Does frailty independently predict long-term survival time in Japanese older patients with colorectal cancer? – A single center retrospective cohort study.

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Abstract

Introduction

The number of older patients with colorectal cancer (CRC) increases due to aging. There are a number of prediction models for the purpose of estimating prognosis so that health providers and patients can select appropriate care and cure. A nomogram provided by the Japanese Society for Cancer of Colon and Rectum (JSCCR) for predicting overall survival probability following colon or rectum surgery includes many parameters that make it difficult to estimate the prognosis of patients in the clinical setting. Also, frailty status is often not included in the nomogram. Upon deciding treatment plan, frailty is often an important parameter to evaluate because older patients should not be assessed by only age without consideration of their physical and cognitive activities. The aim of this study was to assess the relationship between frailty and the long-term outcomes of older patients with CRC and to create a novel simple prognostic prediction model for the long-term outcomes of patients with CRC.

Methods

We conducted a retrospective cohort study for the patients with CRC who had surgery, using the electronic medical data in Nerima Hikarigaoka Hospital during January 1st to Dec 31th of 2015. Frailty was defined by the Fried's Criteria. The primary outcome was

the 5-year overall survival. We used Cox proportional hazards model to check the relationship between the frail group and the non-frail group. Also, we compared the area under the receiver operating curve (AUC) for the 5-year and the 3-year overall survival using the JSCCR nomogram and the new model.

Results

Of 51 subjects, 12 (24 %) were frail. Median age (IQR) was 78 (70.5 - 80.5) in the frailty group and 77 (71 - 79) in the non-frailty group; 5 (41.7 %) in frailty group and 19 (37.3 %) in non-frailty group were female. There was not a significant difference in the 5-year overall survival between the frail group and non-frail group (Log-Rank test; P = 0.59). A new prognostic prediction model using the three variables (gender: female or male; age: 75< years or 75≥ years, and pathological stage: Ⅰ-Ⅲ or Ⅳ) with a total score of 4 points was constructed as follows: 1 point for male, 1 point for 75≥ years, 2 points for pathological stage Ⅳ. The AUC for the 5-year overall survival by the new model was 80.8% (95%CI: [68.0 - 93.6%]), which was higher than that for 5-year overall survival by the JSCCR nomogram (72.8%; 95%CI: [57.7 - 87.8%]).

Conclusions:

In this study, frailty defined by the Fried's criteria did not have a statistically significant relationship against the long-term outcome among older patients with CRC. The novel

prognostic prediction model may be more simple and easier to calculate than the JSCCR nomogram. Further investigation should be done with a larger sample size.

Keywords

mortality, frailty, colorectal cancer, older/elderly

Introduction

Colorectal cancer (CRC) is the third highest diagnosed type of cancer in the world, the proportion of which is 11 % of all cancer diagnoses (Bray et al. 2018). Day et al. (2011) reported that new diagnosis of colorectal cancer in the US was 24% in patients aged 64 – 74 years, 27% in those aged 75 – 84 years, and 12% in those aged 85 years or above. In Japan, Mayumi (2019) showed that the incidence rates of CRC increased with age (21.8 % in patients aged 45-64 years, 32.3 % in patients aged 65-74 years, and 43.3 % in patients aged 75 years or above). From the report provided by Cancer Registry and Statistics (2019), while the incidence rates increased as patients become older, cancer mortality rates from CRC for Japanese males adjusted by gender and age did not constantly increase with advancing years (for males more than 20% in their 40s to 60s and less than 15% for over age 70). According to this discrepancy between incidence rate and mortality rate, it seems that health care providers should not decide care only by the age of patients but should also consider other patients' characteristics such as frailty, activities of daily living (ADL) and any comorbidities patients may have. Therefore, a screening pre-operative risk classification for the older patient is essential not only to predict mortality and morbidity but also to present the patient with appropriate information including the concept of life expectancy and

overall survival after surgical intervention. Several general risk scoring systems for entire populations are commonly used worldwide. For example, there are the: American Society of Anesthesiologists (ASA) physical status scoring system (Committee on Economics, 2020), Goldman's multifactorial index (Goldeman et al. 1977), Detsky modified multifactorial index (Detsky et al. 1986), American Heart Association Guidelines (Fleisher et al. 2007) and Cr-POSSUM (Tekkis et al. 2004). Those scoring systems are not generally included in geriatric risk assessment.

As examples of geriatric risk assessment, there is the: Charlson comorbidity index (Charlson et al. 1987), several models of frailty (Fried et al. 2001; Rockwood 2005; Manhoney et al. 1965), Barthel's activities of daily living index (Solomon 1988) and comprehensive geriatric assessment (Tan et al. 2012); all of which are often used to predict the future conditions among older patients.

Tan et al. (2011) reported that the odds ratio linked to postoperative major complications in patients who meet the criteria of frailty was approximately 4 times higher (4.1, 95%CI: [1.4 -11.6]) than that of non-frail patients. However, there are few reports from Asian countries describing the association between frailty and long-term oncological outcomes, and the scoring systems to predict long-term mortality among older people are very limited. Ommundsen et al. (2014) found that frailty based on a

geriatric assessment was an indicator for one-year and five-year overall survival times after surgical procedure for colorectal cancer among a group of patients aged 75 and older in Norway. In addition, there is only one study investigating the relationship between frailty and long-term mortality of the Japanese patients with CRC (Mima et al. 2020). Therefore similar studies should be conducted in Asian countries.

The purpose of this study is to investigate whether frailty independently predicts the long-term outcomes of the older patients with CRC in a Japanese population. After researching the association between frailty and long-term mortality among older patients with CRC, we also developed a novel mortality prediction model to predict long-term mortality among specifically older patients with CRC in Japan.

