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*World J Gastrointest Surg* 2019 May 27; 11(5): 247-278



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Jie Wang*

Proofing Editorial Office Director: *Jin-Lei Wang*

**NAME OF JOURNAL**

*World Journal of Gastrointestinal Surgery*

**ISSN**

ISSN 1948-9366 (online)

**LAUNCH DATE**

November 30, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Varut Lohsirawat, Shu-You Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

**EDITORIAL OFFICE**

Jin-Lei Wang, Director

**PUBLICATION DATE**

May 27, 2019

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**ARTICLE PROCESSING CHARGE**

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**ONLINE SUBMISSION**

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## Retrospective Cohort Study

**Prediction of overall survival following colorectal cancer surgery in elderly patients**

Isaac Seow-En, Winson Jianhong Tan, Sreemanees Raaj Dorajoo, Sharon Hui Ling Soh, Yi Chye Law, Soo Yeun Park, Gyu-Seok Choi, Wah Siew Tan, Choong Leong Tang, Min Hoe Chew

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**Author contributions:** Chew MH conceived the research and study design; Seow-En I, Dorajoo SR, Soh SHL, Law YC and Park SY contributed to data acquisition and analysis; Seow-En I, Tan WJ, Dorajoo SR and Park SY were involved in interpretation of data and writing of the manuscript; Tan WJ, Choi GS, Tan WS, Tang CL and Chew MH contributed to editing and revision of the article; all authors read and approved the final manuscript.

**Institutional review board**

**statement:** The study was reviewed and approved by the SingHealth Institutional Review Board.

**Informed consent statement:**

Informed consent was not required for this retrospective study and all details that might disclose the identity of the subjects under study was omitted or anonymized.

**Conflict-of-interest statement:** All authors declare no conflict-of-

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**Abstract****BACKGROUND**

With advanced age and chronic illness, the life expectancy of a patient with colorectal cancer (CRC) becomes less dependent on the malignant disease and more on their pre-morbid condition. Justifying major surgery for these elderly patients can be challenging. An accurate tool demonstrating post-operative survival probability would be useful for surgeons and their patients.

**AIM**

To integrate clinically significant prognostic factors relevant to elective colorectal surgery in the elderly into a validated pre-operative scoring system.

**METHODS**

In this retrospective cohort study, patients aged 70 and above who underwent surgery for CRC at Singapore General Hospital between 1 January 2005 and 31 December 2012 were identified from a prospectively maintained database. Patients with evidence of metastatic disease, and those who underwent emergency surgery or had surgery for benign colorectal conditions were

interest.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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**Manuscript source:** Unsolicited manuscript

**Received:** April 1, 2019

**Peer-review started:** April 2, 2019

**First decision:** April 20, 2019

**Revised:** May 9, 2019

**Accepted:** May 23, 2019

**Article in press:** May 23, 2019

**Published online:** May 27, 2019

**P-Reviewer:** M'Koma AE, Uhlmann D

**S-Editor:** Ji FF

**L-Editor:** A

**E-Editor:** Wang J



excluded from the analysis. The primary outcome was overall 3-year overall survival (OS) following surgery. A multivariate model predicting survival was derived and validated against an equivalent external surgical cohort from Kyungpook National University Chilgok Hospital, South Korea. Statistical analyses were performed using Stata/MP Version 15.1.

## RESULTS

A total of 1267 patients were identified for analysis. The median post-operative length of stay was 8 [interquartile range (IQR) 6-12] d and median follow-up duration was 47 (IQR 19-75) mo. Median OS was 78 (IQR 65-85) mo. Following multivariate analysis, the factors significant for predicting overall mortality were serum albumin < 35 g/dL, serum carcinoembryonic antigen  $\geq 20$   $\mu\text{g/L}$ , T stage 3 or 4, moderate tumor cell differentiation or worse, mucinous histology, rectal tumors, and pre-existing chronic obstructive lung disease. Advanced age alone was not found to be significant. The Korean cohort consisted of 910 patients. The Singapore cohort exhibited a poorer OS, likely due to a higher proportion of advanced cancers. Despite the clinicopathologic differences, there was successful validation of the model following recalibration. An interactive online calculator was designed to facilitate post-operative survival prediction, available at [http://bit.ly/sgh\\_crc](http://bit.ly/sgh_crc). The main limitation of the study was selection bias, as patients who had undergone surgery would have tended to be physiologically fitter.

## CONCLUSION

This novel scoring system generates an individualized survival probability following colorectal resection and can assist in the decision-making process. Validation with an external population strengthens the generalizability of this model.

**Key words:** Colorectal cancer surgery; Elderly; Overall survival; Pre-operative prognostic score

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**Core tip:** Ageing results in a decreased functional reserve along with various comorbid diseases. Many elderly patients express age-related concerns when advised for operative intervention. This is the first predictive survival model specific for older patients planned for elective colorectal surgery and provides a visual guide to facilitate the counselling process.

