | | | |
| Operative time | 1 | 0.991-1.003 | 0.324 | | | |
| Blood loss | 1 | 0.998-1.001 | 0.696 | | | |
| Post-operative complications* (presence) | 2.744 | 0.921-8.178 | 0.07 | | | |

ECOG PS: Eastern Cooperative Oncology Group Performance Status, NRC-mortality: The operative mortality calculated by the National Clinical Database risk calculator, *Clavien-Dindo grade 2 or more, HR: Hazard ratio

# Discussion

Surgical resection for elderly patients is accompanied with significant perioperative mortality and frequent various postoperative complications. [4, 5] In addition, their life expectancy is limited in comparison with those of young patients, therefore indication of surgical treatment should be discussed comprehensively based on various patients'- and tumors'-related factors. In this study, 20 patients (27%)

died from other diseases except for gastric cancer during follow-up period up to 5 years after gastrectomy. This is indispensable result, and OS including deaths from diseases other than gastric cancer should be considered as important as DSS in elderly patients, contrary to young patients.

Previous reports have identified gender [16, 17], surgical procedure [4, 7], PNI [7, 18] and postoperative complications [7, 17], as predictors of OS for elderGC after gastrectomy. In our study, NLR and NRC-mortality were found to be independent predictors of OS in addition to surgical procedure. Concerning surgical procedure, total gastrectomy sometimes results in malnutrition [19] and also cause aspiration pneumonia especially [20] in elderly patients. Given these insights, it may be better to avoid total gastrectomy for elderGC. Preoperative high NLR has been reported to be correlated with poor prognosis in previous reports [21–23], which are consistent with our result in this study for elderly patients. On the other hand, postoperative complication has been recognized as reliable prognostic factor after curative resection with various cancers including gastric cancers. [7, 17, 24–26] Recent our analysis demonstrated possible correlation between the adverse prognostic effect and immune status of patients, and the immune compromise of elderly patients might affect our current finding. [27]

NRC is originally a tool for prediction surgical morbidity and short-term surgical mortality. [10] The NRC-mortality is calculated based on logistic analysis from NCD big data, in which surgery-related deaths are registered from various causes including deaths due to complications, worsening of comorbidities and sudden deaths of unknown cause. We found that the NRC-mortality predicted not only the short-term mortality rate also the long-term outcomes of elderGC after gastrectomy in this study. In elderGC after gastrectomy, the perioperative mortality risk might correlate with risks of deaths due to worsening of comorbidities and sudden deaths not only perioperative-phase but also late-phase after gastrectomy, and consequently might related OS in this analysis.

POSSUM [28] and E-PASS [29] are also well-known prognostic scoring systems based on statistical analysis based on actual surgical data. Both scoring systems, however, provide the comprehensive prognostic assessment only after surgery and are not suitable for predicting an accurate surgical risk assessment prior to surgery. Moreover, the E-PASS scoring system shows that postoperative complications mainly depend on the surgical stress score, which is the actual surgical invasive outcome score. [29] In that sense, the NRC-mortality rate should be an ideal predictor for perioperative risk assessment, short- and long-term outcomes compared with POSSUM and E-PASS. The POSSUM scoring system is known to deviate from the risk assessment from the actual results of a limited group, such as low-risk case and the elderly patients. [30, 31] It has been reported that assessments with these scoring systems do not reflect the prognosis of elderly patients. [16]

There are some limitations in this study. First, this study is small-scale with a single institution. Second, this cohort included only small number of patients who underwent laparoscopic gastrectomy, which may affect long-term outcome in elderly patients due to the less invasiveness. Further multi-institutional analyses with large number of patients who underwent open and laparoscopic gastrectomy should be conducted to confirm the clinical usefulness of this predictor.

In conclusion, the NRC-mortality, as well as surgical procedure and NLR value, might be clinical useful for not only predicting surgical mortality but also OS after gastrectomy in elderGC.

## List Of Abbreviations

elderGC: elderly patients with gastric cancer

NCD: National Clinical Database

NRC: National Clinical Database risk calculator

NRC-mortality: operative mortality calculated by the National Clinical Database risk calculator

PS: performance status of Eastern Cooperative Oncology Group

GPS: Glasgow prognostic score

PNI: Onodera's Prognostic nutritional index

NLR: neutrophil-lymphocyte ratio

pStage: pathological stage of gastric cancer

OS: overall survival

DSS: disease specific survival

## Declarations

# Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients for being included in the study.

This article does not contain any studies with human or animal subjects performed by any of the authors.

