의학박사 학위논문

고령의 대장암 환자의 회복과정에서 면역학적 변화와 근감소증의 관계 및 근감소증이 회복에 미치는 영향

Relationship between immunologic changes and sarcopenia in the recovery process of elderly colon cancer patients and the effect of sarcopenia on recovery

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임 벼 리

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이 논문을 의학박사학위 논문으로 제출함

2024 년 2 월

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Abstract

Background

Colorectal cancer is one of the most frequent malignancies, with a rising proportion of elderly patients in an aging society. Therefore, efforts to provide individualized and appropriate treatment for elderly patients are also increasing. Cancer-related inflammation affects cancer progression and prognosis, and immunological variables that influence this process, as well as ones that influence recovery following surgery, are critical. In this study, we attempted to support the establishment of an individualized treatment plan for elderly patients by analyzing modifiable elements among various parameters impacting the treatment.

Methods

In retrospective study, we reviewed the records of colorectal cancer patients (10,271 patients) who received surgical treatment in multi-centers including 8 tertiary centers between March 2018 and September 2020 and also reviewed record of patients who received curative resection for colorectal cancer between January 20005 and November 2011 at Asan Medical Center. In prospective study, total 40 patients who received radical resection for colon cancer between September and November 2023 at Asan Medical Center was involved. We included colon cancer patients treated with surgery, diagnosed with adenocarcinoma histologically and having information regarding preoperative status with abdominopelvic CT. Routine blood sampling and Immunologic tests including interleukin-6 (IL-6), natural killer cell (NK cell), and tumor necrosis factor-alpha (TNF-alpha) were performed at preoperative day, post operative 3rd day (POD#3), and outpatient clinic day (about postoperative 21th day (POD#21)). We attempted to assess the patients' subjective health level using a simple questionnaire, EuroQol group- 5 dimension- 3 level (EQ-5D-3L). The sarcopenia was evaluated by the artificial intelligence software system and defined as an SMI < 41cm2/m2 in women and SMI < 43 cm2/m2 in men with a body mass index (BMI) < 25kg/m2, and < 53 cm2/m2 in men with a BMI ≥ 25 kg/m2. The primary end point was' recovery' represented by hospital stay and secondary end point was 'EQ-5D-3L index value'. 'Recovery' was evaluated by hospital stay and readmission within 30 days after discharge.

Patients who had a shorter-than-average hospital stay rated their recovery as fast, whereas those who had a longer-than-average hospital stay or readmitted within 30 days after discharge rated their recovery as slow.

Results

In retrospective cohort study of multicenter data, American society of anesthesiologists physical status classification (ASA classification), clinical T (cT) stage, clinical N (cN) stage was associated with postoperative recovery in elderly patients (ASA classification; OR 0.92; 95%CI, 0.89-0.96, P <0.001; cT; OR 0.91; 95%CI, 0.87-0.96, P <0.001; cN; OR 0.92; 95%CI, 0.88-0.96, P <0.001). Furthermore, patient who were discharged within 7 days and were not readmitted within 30days were at lower risk of recurrence (HR 0.61; 95%CI, 0.48-0.77, P <0.001).

In retrospective cohort study, neutrophil-lymphocyte ratio (NLR), albumin and sarcopenia were related with recovery after operation in elderly patients**.** (NLR; OR 0.52; 95%CI, 0.28-0.97, P=0.041; albumin; OR 2.01; 95%CI, 1.06-3.79, P=0.032; sarcopenia; OR 0.44; 95%CI, 0.21-0.94, P=0.034). Fast recovery represented by shorter hospital stay without readmission within 30 days after discharge, pathologic N (pN) stage, and lymphovascular invasion (Lvi) was associated OS (HR 0.64; 95%CI, 0.42-0.97; P=0.036, HR 1.61; 95%CI, 1.04-2.47; P=0.032, HR 1.63; 95%CI, 1.06-2.50; P=0.025, respectively).

In prospective cohort study, of 40 patients, 24 (60.0%) were male and the mean age was 66.3 (±13.0) years old. About 60% of all patients had more than one comorbidity. (62.5%, 25 patients). The mean hospital day was 5 days most of all discharged within 5 days (85%, 34 patients). There was no significant difference in clinicopathologic characteristics associated with recovery between non-elderly and elderly-groups. Only ASA classification was associated with recovery (OR: 0.13; 95% CI, 0.01-1.15, P=0.066) in the entire group. Likewise, in elderly group, the only risk factor for recovery was the ASA classification; all other factors including NLR, albumin, and sarcopenia had no significant impact on recovery (P=0.358, P=0.539, and P=0.662, respectively).