**Citation:** Seow-En I, Tan WJ, Dorajoo SR, Soh SHL, Law YC, Park SY, Choi GS, Tan WS, Tang CL, Chew MH. Prediction of overall survival following colorectal cancer surgery in elderly patients. *World J Gastrointest Surg* 2019; 11(5): 247-260

**URL:** <https://www.wjgnet.com/1948-9366/full/v11/i5/247.htm>

**DOI:** <https://dx.doi.org/10.4240/wjgs.v11.i5.247>

## INTRODUCTION

The world is facing a dramatic increase in the number and proportion of its elderly. Driven by remarkable improvements in life expectancy, the number of people aged 60 years and over is projected to grow from 901 million in 2015 to 1.4 billion in 2030, and more than double that in 2015 to 2.1 billion by 2050<sup>[1]</sup>. Whilst being a product of economic success and advancement in healthcare, an ageing population will suffer more death and disability from illnesses such as heart disease, diabetes, and cancer<sup>[2]</sup>. Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer death globally, accounting for 1.4 million new cases and almost 700 000 deaths in 2012<sup>[3]</sup>. The incidence and mortality rates for CRC increases with age, with 90% of new cases and over 90% of deaths occurring at 50 years and beyond<sup>[4]</sup>. This raises genuine concern that CRC will result in a greater burden on healthcare with the shift towards an older demographic.

The normal physiological process of ageing reduces functional capacity and

reserve, leading to a decreased ability to mount an adequate response to stress and resulting in a worse outcome should post-operative complications arise. Another problem is the increasing number and severity of comorbidities with age which may impact patient tolerance of anesthesia. With advanced age and chronic illness, the decision to undergo major surgery in the elderly patient can be challenging. Not infrequently, patients and their family members decline operative intervention due to age-related concerns. Even to the surgeon, the benefit of resection in certain individuals may not be so clear-cut. Moreover, the elderly are under-represented and under-prioritized in randomized trials<sup>[5]</sup>, resulting in difficulty in generalizing existing data. Many clinicians now recognize that surgery in the elderly is different in terms of risks and meaningful outcomes<sup>[6]</sup>.

We aimed to analyze our outcomes following major elective colorectal surgery in the elderly to determine factors significantly influencing mortality. A pre-operative scoring system predicting post-operative outcomes more objectively could then be derived, facilitating the decision-making process for both surgeons and patients.

## MATERIALS AND METHODS

Data for all patients aged 70 and above who underwent elective surgery for non-metastatic CRC at Singapore General Hospital (SGH) Department of Colorectal Surgery from 1 January 2005 to 31 December 2012 were obtained from hospital electronic records. Patients with evidence of distant disease, those who underwent emergency surgery or had surgery for benign colorectal conditions were excluded from the analysis. Instances of surgery for CRC recurrence occurring in the same patient over the study period were also excluded. Information for an equivalent group of elderly patients electively operated on at Kyungpook National University Chilgok Hospital (KNUCH), Daegu, South Korea, was retrieved over the same duration.

### Statistical analysis

Missing data were filled using multiple imputation, performed via sequential imputation using chained equations with predictive mean matching. The variable with the highest proportion of missing values in the model derivation dataset was 11.5%. All variables, apart from the variable being imputed, were included in the imputation model to avoid bias. A total of 100 imputations were performed. To simplify the eventual prognostic scoring, the “minimum *P* value approach” was adopted to detect appropriate cut points for continuous variables<sup>[7,8]</sup>. Cut point selection was guided by upper and lower limits of normal laboratory values and an attempt was made to keep cut points to the nearest whole number, tens or fives to facilitate clinical ease of use. As Cox models do not provide a straightforward estimation of the baseline survival function required for predicting absolute survival probabilities, a flexible parametric model [Royston-Parmer (RP)] was constructed instead with all-cause mortality as the outcome<sup>[9]</sup>. All outcomes were truncated at three years from the time of surgery and patients who had not died were censored at three years. All independent variables were included in the multivariate regression and backward elimination was used to remove variables with *P* values greater than or equal to 0.05 until all the remaining variables had *P* values of < 0.05. A survival score was calculated for all patients using the final RP model’s beta coefficients. Patients were stratified by survival score and categorized into three arbitrary prognostic groups, defined using the 20<sup>th</sup> and 80<sup>th</sup> percentiles of the survival score. The observed survival profiles of the three prognostic groups were assessed using the Kaplan-Meier estimator and compared using the log-rank test. Calibration was evaluated by visually inspecting the agreement between observed and predicted 3-year survival by superimposing predicted survival profiles over the Kaplan-Meier curves.

### External validation

The final RP model derived on the cohort from SGH to predict 3-year post-operative survival was applied on the group of patients from KNUCH. Discrimination and calibration were evaluated as previously described. Where evidence of model miscalibration was observed, recalibration was performed by fitting an RP model to the validation data using the linear predictor of the existing model on the log relative hazard scale. All statistical analyses were performed using Stata/MP Version 15.1 (College Station, TX, United States) and R Version 3.3.4 ([www.r-project.org](http://www.r-project.org)).