Methods

The subjects in this study were retrospectively enrolled from among the patients with CRC who had surgery. We used the electronic medical data in Nerima Hikarigaoka Hospital during January 1st to December 31th in 2015. In a recent article, Kanematsu et al (2019) suggested a nomogram predicting survival and recurrence of colon cancer in the Japanese Society for Cancer of the Colon and Rectum (hereby, the JSCCR model). By reference to this nomogram, the following parameters were

collected: age, gender, tumor location (cecum, ascending, transverse, descending, sigmoid and rectum), macroscopic type (0 - 5), tumor differentiation (well, moderate, poor, signet or mucinous), extent of lymphadenectomy (D0 - D3), preoperative carcinoembryonic antigen (CEA: ng/ml), pathological tumor category (pT1-4), lymphatic invasion (ly0-ly3), venous invasion (V0-V3), number of lymph nodes examined, number of metastatic lymph nodes, adjuvant chemotherapy (yes or no), and pathological disease stage (pStage Ⅰ - Ⅳ). Also, we gathered the data on body mass index (BMI), Hasegawa's Dementia Rating Scale-Revised (HDS-R), performance status (PS), Charlson Comorbidity Index (CCI), overall survival time and frailty. According to the definition of frailty in this study, we used the Fried's Frailty Index (Fried et al. 2001). This Index is one of the most well known and well-discussed scale for frailty proposed by Linda Fried at the Cardiovascular Health Study. After describing the ability of these criteria to prognosticate physical disability and mortality among a sample population of older people in a community setting, this functional index is frequently investigated to recognize persons with frailty for high risk of negative health-related outcomes. After checking the following physical components: weight loss, walking speed, grip strength, physical activity, and exhaustion, subjects are diagnosed as frailty if they have three or more of the items.

We included the subjects with CRC who had a scheduled operation, which was excision of primary colorectal cancer by open or laparoscopic procedure. Also, the patients who were diagnosed as clinical stage Ⅳ before surgery and whose primary site of cancer was resected, were included. We excluded the patients who had not only CRC but also other types of cancer. Also, patients who did not have a resection of the primary site of colorectal cancer or who had only palliative care were excluded.

The primary outcome was defined as the 5-year overall survival. The secondary outcomes were set as the 3-year overall survival, length of hospital stay, Charlson Comorbidity Index, and complications after operation.

Statistical Analyses

To assess the demographics of the frail group and the non-frail group, we used two-sample t-test if a variable was continuous and normally distributed and used Wilcoxon Rank-Sum test if a variable was not normally distributed. Also, when variables were categorical ones, Chi-square test was selected. To compare the primary outcome between the frail group and the non-frail group, we used Kaplan-Meier Survival curves and Cox proportional hazards model. We conducted sample-size estimation with significant level 0.05 and a power of 0.8 for the comparison of survival curves between the two groups under the log-rank test. Significant levels were set at the

5% level. A p value <0.05 was considered significant and all analysis was carried out using STATA 16.0 and R version3.6.1.

Results

In this study, 74 subjects were enrolled and 16 subjects were excluded due to transfer (n=8), moving (n=2), and drop out (n=6). Then, 7 patients were omitted because of age leaving 51 subjects eligible for this study (Figure 1). Of the 51 patients, 12 (24 %) were frail and 39 (76 %) were non-frail. Among the two groups, median ages (IQR) were 78 (70.5 - 80.5) in frailty and 77 (71 - 79) in non-frailty while 5 (41.7 %) in frailty and 19 (37.3 %) in non-frailty were female. In terms of BMI, HDS-R, Performance Status (PS), there were statistically significant differences between the frail and non-frail groups (all P < .05). In addition, comparing the two groups, the length of hospital stay (IQR) was 21.5 (17.5 - 38) in frailty group and 16 (8 - 22) in non-frailty group was significantly different (P < .01). Also, postoperative complications had a significant difference between the two groups (P = .03). For the details of postoperative complications, four out of six subjects in the frail group had paralytic ileus, one had enteritis, and one had a parastomal hernia. In the non-frail group, four patients had paralytic ileus, and each of the other three had urinary tract infection (UTI), superficial

incisional surgical site infection (SSI), and Clostridium Difficile colitis, respectively. In terms of pathological stage, there was not a significant difference between the two groups (P = 0.19). Furthermore, statistically significant differences were not found in the following characteristics: age, gender, tumor location, macroscopic type, tumor differentiation, extent of lymphadenectomy, preoperative carcinoembryonic antigen (CEA), lymphatic invasion, venous invasion, number of lymph nodes examined, number of metastatic lymph nodes, adjuvant chemotherapy, operation methods, and Charlson comorbidity index. For more information of adjuvant chemotherapy by frailty, two out of 12 (16.7 %) among frail group had a adjuvant chemotherapy and both were categorized as pathological stage Ⅲ. On the other hand, 14 out of 39 (35.9 %) among the non-frail group had adjuvant chemotherapy (three subjects in pathological stage Ⅱ, five subjects in pathological stage Ⅲ, six subjects in pathological stage Ⅳ).

Figure 2 shows that there was not a significant difference in the 5-year overall survival between the frail and non-frail groups (Log-Rank test; P = 0.59). Also, as Figure 3 presents, no statistically significant difference in the 3-year overall survival between the two groups was found (Log rank test; P=0.21).