There were no significant variables associated with recovery and sarcopenia in the distribution of immunologic factors including IL-6, NK cell, and TNF-alpha regardless of the timing, preoperative,

POD#3 and POD#21. However, levels of preoperative IL-6 and NK cell at preoperative, POD#3, and POD#21 were significantly higher in elderly group than non-elderly group. In addition, patients with higher pre-operative EQ-5D-3L index values were more prevalent in the fast recovery group (64.7% vs. 33.3% in the elderly patient group), though it was not significant statistically (P=0.701)

Conclusion

According to the results of this study, NLR, albumin and sarcopenia were associated with postoperative recovery in elderly patients and correlation between recovery and oncologic outcomes was also identified. In addition, no significant immunologic variables were identified to be associated with recovery or sarcopenia, however, elderly patients tended to have higher NK cell and IL-6 levels. The NK cell, which were not lower in the elderly group, demonstrated that, in contrast to the non-elderly group, elderly patients do not always have poor outcome prior and after surgery. As a result, we have to focus on improving the recovery-related factors discussed in this study before surgery, and further research is needed to ascertain whether variables evaluated in this study or other than the cytokines used in this study was also affect recovery.

Keywords: colon cancer, immune, sarcopenia, aged

1. Introduction

Colorectal cancer (CRC) is one of the most common malignancies, with an increasing prevalence, and one of the common causes of cancer-related death worldwide [1-4]. CRC constitutes 10% of worldwide cancer incidence and 9.4% of cancer death in 2020, just below lung cancer, which accounts for 18% of fatalities [5]. Based on expectations of aging, population expansion, and human progress, the worldwide number of new CRC cases is expected to rise to 3.2 million in 2040. Globally, the aged population is quickly expanding and the portion of cancer patients who are elderly is also increasing significantly[6]. More over 600 million individuals are 65 or older worldwide, and this figure is anticipated to reach 1.6 billion by 2050, accounting for approximately 20% of the world's population. The population of people aged 80 and over seems to be reach nearly half a billion globally [7]. Even, South Korea is on track to become a so-called super-aged society by 2025, with those aged 65 and up representing 20% of the overall population and this number is expected to increase to 44% by 2050 [8, 9] . In Europe and the United States, patients aged 65 and up account for more than 60% of new cancer diagnoses and 70% of cancer deaths [10]. At the time of diagnosis, about 60% of CRC patients are over the age of 70, and 43% are over the age of 75 [11].

In elderly patients, unlike non-elderly patients, the possibility of differences in underlying diseases, physiological changes related to aging, general performance, complications, and postoperative immunological changes should be considered. Furthermore, due to high frequency of comorbidities, postoperative recovery is likely to be delayed, which might result in an increase in social medical expenses [12]. Since the elderly patients is expected to continue to increase, it is necessary to prepare for a personalized treatment approaches taking into account the vulnerability and chronological age of elderly patients. Moreover, the aging process is heterogenous, which adds to the complexity of treatment decisions. These variables contribute to age-related changes in treatment patterns and results, thereby increasing the possibility of under-or-overtreatment, which can impact both the risk of treatment toxicity and survival [13-15]. Therefore, the International Society of Geriatric Oncology (SIOG) assembled a panel of geriatric oncology experts to create consensus statement related with geriatric assessment and

mentioned that many oncologic studies have utilized the age of 70 as the starting point for introducing geriatric assessment [13].

In colon cancer, cancer-related inflammation corresponds to disease progression and survival, and can contribute to the tumor angiogenesis, invasion, and metastatic dissemination[16]. Tumor characteristics such as underlying mutations, progression, vascularization, metabolism and the soluble factors it generates all contribute to the tumor microenvironment and have an influence on immune cell infiltration and activation [17, 18]. Inflammation can show two- sided functions in cancer: (1) Cytotoxic T lymphocytes targeting particular cancer cells or regulatory T lymphocytes reducing nonspecific inflammation may lead to an anti-tumorous response. These protective responses are related with Th1 polarization and correspond with lower CRC recurrence. Meanwhile, (2) nonspecific chronic inflammation, which is commonly couple with Th17-related cytokines, allows proliferative signals or generates new mutations to enhance carcinogenesis [19].