### Model productization

An online calculator was developed from our model to predict three-year survival profiles. The interactive calculator, generated *via* <https://www.shinyapps.io/>,

facilitates individualized point-of-care survival probability and aids the visualisation of the predicted survival probability profile over time, given the unique combination of risk factors present<sup>[10]</sup>. The study protocol has been approved by the SingHealth Institutional Review Board (CIRB Ref No. 2015/2374).

## RESULTS

A total of 1643 elective colorectal resections were performed for 1623 patients aged 70 and above over the study duration. One hundred and eighty-seven patients who underwent surgery for non-malignant conditions and 169 patients known to have distant metastasis at the time of surgery were excluded from the analysis. Twenty instances of repeat surgery for cancer recurrence performed for the same patient during the study period were also excluded. Analysis of 1267 resections for colorectal malignancy was performed. Clinical characteristics are shown in [Table 1](#).

Outcome measures used were the 30-d post-operative complication rate, classified according to the Clavien-Dindo tool, and overall survival (OS). Complication details are summarized in [Table 2](#). While just under one-quarter of patients experienced early complications, high grade complications of Clavien-Dindo III or higher only occurred in 82 patients (6.5%). These included 30 deaths within the initial 30 post-operative days; 21 were secondary to cardiorespiratory complications, eight were attributable to anastomotic leaks and the remaining one was due to a cerebrovascular accident.

The median post-operative length of stay was 8 (IQR 6-12) and median follow-up duration was 47 (IQR 19-75) mo. Median OS was 78 (IQR 65-85) mo. Of 670 deaths occurring within the follow-up period, 339 were attributable to CRC (51%), while 331 (49%) died of other causes. Disease recurrence occurred in 276 (22%), with a median time from surgery to recurrence of 13 (IQR 7-23) mo. Most cancer recurrences presented at distant locations only (65%), while locoregional recurrence without distant metastasis occurred in 30 patients (11%). Disease relapse in both local and distant organs accounted for a quarter of all recurrences (24%).

Univariate analysis of all suitable pre-operative variables is shown in [Table 3](#). The final multivariate model for predicting OS is provided in [Table 4](#) with the resultant survival curves generated from this model in [Figure 1](#). The model stratifies OS reasonably well in terms of discrimination (separation of the three risk category curves) and calibration (agreement between observed and predicted survival curves for each risk category).

Baseline characteristics of patients from the Singapore and the Korean cohorts are compared head-to-head in [Table 5](#). The SGH and KNUCH cohorts differ considerably in terms of survival, with the 80<sup>th</sup> percentile surviving 18 mo *vs* 85 mo respectively ([Figure 2](#)). Applying the model developed from the SGH cohort to stratify patients in the KNUCH dataset expectedly revealed model miscalibration. However, relative separation between the observed survival curves of patients in the three risk categories showed acceptable model discrimination ([Figure 3](#)). Model recalibration improved the agreement between the observed and predicted survival curves ([Figure 4](#)).

### **Interactive online calculators**

Following successful external validation, the model was productized as an interactive online calculator, available at [http://bit.ly/sgh\\_crc](http://bit.ly/sgh_crc).

## DISCUSSION

One of the biggest challenges in healthcare is coping with an ageing population. In Singapore, the proportion of over 65-year-old has doubled from 6.0% in 1990 to 11.8% in 2015. With an annual increase of 0.5%-0.7% per year, this figure is expected to reach 20%-25% of the population by 2030. Life expectancy at birth in 2015 was 82.9 years (males 80.5 years, females 85.1 years), with the old age-dependency ratio climbing steadily to reach 16.2 per 100 residents (aged 15 to 64 years old)<sup>[11]</sup>. This census highlights not only the increasing proportion of the elderly but the potential strain on the rest of the working population. A similar trend can be observed in many developed nations worldwide.

In 2000, the Colorectal Cancer Collaborative Group published a systemic review of 28 studies consisting of more than 34000 patients, looking at outcomes post-colorectal surgery<sup>[12]</sup>. Patients were stratified by age group; less than 65 years, 65-74 years, 75-84 years, and above 84 years. The median post-operative mortality rates across these age groups were 3.0%, 6.4%, 8.6%, and 19.4% respectively. Median anastomotic leak rates

**Table 1 Patient, surgery, and disease characteristics**

Variable	SGH cohort (n = 1267)
Age, median (range), yr	77 (70-102)
Gender	
Male	658 (51.9)
Female	609 (48.1)
Race	
Chinese	1148 (90.6)
Malay	50 (4.0)
Indian	30 (2.4)
Others	39 (3.1)
ECOG status	
0 (asymptomatic)	751 (59.3)
1	401 (31.6)
2	85 (6.7)
3	23 (1.8)
4 (bedbound)	7 (0.2)
ASA score	
1	178 (14.0)
2	857 (67.6)
3	225 (17.8)
4	7 (0.6)
Tumor site	
Colon	790 (62.3)
Rectum	477 (37.6)
Surgical approach	
Open	888 (70.1)
Laparoscopic	379 (29.9)
Surgery	
High Anterior resection	505 (40.0)
Low Anterior resection	163 (12.9)
Ultra-Low Anterior resection	150 (11.8)
Right Hemicolectomy	286 (22.6)
Abdominoperineal resection	58 (4.6)
Others	105 (8.3)
TMN stage <sup>a</sup>	
1	240 (18.9)
2	416 (32.8)
3	442 (34.9)
Tumor diameter, median (IQR), cm	4.5 (3-6)
Number of lymph nodes harvested, median (IQR)	15 (11-20)
Neoadjuvant therapy	22 (1.8)
Adjuvant therapy	219 (17.6)