We assessed the accuracy of the JSCCR nomogram that Kanematsu et al (2019) had presented for estimation of long-term outcome among patients with

colorectal cancer using the data from our study. In Figure 4, the area under the receiver operating curve (AUC) for 5-year overall survival by the JSCCR nomogram was 72.8% (95%CI: [57.7 - 87.8%]). Also, Figure 5 showed that AUC for 3-year overall survival by the JSCCR nomogram was 70.9% (95%CI: [54.4 - 87.4 %]). Both of the values of AUC for long-term outcomes were relatively high. To make a new, more simple model for the estimation of long-term outcome among patients with CRC, the variables of the new prediction model I selected were gender, age (<75 years, or 75≥), and pathological stage (Ⅰ-Ⅲ or Ⅳ). If gender was male, the score increased 1 point. If the age was 75 years or more, the score increased 1 point. If the pathological stage was Ⅳ, the score increased 2 points. Then the sum of the scores was the total score. From the total score the subjects were divided into three categories; A: 0 - 1, B: 2, and C: 3 - 4 (Table 2). Figure 6 describes the Kaplan-Meier survival curve by the three categories. As the score increased, survival time decreased. Then, from Figure 7 and 8, AUC for the 5-year overall survival by the new model was 80.8% (95%CI: [68.0 - 93.6%]) and the AUC for the 3-year overall survival was 76.1 % (95%CI: [61.7 - 90.5 %]).

Discussion

Our study did not show a statistically significant different relationship between frailty and the long-term outcomes of CRC patients, while there was a significant difference between frailty and the short-term outcomes such as length of hospital stay, and postoperative complications. Also, the novel prognostic prediction model for the long-term outcome among the CRC patients had smaller number of variables, and higher AUC than the JSCCR nomogram. In addition, it was easy to calculate because of the simplicity of the new model.

From the study conducted in Norway, Ommundsen et al. (2014) revealed opposite results from our study, showing that frailty based on a geriatric assessment which is composed of ADL, use of medication, comorbidity, nutritional status, cognitive function, and depression, is an independent predictor of survival in older patients with colorectal cancer. This might be caused by the definition of frailty. The difference between the definition of frailty in our study and that of Ommundsen's study was an item about physical activities. The Fried's criteria is focusing mainly on physical activities, not including patients' comorbidity, nutritional status, mental status, and cognitive conditions (Fried et al. 2001), so that the results that Ommundsen et al. (2014) reported might be different if they had used the Fried's criteria as the definition of frailty.

Mima et al. (2020) reported a strong association between frailty and recurrence and mortality among colorectal cancer patients in pathological stage Ⅰ- Ⅲ who had curative resection. This study was conducted in Japan. The hazard ratios of recurrence free survival and overall survival were 1.70 (95%CI: [1.25 - 2.31], P < .001) and 2.04 (95%CI: [1.40 - 2.99], P < .001), respectively. In this study, frailty was defined using the Clinical Frailty Scale (CFS), which divided into nine stages mainly based on physical functions and ADL, similar to the Fried criteria (Rockwood et al. 2005). However, in the characteristics of the study that Mima et al. (2020) conducted, the variable, disease stage, had a significant difference between non-frail group and frail group (P = .002). The proportion of those in disease stage Ⅱ and Ⅲ among the frail group is higher than among the non-frail group (85% vs 74%). This might have an impact on the results even if the variable, disease stage, were adjusted in the multivariable cox regression analyses. Also, the CFS has a disadvantage because it grades by semi-quantitative classification comparing to the Fried's criteria, which is defined by quantitative values. This semi-quantitative and subjective aspect may affect the results because of interobserver variability. The two reports we mentioned above showed the opposite results compared to our study. One of the reasons for this may be differences among the definitions of frailty and the variations of sample population.

From the aspect of the definition of frailty, we might suggest that preoperative frailty status defined by the Fried's criteria be not an independent indicator for the long-term outcomes among CRC patients following resection.

According to several previous cohort studies which investigated the relationship between frailty and long-term prognosis following resection in older patients with CRC, the three variables (age, gender, and pathological stage) were important prognostic indicators (Aaldriks et al. 2013; Boakye et al. 2018; Mima et al. 2020; Ommundsen et al. 2018). Hence, the new model in this study adopted the three variables and revealed its usefulness to evaluate overall mortality of older patients with CRC following resection.

There are other reasons why this study did not show a statistically significant difference between frailty and long-term overall survival. The distribution of pathological stage among frail and non-frail group might influence the result. Generally, the prognosis of CRC worsens by an increase of pathological stage. In this study, the proportion of the frail subjects in pathological stage Ⅱ and Ⅲ was 11/12 (91.7 %), while the proportion of the non-frail subjects in pathological stage Ⅱ and Ⅲ was 23/39 (60.0 %). Also, the proportion of the frail patients in pathological stage Ⅳ (1/12: 8.3 %) was lower than that of the non-frail patients in pathological stage Ⅳ (8/39:

20.5 %). This difference might not show a statistical relationship between frailty and long-term prognosis.

Limitations

On the whole, as a limitation of this study, small sample size and low power of this study might lead to opposite results compared to previous studies. In a sample size estimation under the log-rank test, estimated sample size should be more than 138 if we set α=0.05, 1-β (Power) = 0.8, hazard ratio = 0.5 and the allocation ratio = 0.3 (frail subjects / non-frail subjects). Also, the power of this study was under the condition of α = 0.05, total sample size = 51, the allocation ratio = 0.3 (frail subjects / non-frail subjects), and hazard ratio = 0.5, was 0.40. The power of this study is lower than 0.80. For future research, we should perform and analyze the relationship between frailty and long-term outcome of CRC patients in a larger sample size, considering the definition of frailty. In addition, I should check external validation of the new prediction model in larger sample size.

Conclusion

This study did not find a strong relationship between frailty based on the Fried criteria and the long-term outcomes among the older patients with CRC, whereas our

new prediction model for the long-term outcome among older patients with CRC had a higher predictive ability than the JSCCR nomogram. However, further studies with a larger sample size should be done.

Statement about Institutional Review Board (IRB) approval: This study was approved by the IRB in Nerima Hikarigaoka hospital.