Major cell types in cancer-related inflammation include the innate immune system like neutrophils, macrophages, innate lymphoid cells, natural killer cells (NK cells) and so on. The NK cells are cytotoxic lymphocytes, killing target cells without prior antigen presentation and help to harmonize the adaptive immune response. Moreover, it is a significant prognostic factor in CRC and is related with improved overall survival [20, 21]. Several studies have examined the relationship between inflammatory cytokines such as interleukin 6, 8 and tumor necrosis factor alpha (TNF-alpha) and colorectal cancer [22-27]. Interleukin 6 (IL-6) induced Th17 cells differentiation and modulated downstream STAT3 signaling to promote cancer cell survival and proliferation [19, 28, 29]. It is often found in the tumor environment of CRCs and is associated with poorer survival and recurrence [30, 31]. In addition, TNF-alpha is a proinflammatory cytokine that is primarily generated by macrophages as well as tumor cells and interaction between TNF family-TNF receptor may drive the progression of CRC[32].

With aging, there is a change in body composition, especially gradual reduction in muscle mass and strength. Excessive fat infiltration in the skeletal muscle, which is called as ‘Myosteatosis’ can occur in elderly people. Also, ‘Sarcopenia’, which is characterized by a decrease in muscle protein mass as well

as a decrease in muscle function, develops with age and is a crucial factor in the development of frailty in elderly individuals [33, 34]. Some studies demonstrated that a series of changes in body composition, especially related to decrease in muscle mass, are associated to short-and long-term prognosis of colon cancer patients. CRC patients with sarcopenia showed poor oncologic outcomes and increased morbidity[35-37]. Sarcopenia was also related with postoperative recovery, showing higher risks of post-operative 90-day morbidity in the elderly [38] and significant adverse postoperative outcomes, including prolonged hospital stay and mortality [39, 40]. Moreover, there was a study on relationship between elderly sarcopenia and inflammatory cytokine like IL-6, showing that IL-6 levels were increased in elderly individual with sarcopenia and sarcopenia was associated with IL-6 [41].

We focused on the two major topics and intended to emphasize on two: “immunity” which is represented by somatic and “sarcopenia” which is represented by changes in body composition and decreased muscular mass in old age. Currently, no factors have been found to predict the degree of recovery following colon cancer surgery in elderly patients, and the same treatment, follow-up interval, and follow-up period are applied to non-aged patients without taking these aspects into consideration. If modifiable factors associated to postoperative recovery are identified, the recovery of elderly CRC patients can be improved by adjusting these factors before and after surgery. By identifying variables that might predict and promote recovery, it will be feasible to provide suitable treatment plans for elderly patients individually.

The purpose of this study was to identify indicators that could predict postoperative recovery in elderly colon cancer patients using blood and imaging test by applying the results validated by retrospective data to prospective study, and identify a modifiable factor that could affect postoperative treatment and follow-up guidelines.

2. Methods

2-1. Patient selection

(1) Retrospective cohort

We reviewed records of colorectal cancer patients who received surgical treatment in multi-centers between March 2018 and September 2020 was conducted. A total 8 institutions in South Korea participated in this study: Asan Medical Center, Seoul ST. Mary's Hospital, Korea University Anam Hospital. Samsung Medical Center, Pusan National University Yangsan Hospital, Gangnam Severance Hospital, Kyungpook National University Chilgok Hospital, and Chonnam National University Hwasun Hospital. They are all tertiary medical center although location and size were various.

We also reviewed the record of patients who received curative resection for colorectal cancer between January 2005 and November 2011 at Asan Medical Center, Seoul with longer follow-up periods than previous cohort. All patients' records were retrospectively reviewed for clinicopathologic features, recurrences and survival status. Data on the existence or non-existence of sarcopenia or not was also provided for this cohort.

All patients with primary colorectal adenocarcinoma who underwent any surgical procedures in the study periods were included. However, familial colorectal cancer, malignancies other than adenocarcinoma, and inflammatory bowel disease-associated cancer were excluded, and recurrence or metastasis were not included as inappropriate cases.

(2) Prospective pilot study

The study involved 40 patients who received radical resection for colon cancer between September 2023 and November 2023 at Asan Medical Center, Seoul, Korea. Eligibility criteria included colon cancer treated with surgery and diagnosed with adenocarcinoma histologically. Patients who had information regarding preoperative status with abdominopelvic CT were included. Patients with concurrent distant metastasis at diagnosis or those with concurrent or prior malignancies within 5 years of the diagnosis of colon cancer or those who were pregnant or on breast feeding were excluded. Patients were excluded if they did not undergo surgical treatment, had no available pre/post-treatment CT, or were pregnant or breastfeeding. Patients with hereditary nonpolyposis colorectal cancer (HNPCC) or familial adenomatous polyposis (FAP) also excluded in this study.