<sup>a</sup>American Joint Committee on Cancer Staging, 7<sup>th</sup> edition. All values are reported as n (%) unless otherwise stated. ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; IQR: Interquartile range; SGH: Singapore General Hospital.

were 4.0%, 5.0%, 4.0% and 3.0% respectively. The data does suggest that good surgical outcomes can be achieved in the elderly, but individualized evaluation of treatment goals and communication of realistic anticipated outcomes are essential<sup>[13]</sup>.

Several risk stratification systems have been developed. Established scoring methods such as the American Society of Anesthesiologists score and Charlson Comorbidity Index are commonly used but have well described flaws; the former is too subjective with little specificity, and the latter was not designed to predict peri-operative risks in surgical patients. Colorectal surgery-specific scoring, such as the

**Table 2** 30-d post-operative complications *n* (%)

	SGH cohort ( <i>n</i> = 1267)
Overall 30-d complications	297 (23.4)
Clavien-Dindo classification	
I	75 (5.9)
II	140 (11.0)
III	21 (1.7)
IV	31 (2.4)
V (death)	30 (2.4)
Type of complication	
Cardiac/CVA	97 (7.7)
Respiratory	28 (2.2)
Urinary	24 (1.9)
Wound/stoma	55 (4.3)
Anastomotic leak	16 (1.3)
Others	77 (6.1)

SGH: Singapore General Hospital; CVA: Cerebrovascular accident.

ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (Cr-POSSUM) and the Association of Coloproctology of Great Britain and Ireland scoring systems are validated as accurate predictors of 30-d post-operative mortality<sup>[14]</sup>, but contain intraoperative or tumor staging parameters, which limit their use as a pre-operative optimization or counselling tool. This motivated us to develop a prognostic assessment tool to quantify the risk of mortality and predict survival after surgery in the elderly.

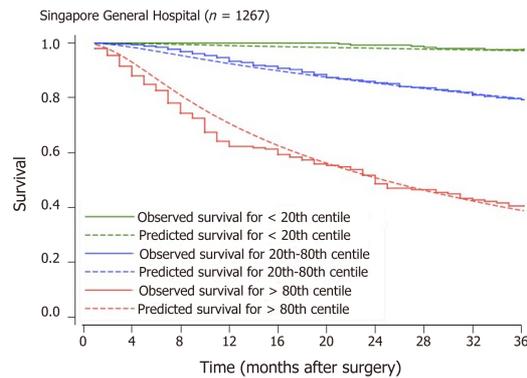
In the Singapore cohort, the rates of anastomotic leak, 30-d morbidity and 30-d mortality were 1.3%, 23.4% and 2.4% respectively. These outcomes are comparable to existing data on the elderly published during the past 10 years, with reported anastomotic leak rates ranging from 0.8%-5.9%, 30-d complications rates 17%-38% and 30-d mortality rates 0%-16%<sup>[15-22]</sup>.

Only the OS prediction model was selected for validation with the external cohort, for several reasons. High grade morbidity of Clavien-Dindo grade III or IV accounted for less than one-fifth of the overall complications arising within 30 d. This limited the clinical applicability of a model predicting early clinically-relevant morbidity due to the small number of events. Moreover, the main causes of post-operative morbidity in elderly patients are known to be cardiovascular or pulmonary in nature<sup>[12,22]</sup>, each of which already have existing specific risk assessment tools<sup>[23,24]</sup>. Compared to OS, predicting disease-free survival may also not be as practical to the geriatric patient with several life expectancy-limiting illnesses. Cancer-specific survival in the elderly has previously already been shown to be similar to that of the younger age group<sup>[12]</sup>. In the multivariate model, factors significant for predicting 3-year all-cause mortality were serum albumin < 35 g/dL, serum carcinoembryonic antigen ≥ 20 µg/L, T stage 3 or 4, tumor cell differentiation of moderate or worse, mucinous histology, rectal tumors, and the presence of existing chronic obstructive lung disease (COPD). As the model was intended to serve as a pre-operative patient counselling tool, intra-operative findings and information only available following final histopathological examination of the resected specimen were not included in the analysis.

Determination of the local stage of colorectal cancer can be difficult before surgery. A recent meta-analysis of 13 studies showed that computed tomography had good overall sensitivity of 90% at differentiating T1-T2 from T3-T4 colonic tumors<sup>[25]</sup>, although a lower specificity estimate of 69% likely stemmed from radiologists interpreting benign pericolic desmoplastic reaction as tumor invasion to reduce the risk of understaging. Nodal stage prediction pre-operatively is even less precise and this was therefore not included in the univariate analysis.