# Consent for publication

This manuscript is not applicable because it does not contain personal data.

# Availability of data and materials

This manuscript is not applicable.

# Competing interest

All authors had no potential conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

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# Author's contributions

Hidenori Akaike conducted majority of experiments and wrote the manuscript. Yoshihiko Kawaguchi and Daisuke Ichikawa designed the research and helped to draft the manuscript. All other authors contributed to collection and interpretation of the data and reviewed the manuscript critically.

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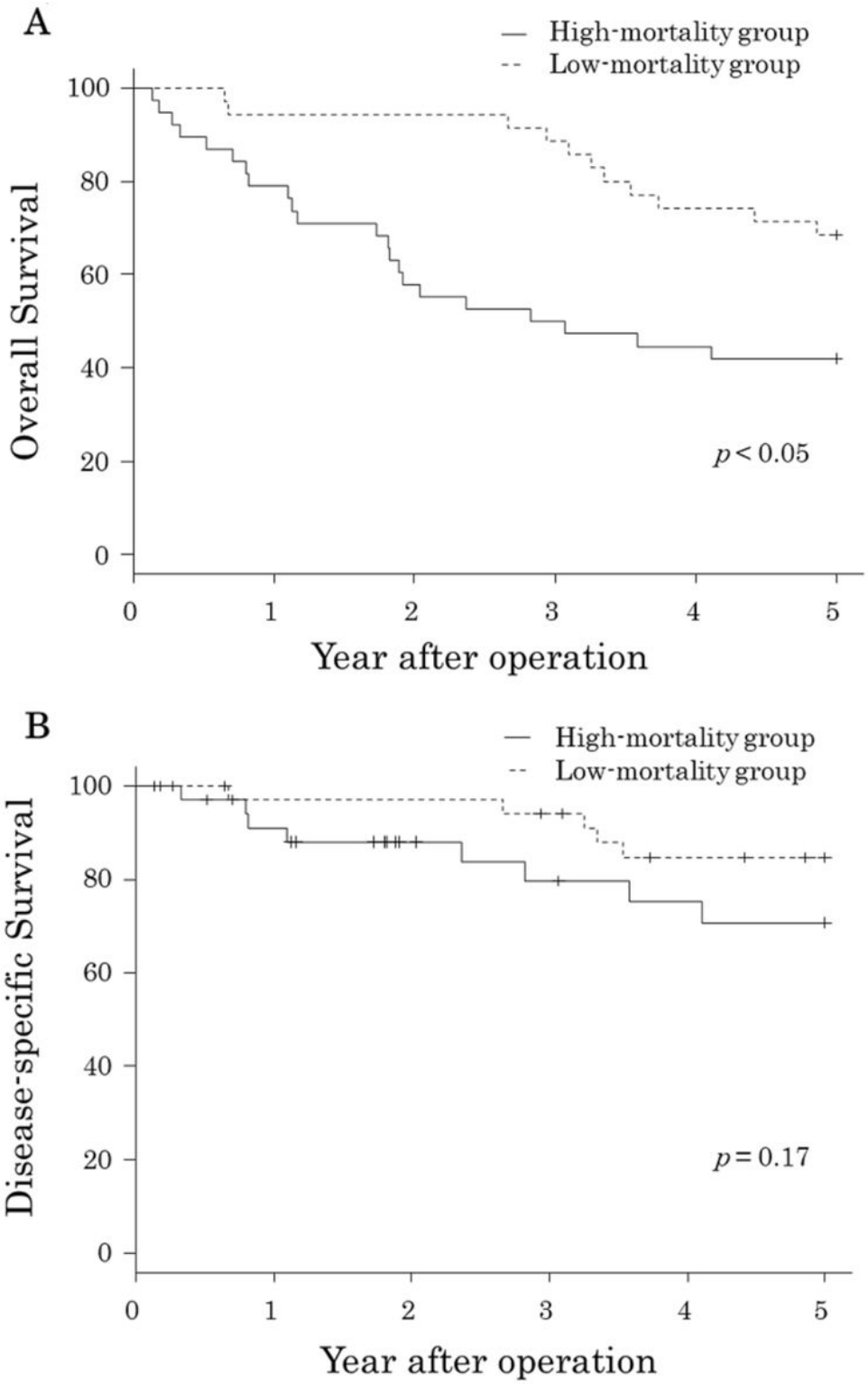
# Figures




## Figure 1

Survival curves of elderly patient with gastric cancer after gastrectomy between the groups classified by operative mortality calculated using National Clinical Database risk calculator. A: Overall survival, B: Disease specific survival