Of 43 patients who received radical resection, one had synchronous lesion and one had peritoneal

seeding, and one showed diffuse B cell lymphoma in final pathologic reports, therefore they were excluded from the patient selection (Figure 1). Patients aged ≥70years were defined as elderly, whereas those aged <70 years were defined as non-elderly.

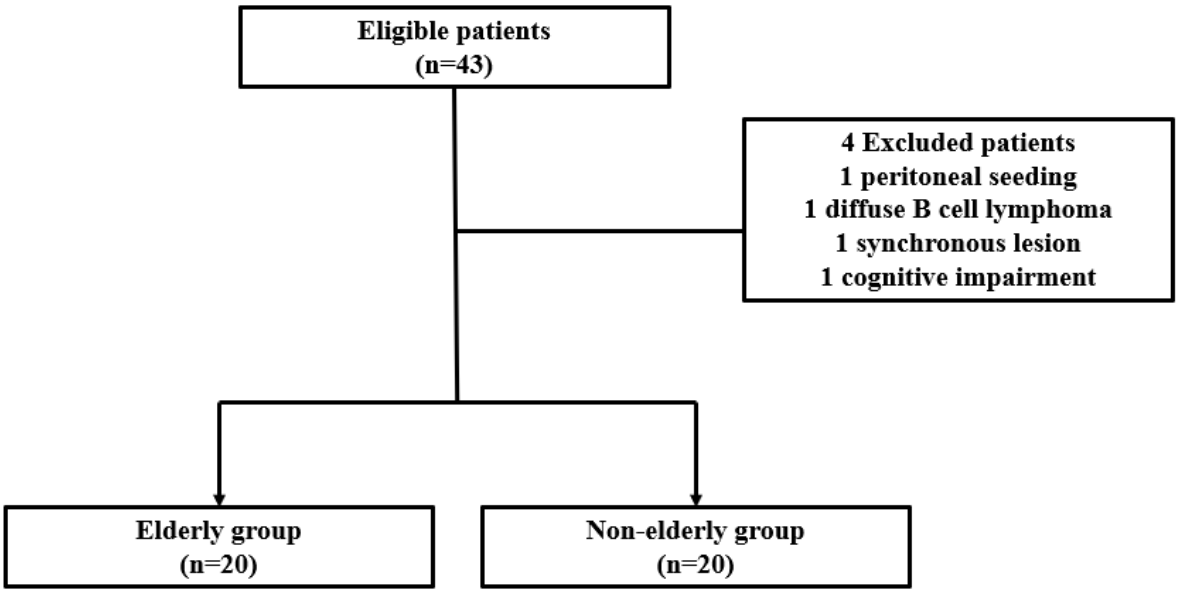


Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram

Prior to curative resection, all patients were assessed based on blood test including carcinoembryonic antigen (CEA) levels, White blood cell (WBC), neutrophil, lymphocyte, albumin and globulin, and colonoscopy for evaluation and biopsy, and abdomino-pelvic computed tomography (CT) for staging of disease.

2-2. Evaluation of clinicopathologic characteristics associated with recovery

(1) Assessment of clinicopathologic characteristics in retrospective cohort

In multicenter data, clinicopathologic features, American Society of Anesthesiologists (ASA) classification and hospital stay was included and sarcopenia was not included. Clinicopathologic features, presence or absence of sarcopenia, hospital stay, recurrences and survival status in retrospective cohort was evaluated. Laboratory tests including neutrophil, lymphocyte, albumin, and

globulin was also reviewed for analyzing the risk factors affecting the recovery. Some variables contained in our center data, such as sarcopenia, globulin, and neutrophil, were not included in the multicenter data, and thus, only the out center data with more diverse variables were used to generate nomograms.

(2) Measurement of immunologic marker/Quality of life in prospective cohort

Preoperative blood sampling including WBC, lymphocyte, neutrophil, albumin, globulin was performed for all patients. Based on the sample data, we estimated and reported neutrophil lymphocyte ratio (NLR) and albumin globulin ratio (AGR). Immunologic tests such as IL-6, NK cell and TNF-alpha were done in addition to the routine blood test. These blood tests including immunologic markers were conducted before surgery, on the third day following surgery, and on the first outpatient visit day (approximately 21 days after surgery) (Figure 2). The IL-6 and NK cell tests were carried out in our hospital, whereas TNF-alpha test was conducted through consignment inspection at Green Cross South Korea company. IL-6 samples were collected, centrifuged and analyzed in-hospital. TNF-alpha samples were collected, centrifuged, stored in a freezer at minus 80 degrees Celsius, and transferred to Green Cross South Korea company for analysis after obtaining the last sample.