Of all comorbidities analyzed (Table 3), only COPD remained significant for poorer OS on multivariate analysis. While COPD is known to confer a higher risk of early morbidity and mortality following abdominal surgery<sup>[26]</sup>, longer term survival may be adversely influenced by associated pulmonary hypertension as well as the extra-pulmonary inflammatory effects of the disease<sup>[27]</sup>. Active smoking per se did not prove significant on univariate analysis.

Interestingly, age did not significantly influence OS on multivariate analysis, unlike



**Figure 1** Observed survival probabilities of patients in the three risk score categories compared against model-based predicted probabilities for each group.  $P$  value < 0.001 for separation of Kaplan-Meier survival curves (solid lines).

in previous studies<sup>[12,22]</sup>. This demonstrates that advanced age alone without the presence of other predictors will not necessarily lead to a poorer outcome and should not be a contraindication to major resection.

The Singapore and Korean cohorts were similar in terms of patient age, cancer location and tumor differentiation. Disparity in survival between the populations was likely a result of a larger distribution of advanced cancers in the Singapore group; 18.2% *vs* 11.5% had T4 tumors, and 19.1% *vs* 10.9% had N2 disease. Median pre-operative CEA levels were also significantly higher in the SGH cohort (4.3  $\mu\text{g/L}$  *vs* 2.4  $\mu\text{g/L}$ ). This may reflect a trend of elderly patients presenting later in the disease process in the Singapore population compared to Korean. The advent of national healthcare electronic records implemented in Singapore may also mean that mortality events are more readily captured even if they had discontinued follow-up at our institution.

Despite the differences in OS between the Singapore and Korea cohorts, observably distinct separation between survival curves was displayed when the Singapore model was applied to the external population (Figure 3). This suggests discriminatory capacity of the predictors for revealing relative survival differences amongst elderly patients who had undergone surgery for CRC. In absolute terms, however, the predicted survival probabilities generated did not match the observed survival profile of the external validation cohort and appeared miscalibrated. Regressing the original scores on observed survival in the external cohort allowed for the identification of an appropriate correction factor (beta coefficient). This was used to recalibrate the original scores following which successful validation was evident in the improved agreement between the observed and predicted survival curves (Figure 4).

Our study was subject to the limitations and bias inherent in observational retrospective research. The most important limitation was selection bias. Elderly patients who had already undergone elective surgery would have tended to be physiologically fitter based on traditional methods of patient evaluation. While it would have been ideal to compare our cohort with cancer patients who had not had surgery over the study duration, this information was unavailable. Measures of patient frailty or function, *e.g.*, hand grip strength or ambulatory distance, while increasingly recognized as predictors of surgical morbidity and mortality in the elderly<sup>[28]</sup>, was neither consistently recorded during the study duration nor has any part of current practice at our institution. The dissimilarity in survival between the cohorts may reflect the shortcomings of comparison between the populations of two distinct geographical locations, but eventual validation of the model notwithstanding these variations can be considered a strength. To ensure predictive accuracy of the model, further validation including re-identification of a correction factor with possible recalibration should be undertaken before use in separate populations.

In conclusion, while clinical decision-making for elderly patients with CRC can be challenging, advanced age *per se* is not a risk factor for poorer survival outcomes and patients should not be denied surgery based on age alone. However, there is a need for more objective pre-operative risk stratification in this vulnerable group of patients. Our novel scoring system predicting mortality following major resection uses parameters which are available before the surgery and can assist in the counselling and decision-making process between surgeons, their patients and families. Validation with an external Asian population strengthens the generalizability of this scoring method, although further validation may be necessary prior to adoption in

**Table 3 Unadjusted hazard ratios of individual predictors in association with 3-year survival duration obtained via univariate Royston-Parmar regression**