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Tables and Figures

Characteristic[a]	**Total**	**Frailty**		**P-value[b]**
	All patients (n = 51)	Frailty (n = 12)	No-Frailty (n = 39)	
Age in years (IQR)	77 (71, 80)	78 (70.5, 80.5)	77(71, 79)	0.56
Sex				0.13
Female	19 (37.25 %)	5 (41.67 %)	14 (35.90 %)	
Male	32 (62.75 %)	7 (58.33 %)	25 (64.10 %)	
BMI - kg/m^2	23.2	21.0	24.9	0.025*
(IQR)	(20.3, 26.6)	(18.0, 23.6)	(20.7, 27.1)	
HDS-R - Points	27	25	27	0.03*
(IQR)	(23, 29)	(19, 27)	(24, 30)	
Performance Status (PS)				
0	36 (70.5 %)	33 (84.6 %)	3 (25 %)	<0.01*
1	10 (19.6 %)	5 (12.8 %)	5 (41.7 %)	

2	3 (5.9 %)	1 (2.6 %)	2 (16.7 %)	
3	1 (2.0 %)	0 (0 %)	1 (8.3 %)	
4	1 (2.0 %)	0 (0 %)	1 (8.3 %)	
Tumor location				
Ascending	9 (17.7 %)	3 (25.0 %)	6 (15.4 %)	0.10
Transverse	5 (9.8 %)	0 (0 %)	5 (12.8 %)	
Descending	3 (5.9 %)	2 (16.7 %)	1 (2.5 %)	
Sigmoid	17 (33.3 %)	1 (8.3 %)	16 (41.0%)	
Rectum	12 (23.5 %)	5 (46.7 %)	7 (18.0 %)	
Cecum	4 (7.8 %)	1 (8.3 %)	3 (7.7 %)	
Vermiform	1 (2.0 %)	0 (0 %)	1 (2.6 %)	
Macroscopic type				
1	5 (9.80 %)	0 (0 %)	5 (12.82 %)	
2	4 (7.84 %)	0 (0 %)	4 (10.26 %)	0.45
3	29 (56.86 %)	9 (75.00 %)	20 (51.28 %)	
4	9 (17.65 %)	2 (16.67 %)	7 (17.95 %)	
5	4 (7.84 %)	1 (8.33 %)	3 (7.69 %)	

Tumor differentiation				0.69
Well	20 (39.22 %)	6 (50.00 %)	14 (35.90 %)	
Moderate	28 (54.90 %)	6 (50.00 %)	22 (56.41 %)	
Poor	2 (3.92)	0 (0 %)	2 (5.13 %)	
mucinous	1 (1,96)	0 (0 %)	1 (2.56 %)	
Extent of lymphadenectomy				0.79
D1				
D2	1 (1.96 %)	0 (0 %)	1 (2.56 %)	
D3	3 (5.88 %)	1 (8.33 %)	2 (5.13 %)	
	47 (92.16 %)	11 (91.67 %)	36 (92.31 %)	
Preoperative CEA				0.31
<5 ng/ml	24 (47.06 %)	3 (25.00 %)	21 (53.85 %)	
5≤ <10 ng/ml	9 (17.65 %)	3 (25.00 %)	6 (15.38 %)	
10≤ <20 ng/ml	8 (15.69 %)	2 (16.67 %)	6 (15.38 %)	
≤20 ng/ml	10 (19.61 %)	4 (33.33%)	6 (15.38 %)	
Lymphatic invasion				
ly0	31 (60.78 %)	8 (66.67 %)	23 (58.97 %)	0.81

ly1	15 (29.41 %)	3 (25.00 %)	12 (30.77 %)	
ly2	2 (3.92 %)	0 (0 %)	2 (5.13 %)	
ly3	3 (5.88 %)	1 (8.33 %)	2 (5.13 %)	
Venous invasion				
V0	10 (19.61 %)	0 (0 %)	10 (25.64 %)	0.19
V1	13 (25.49 %)	5 (41.67 %)	8 (20.51 %)	
V2	16 (31.37 %)	4 (33.33 %)	12 (30.77 %)	
V3	12 (23.53 %)	3 (25.00 %)	9 (23. 08 %)	
Number of Lymph nodes examined (IQR)	22 (15, 29)	26 (18, 37)	21 (14, 26)	0.16
Number of metastatic lymph nodes (IQR)	0 (0, 1)	0 (0, 0.5)	0 (0, 3)	0.37
Adjuvant chemotherapy				
No	35 (68.6 %)	10 (83.3 %)	25 (64.1 %)	0.21
Yes	16 (31.4 %)	2 (16.7 %)	14 (35.9 %)	

Details of adjuvant chemotherapy - yes				0.23
Pathological stage Ⅰ	0 (0 %)	0 (0 %)	0 (0 %)	
Pathological stage Ⅱ	3 (18.8 %)	0 (0 %)	3 (21.4 %)	
Pathological stage Ⅲ	7 (43.7 %)	2 (100 %)	5 (35.7 %)	
Pathological stage Ⅳ	6 (37.5 %)	0 (0 %)	6 (42.9 %)	
Operation method				0.19
Laparoscopy	44 (86.27 %)	9 (75.00 %)	35 (89.74 %)	
Open	7 (13.73 %)	3 (25.00 %)	4 (10.26 %)	
Length of Hospital Stay	16 (9, 23)	21.5 (17.5, 38)	10 (8, 22)	<0.01*
CCI				
Low	32 (62.75 %)	7 (58.33 %)	25 (64.10 %)	0.19
Medium	18 (35.29 %)	4 (33.33 %)	14 (35.90 %)	
High	1 (1.96%)	1 (8.33 %)	0 (0 %)	
Very high	0 (0 %)	0 (0 %)	0 (0 %)	