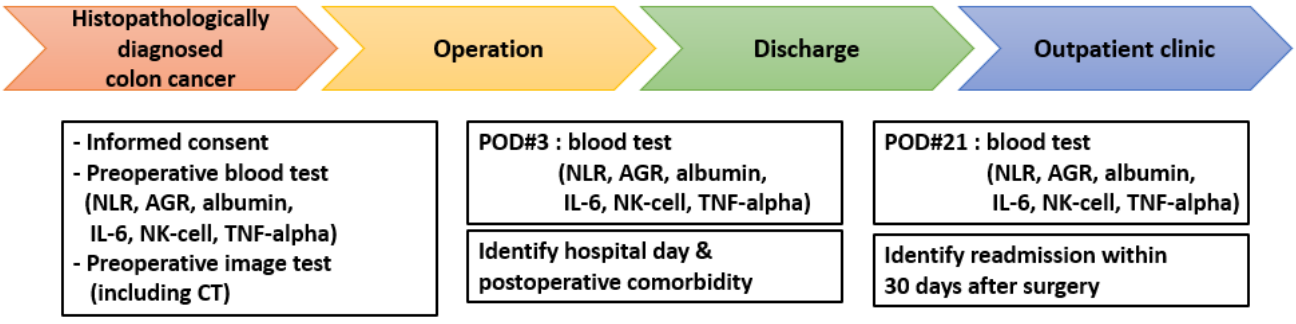


Figure 2. Flow chart from diagnosis to postoperative follow up. NLR, neutrophil lymphocyte ratio; AGR, albumin-globulin ratio; IL-6, interleukin-6; NK cell, natural killer cell; TNF-alpha, tumor necrosis factor-alpha.

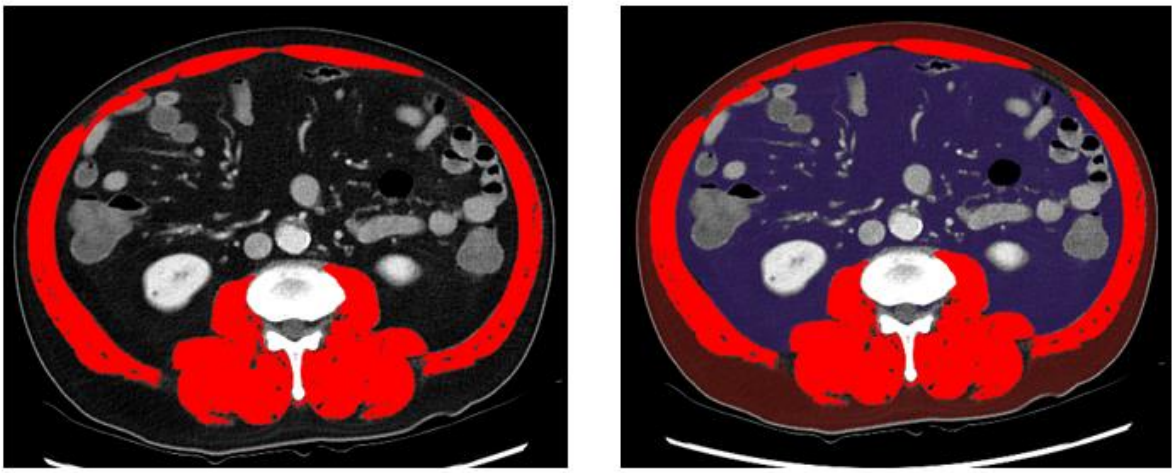
We also attempted to establish the patient's subjective health level using a simple questionnaire, and we compare preoperative basal status with postoperative basal status using the same questionnaire. We

used EuroQol group-5dimension-3level (EQ-5D-3L), a standardized measure of health status developed by EuroQol Group to offer a basic, general measure of health for clinical and economic evaluation [42]. We employ the EQ-5D-3L descriptive system, which includes the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is divided into three levels: no problem, some problems, and severe problems. The respondent is asked to identify his or her health status by checking the box next to the most applicable statement in each of the five dimensions [43]. The index value was derived using the following formula: EQ-5D-3L index=1 -(0.050 + 0.096*M2 + 0.418*M3 + 0.046*SC2 + 0.136*SC3 + 0.051*UA2 + 0.208*UA3 + 0.037*PD2 + 0.151*PD3 + 0.043*AD2 + 0.158*AD3 + 0.050*N3). 'M' means mobility, 'SC' means self-care, 'UA' means usual activity, 'PD' means pain/discomfort, and 'AD' anxiety/depression. The number 2 or 3 after each letter is the level of response per dimension, with a '1' if it is 2 or 3, and a '0' if it is not, and N3 is replaced with '1' if there is at least one level 3 and '0' otherwise. A the calculated score means a healthier state as it is closer to 1.[44]