Predictors	n	HR (95%CI)	P value
Gender	1267	1.03 (0.81-1.31)	0.807
Age	1267	1.00 (0.98-1.03)	0.826
Race			
Chinese	1148	1.00 (ref)	
Malay	50	1.14 (0.60-2.14)	0.682
Indian	30	1.43 (0.78-2.68)	0.272
Others	39	0.67 (0.25-1.82)	0.433
Smoking status			
Non-smoker	1055	1.00 (ref)	
Smoker	212	1.07 (0.78-1.47)	0.692
Primary lesion site			
Colon	790	1.00 (ref)	
Rectum	477	1.40 (1.09-1.80)	0.008
Tumor stage			
Tis/T1	97	1.00 (ref)	
T2	188	1.52 (0.31-7.41)	0.605
T3	752	10.8 (2.7-43.1)	0.001
T4a	97	42.9 (10.5-173.5)	< 0.001
T4b	133	37.9 (9.38-153.2)	< 0.001
Tumor grade			
Well differentiated	117	1.00 (ref)	
Moderately differentiated	1009	3.85 (1.82-8.15)	< 0.001
Poorly differentiated or mucinous	141	8.59 (3.90-18.94)	< 0.001
Past medical history			
Diabetes Mellitus	331	1.07 (0.81-1.41)	0.655
Hypertension	416	1.17 (0.91-1.51)	0.217
End stage renal failure	26	1.73 (0.54-5.53)	0.354
Previous myocardial infarction	47	0.95 (0.50-1.81)	0.881
Previous PCI, cardiac surgery or angina	140	1.36 (0.88-2.09)	0.161
Congestive heart failure	41	1.18 (0.52-2.69)	0.698
Peripheral vascular disease	30	1.14 (0.52-2.53)	0.744
Impaired sensorium, e.g., dementia	14	2.77 (0.40-19.2)	0.304
Chronic obstructive pulmonary disease	61	0.44 (0.29-0.68)	< 0.001
Previous stroke or TIA	90	1.08 (0.66-1.76)	0.758
Previous stroke with neurological deficits	38	1.19 (0.53-2.69)	0.675
Dependent functional status	60	0.81 (0.43-1.54)	0.529
ECOG			
0	751	1.00 (ref)	
1	404	0.98 (0.76-1.28)	0.903
2 or more	116	1.13 (0.72-1.79)	0.595
ASA			
1	178	1.00 (ref)	
2	857	0.75 (0.53-1.06)	0.099
3 or more	232	0.78 (0.51-1.19)	0.250
Laboratory parameters			
Serum albumin (g/L)	1119	0.94 (0.92-0.96)	< 0.001
Carcinoembryonic antigen (µg/L)	1196	1.01 (1.00-1.01)	< 0.001
White blood cell count ( $\times 10^9/L$ )	1267	1.11 (1.06-1.15)	< 0.001
Platelet count ( $\times 10^3/L$ )	1267	1.00 (1.00-1.00)	< 0.001
Serum sodium (mmol/L)	1247	0.95 (0.91-0.98)	0.002
Serum creatinine (µmol/L)	1265	1.00 (0.99-1.00)	0.244
Serum potassium (mmol/L)	1263	0.75 (0.56-0.99)	0.049

Serum urea (mmol/L)	1264	0.98 (0.93-1.04)	0.517
Hemoglobin (g/dL)	1243	0.85 (0.79-0.91)	0.002
Lesion size (cm)	1267	2.03 (1.53-2.70)	< 0.001
Dichotomized predictors <sup>a</sup>			
Age ≥ 80 yr	1267	0.92 (0.70-1.21)	0.540
Serum albumin < 35 g/L	1266	2.16 (1.69-2.76)	< 0.001
Carcinoembryonic antigen ≥ 20 µg/L	1247	4.33 (3.39-5.54)	< 0.001
White blood cell count ≥ 8.5 × 10 <sup>9</sup> /L	1265	1.78 (1.40-2.28)	0.001
Platelet count ≥ 450 × 10 <sup>3</sup> /L	1263	2.36 (1.67-3.35)	< 0.001
Serum sodium < 135 mmol/L	1264	1.62 (1.20-2.20)	0.002
Serum creatinine ≥ 135 µmol/L	1243	0.56 (0.31-1.02)	0.057
Serum potassium < 3.5 mmol/L	1267	1.37 (1.01-1.85)	0.043
Serum urea ≥ 7 mmol/L	1267	1.00 (0.71-1.40)	0.999
Hemoglobin < 11 g/dL	1243	1.48 (1.16-1.89)	0.002
Lesion size ≥ 4 cm	1267	2.03 (1.53-2.70)	< 0.001

<sup>a</sup>Corrected *P* values for dichotomized variables due to multiple testing. ECOG: Eastern Cooperative Oncology Group; Ref: Reference; PCI: Percutaneous coronary intervention; TIA: Transient ischemic attack.

differing patient cohorts.

**Table 4** Multivariable model predicting all-cause mortality, truncated at 3 years from time of surgery

Variable	Hazard ratio	2.5 <sup>th</sup> percentile	97.5 <sup>th</sup> percentile	P value
Serum albumin < 35 g/dL	1.41	1.08	1.83	0.011
CEA ≥ 20 µg/L	2.51	1.92	3.28	< 0.001
T stage				
T1/Tis	1.00 (ref)	-	-	-
T2	1.11	0.23	5.41	0.894
T3	6.18	1.55	24.6	0.010
T4	17.9	4.45	72.1	< 0.001
Tumor grade				
Well differentiated	1.00 (ref)	-	-	-
Moderately differentiated	2.24	1.04	4.82	0.040
Poorly differentiated or mucinous	3.54	1.54	8.15	0.003
Rectal lesion	1.47	1.11	1.96	0.007
Chronic obstructive lung disease	1.87	1.11	3.17	0.019

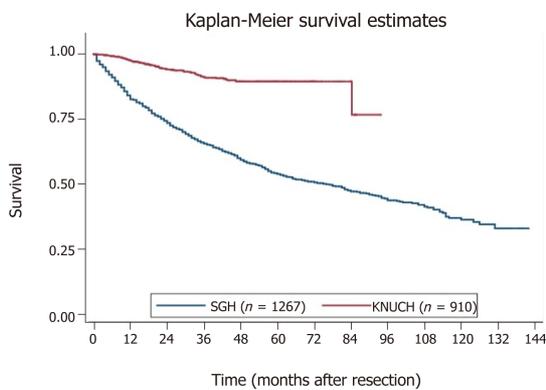
These factors were identified following progressive elimination of non-significant candidate predictors until all predictors retained in the final model had *P* values below 0.05. CEA: Carcinoembryonic antigen; ref: Reference.