Postoperative complication				
Yes	13 (25.49 %)	6 (50.0 %)	7 (17.95 %)	
No	38 (74.51 %)	6 (50.0 %)	32 (82.05 %)	0.03*
Pathological Stage (%)				
Ⅰ	8 (15.6 %)	0 (0 %)	8 (20.5 %)	0.19
Ⅱ	25(49.0 %)	8 (66.7 %)	17 (43.6 %)	
Ⅲ	9(17.7 %)	3 (25.0 %)	6 (15.4 %)	
Ⅳ	9(17.7%)	1 (8.3 %)	8 (20.5 %)	

Table 1. Characteristics of the subjects

Abbreviations: BMI, Body Mass Index; HDS-R, Hasegawa's Dementia Rating Scale-Revised; PS, Performance Status; CEA, Carcinoembryonic antigen, IQR; InterQuartile Range, CCI; Charlson Comorbidity Index

[a]Categorical variables were presented as proportions. Non-normally distributed variables are showed as medians with interquartile ranges.

[b]Categorical data were tested using the chi-square test or Fisher's exact test.

Non-parametrically distributed data were analyzed using Wilcoxon Rank-Sum test.

Normally distributed data were compared using t-test.

	Score
Sex	
Female	0
male	1
Age	
<75 years	0
≥75 years	1
Pathological stage	
Ⅰ－ Ⅲ	0
Ⅳ	2
Total Score = (Sex score) + (Age score) + (Pathological stage Score) A: Score 0-1 B: Score 2 C: Score 3-4	

Table 2. Scoring system for the new model

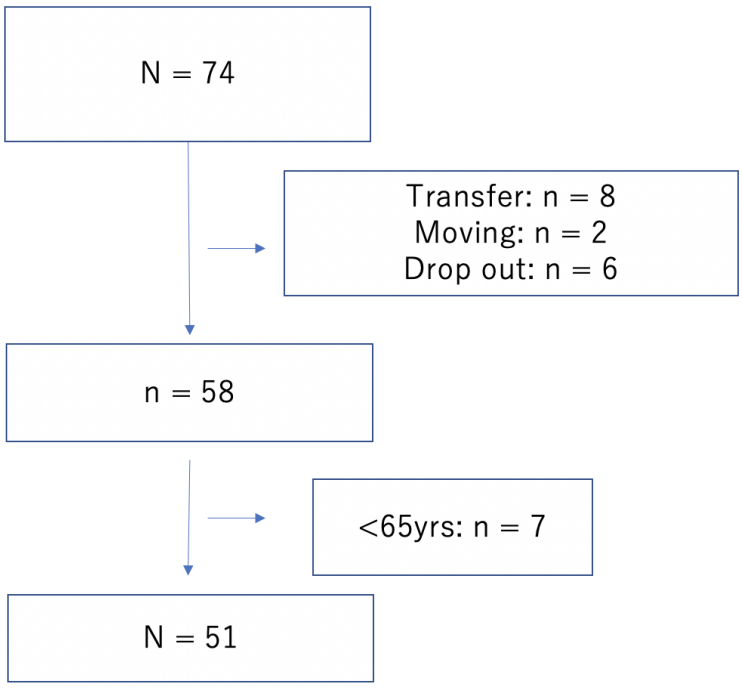

Figure 1. Flow gram of subjects who were included and excluded

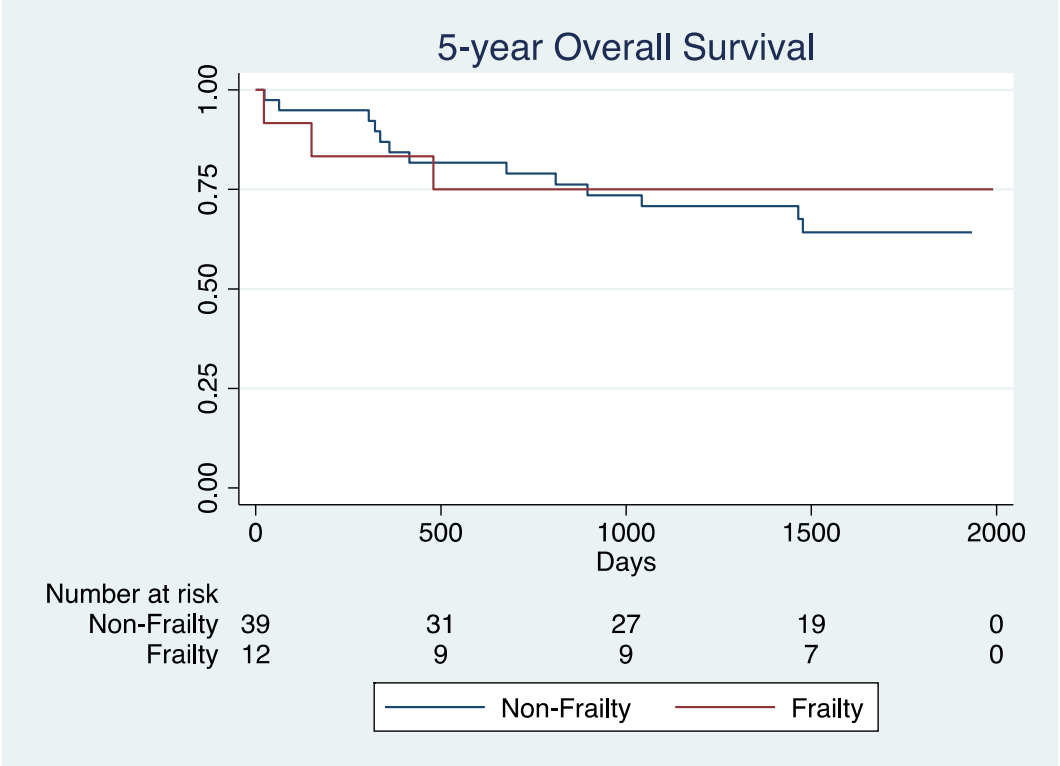

Figure 2. Kaplan-Meier curves for the 5-year Overall Survival by Frailty

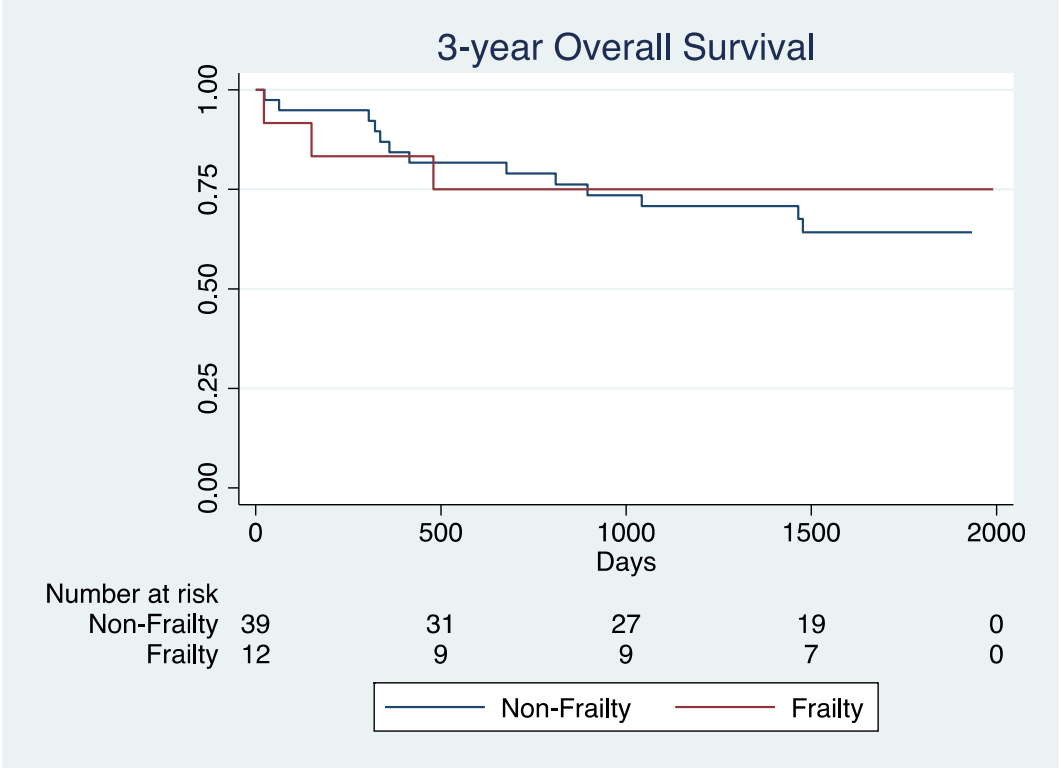

Figure 3. Kaplan-Meier curves for the 3-year Overall Survival by Frailty

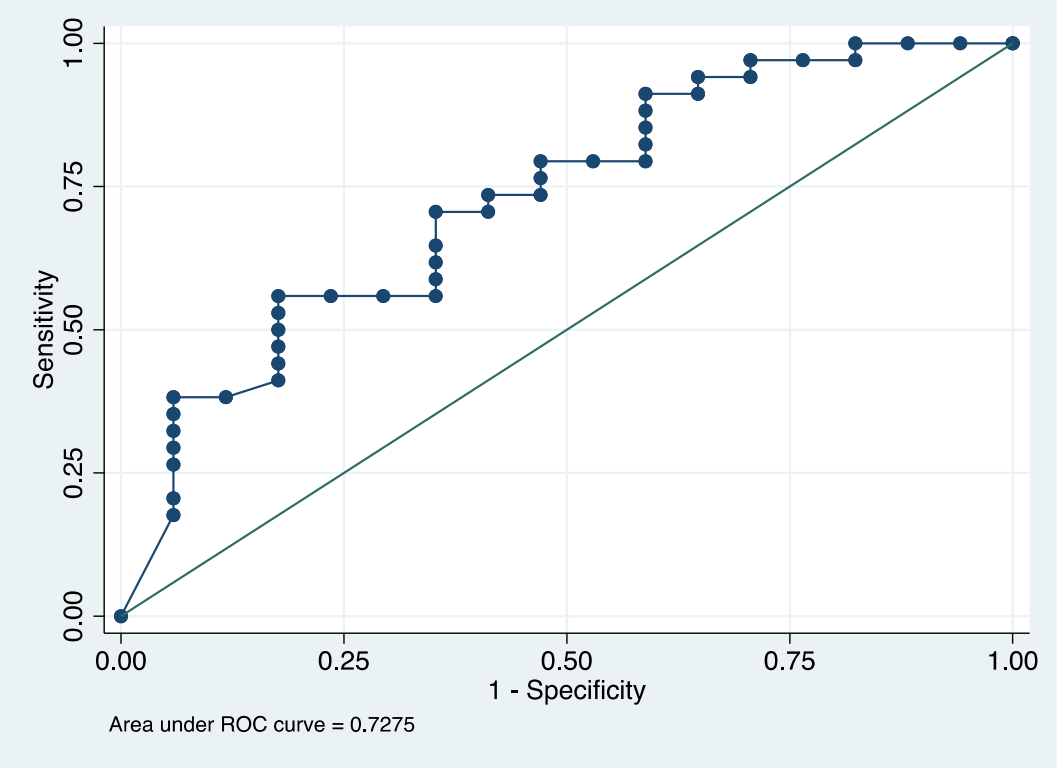

Figure 4. Area under the receiver operating curve (ROC) for 5-year overall survival by the nomogram (72.8; 95% CI: 57.7 - 87.8%)