**Table 5** Comparison between Singapore General Hospital; and Kyungpook National University Chilgok Hospital cohorts

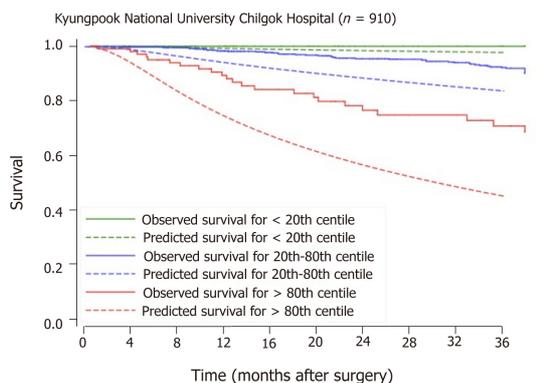
Variable	SGH( <i>n</i> = 1267)		KNUCH( <i>n</i> = 910)	
	<i>n</i>		<i>n</i>	
Age, median (range), yr	1267	77 (70-102)	910	75 (70-96)
Gender				
Male	658	(51.9)	496	(54.5)
Female	609	(48.1)	414	(45.5)
Lesion sites				
Colon	790	(62.3)	540	(59.3)
Rectum	477	(37.6)	370	(40.7)
Tumor grade				
Well differentiated	117	(9.0)	29	(3.2)
Moderately differentiated	1009	(79.6)	809	(88.9)
Poorly differentiated	70	(5.5)	29	(3.2)
Mucinous/signet ring cell	71	(5.6)	43	(4.7)
Laboratory parameters, mean (SD)				
Creatinine, µmol/L	1267	88.9 (54.9)	910	83.8 (38.6)
Urea, mmol/L	1267	5.5 (2.7)	910	2.7 (1.1)
Hemoglobin, g/dL	1267	11.8 (1.8)	910	12.0 (2.1)
WBC count, × 10 <sup>9</sup> /L	1267	7.9 (2.6)	908	8.0 (18.2)
Platelet count, × 10 <sup>9</sup> /L	1267	300.6 (104.6)	910	287.1 (95.3)
Serum albumin, g/L	1119	33.7 (5.5)	910	39.9 (4.6)
CEA, median (IQR), µg/L	1196	4.3 (2.6-14.2)	887	2.4 (1.5-4.8)
Comorbidities				
Diabetes	331	(26.1)	167	(18.4)
Hypertension	416	(32.8)	415	(45.6)
Ischemic heart disease	47	(3.7)	14	(1.5)
Congestive heart failure	41	(3.2)	20	(2.2)
PVD	30	(2.4)	0	(0.0)
COPD	61	(4.8)	66	(7.3)
Previous stroke	90	(7.1)	50	(5.5)
End stage renal disease	26	(2.1)	6	(0.7)
ASA				

1	178	(14.0)	152	(16.7)
2	857	(67.6)	724	(79.6)
3	225	(17.8)	34	(3.7)
4	7	(0.6)	0	(0.0)
<b>T stage<sup>a</sup></b>				
Tis	2	(0.2)	8	(0.9)
T1	95	(7.5)	72	(7.9)
T2	188	(14.8)	134	(14.7)
T3	752	(59.4)	587	(64.5)
T4a	97	(7.7)	76	(8.4)
T4b	133	(10.5)	29	(3.2)
ypCR	0	(0.0)	4	(0.4)
<b>N stage<sup>a</sup></b>				
N0	688	(54.3)	577	(63.4)
N1a	148	(11.7)	124	(13.6)
N1b	185	(14.6)	109	(12.0)
N1c	4	(0.3)	1	(0.1)
N2a	99	(7.8)	58	(6.4)
N2b	143	(11.3)	41	(4.5)
<b>Short term outcomes</b>				
Anastomotic leak	16	(1.3)	44	(4.8)
30-d morbidity	297	(23.4)	212	(23.3)
30-d mortality	30	(2.4)	1	(0.001)

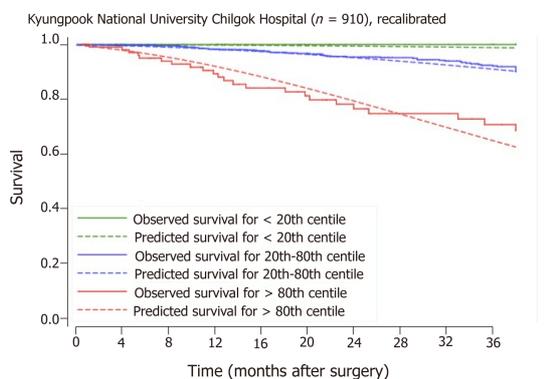
<sup>a</sup>American Joint Committee on Cancer Staging, 7<sup>th</sup> edition. All values are reported as *n* (%) unless otherwise stated. KNUCH: Kyungpook National University Chilgok Hospital; SGH: Singapore General Hospital; WBC: White blood cell; CEA: Carcinoembryonic antigen; PVD: Peripheral vascular disease; COPD: Chronic obstructive pulmonary disease; ASA: American Society of Anesthesiologists; ypCR: Pathological complete response following neoadjuvant therapy.