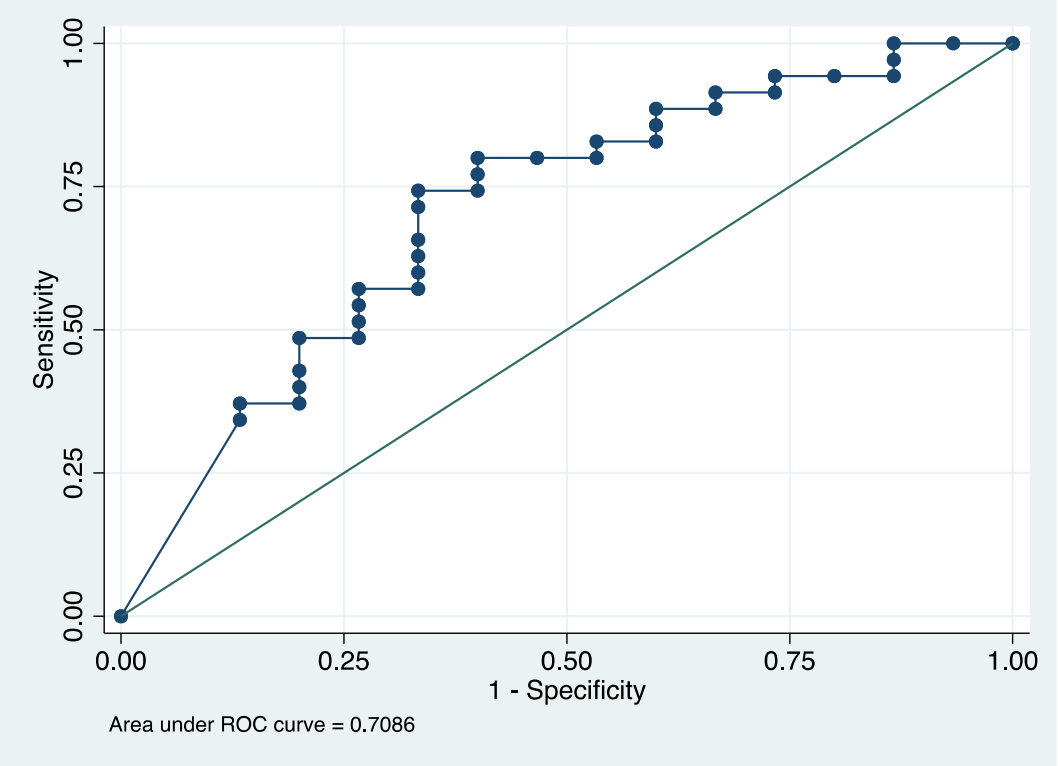

Figure 5. Area under the receiver operating curve (ROC) for 3-year overall survival by the nomogram (70.9%; 95% CI: 54.4 - 87.4 %)

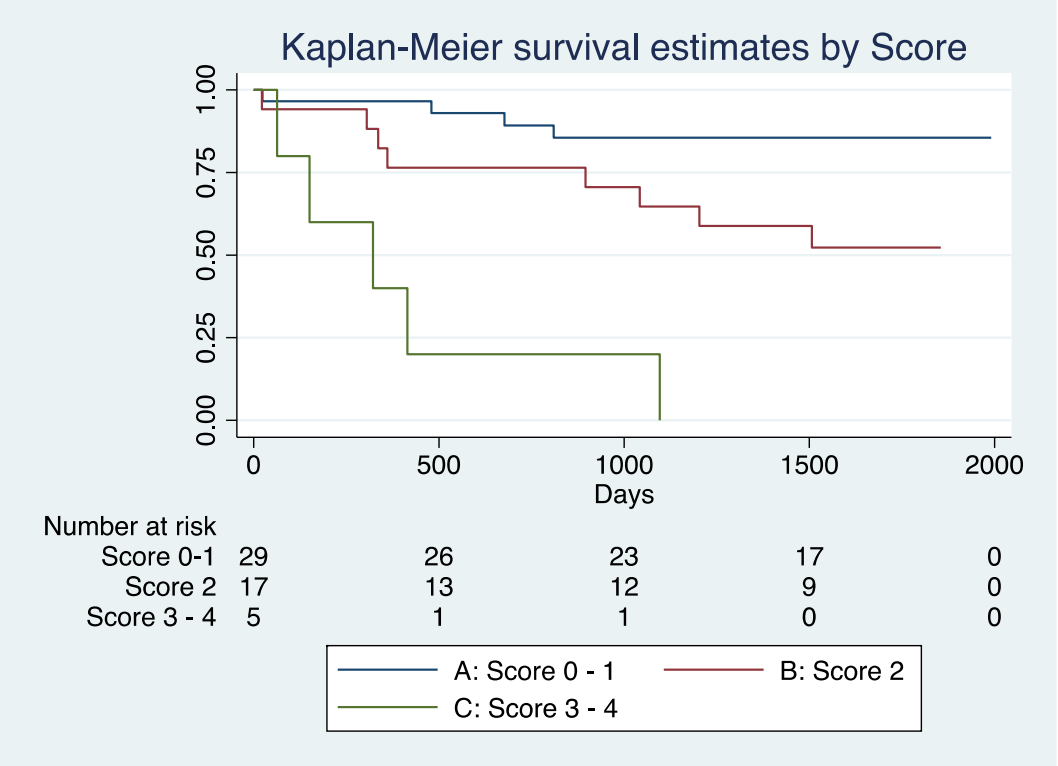

Figure 6. Kaplan-Meier survival curve by the new model

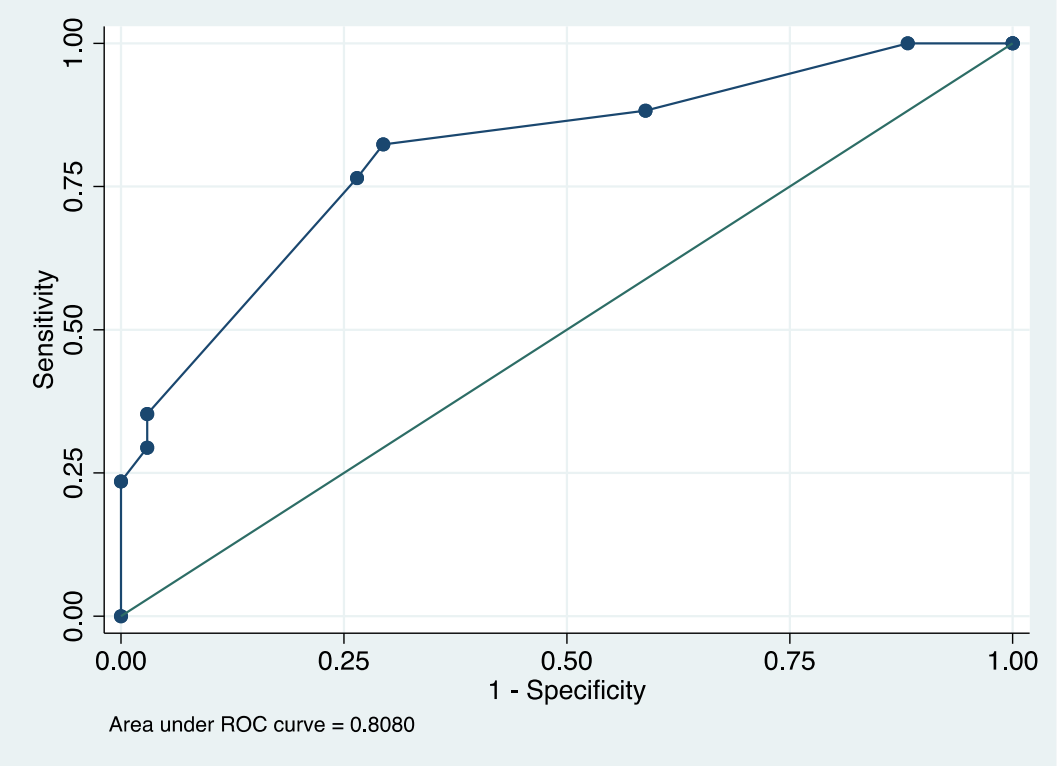

Figure 7. Area under the receiver operating curve (ROC) for 5-year overall survival by the new model (80.8%; 95% CI: 68.0 - 93.6%)

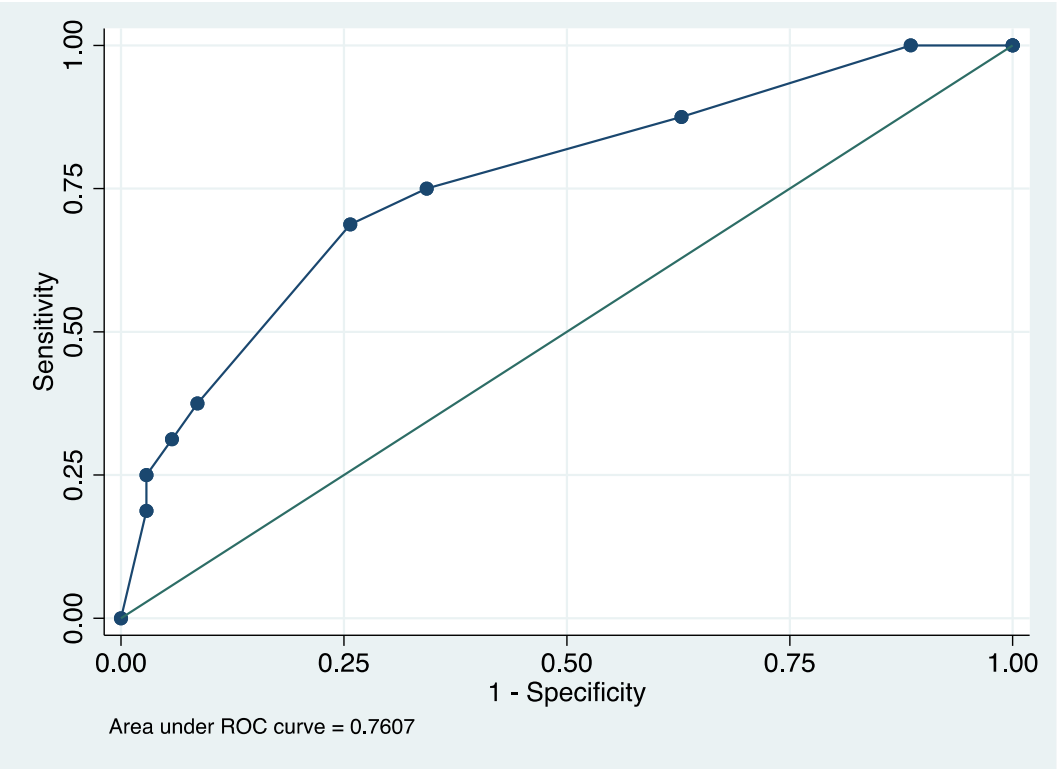

Figure 8 Area under the receiver operating curve (ROC) for 3-year overall survival by the new model (76.1 %; 95% CI: 61.7 - 90.5 %)