**Figure 2** Kaplan-Meier overall survival curves of the 2 cohorts. SGH: Singapore General Hospital; KNUCH: Kyungpook National University Chilgok Hospital.



**Figure 3** Observed survival probabilities of patients in the three risk score categories of the validation cohort compared against model-based predicted probabilities for each risk categories.  $P$  value < 0.001 for separation of Kaplan-Meier survival curves (solid lines).



**Figure 4** Recalibrated model applied to the Korean cohort.  $P$  value < 0.001 for separation of Kaplan-Meier survival curves (solid lines).

## ARTICLE HIGHLIGHTS

### Research background

Driven by remarkable improvements in life expectancy, the world is facing a dramatic increase in the number and proportion of its elderly. The incidence and mortality rates for colorectal cancer (CRC) increases with age, resulting in a greater burden on healthcare. Moreover, the life expectancy of an elderly patient with CRC may depend less on the malignant disease and more on their pre-morbid condition. Data shows that good surgical outcomes can be achieved in the elderly, but individualized evaluation of treatment goals and communication of realistic anticipated outcomes are essential.

### Research motivation

With advanced age and chronic illness, the decision to undergo major surgery in the elderly patient can be challenging. Not infrequently, patients and their family members decline operative intervention due to age-related concerns. Even to the surgeon, the benefit of resection in certain individuals may not be so clear-cut. Moreover, the elderly are under-represented and under-prioritized in randomized trials, resulting in difficulty in generalizing existing data. Established risk stratification methods are commonly used but have well described flaws. This motivated us to develop a specific prognostic assessment tool to quantify the risk of mortality and predict survival after surgery in the elderly.

### Research objectives

We aimed to analyze our outcomes following major elective colorectal surgery in the elderly to determine factors significantly influencing mortality. A pre-operative scoring system predicting post-operative outcomes more objectively could then be derived, facilitating the decision-making process for both surgeons and patients.

### Research methods

Data for all patients aged 70 and above who underwent elective surgery for non-metastatic CRC at Singapore General Hospital Department of Colorectal Surgery from 1 January 2005 to 31 December 2012 were obtained from hospital electronic records. Patients with evidence of distant disease, those who underwent emergency surgery or had surgery for benign colorectal conditions were excluded from the analysis. Instances of surgery for CRC recurrence occurring

in the same patient over the study period were also excluded. Information for an equivalent group of elderly patients electively operated on at Kyungpook National University Chilgok Hospital, Daegu, South Korea, was retrieved over the same duration.

### Research results

A total of 1267 patients were identified for analysis. The median post-operative length of stay was 8 [interquartile range (IQR) 6-12] d and median follow-up duration was 47 (IQR 19-75) mo. Median OS was 78 (IQR 65-85) mo. Following multivariate analysis, the factors significant for predicting overall mortality were serum albumin < 35 g/dL, serum carcinoembryonic antigen  $\geq$  20  $\mu\text{g/L}$ , T stage 3 or 4, moderate tumor cell differentiation or worse, mucinous histology, rectal tumors, and pre-existing chronic obstructive lung disease. Advanced age alone was not found to be significant. The Korean cohort consisted of 910 patients. The Singapore cohort exhibited a poorer OS, likely due to a higher proportion of advanced cancers. Despite the clinicopathologic differences, there was successful validation of the model following recalibration. An interactive online calculator was designed to facilitate post-operative survival prediction, available at [http://bit.ly/sgh\\_crc](http://bit.ly/sgh_crc).

### Research conclusions

Advanced age per se is not a risk factor for poorer survival outcomes and patients should not be denied surgery based on age alone. However, there is a need for more objective pre-operative risk stratification in this vulnerable group of patients. Our novel scoring system predicting mortality following major resection uses parameters which are available before the surgery and can assist in the counselling and decision-making process between surgeons, their patients and families. Validation with an external Asian population strengthens the generalizability of this scoring method.

### Research perspectives

While it was not possible compare our cohort with cancer patients who had not had surgery over the study duration, this information should be considered for future studies. The dissimilarity in survival between the cohorts may reflect the shortcomings of comparison between the populations of two distinct geographical locations, but eventual validation of the model notwithstanding these variations can be considered a strength. To ensure predictive accuracy of the model, further validation including re-identification of a correction factor with possible recalibration should be undertaken before use in separate populations.

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## ACKNOWLEDGEMENTS

The authors thank Fung Joon Foo and Wan Qi Ng for their assistance in preparing the manuscript.

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