(3) Sarcopenia

Body composition on CT was evaluated with artificial intelligence software (AID-U^{TM}, iAID inc, Seoul, Korea), a fully automatic deep learning system for both L3 selection and body composition assessment. The software uses a YOLOv3-based algorithm for automatic L3 inferior endplate level selection and a fully convolution network (FCN) for segmentation of abdominal muscle area and fat areas. Selected L3 level CT images were automatically segmented to generate boundary of total abdominal muscles and measured the abdominal muscle and fat area. Then, experienced operators (Y.K. and K.W.K.) checked the quality of the muscle segmentation in all images. Skeletal muscle area (SMA) including all muscles on the selected axial images, i.e., psoas, paraspinal, transversus abdominis, rectus abdominis, quadratus lumborum, and internal and external obliques, were demarcated using predetermined thresholds of -29 to +150 Hounsfield units. The visceral fat area and the subcutaneous fat area were also demarcated using fat tissue thresholds of -190 to -30 Hounsfield units (Figure 3).

(A)



(B)

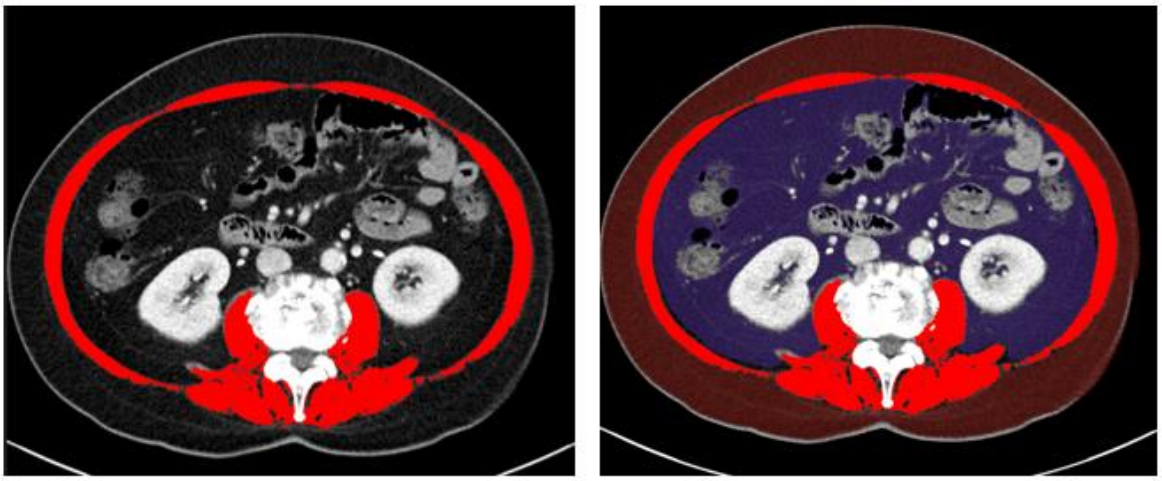


Figure 3. Body composition on Computed Tomography evaluated with artificial intelligence software. Red color: skeletal muscle area, including all muscles on the selected axial images; purple color: visceral fat; dark red color: subcutaneous fat (A) normal patient (B) sarcopenia patient

The skeletal muscle index (SMI) was calculated by dividing the SMA (cm^2) by the patient's height (m^2). In this study, sarcopenia was defined as an SMI < 41cm2/m2 in women, SMI < 43 cm2/m2 in men with a body mass index (BMI) < 25kg/m2, and <41cm2/m2 in women, < 53 cm2/m2 in men with a BMI ≥ 25 kg/m2 [45]

2-3. Statistical analysis

In this study, primary end point was recovery represented by hospital stay defined as the day from operation to discharge and readmission within 30days after discharge. Secondary end point was EQ-5D-3L (only in prospective cohort). 'Recovery' was evaluated by hospital stay and readmission within 30 days after discharge. Patients who had a shorter-than-average hospital stay rated their recovery as fast, whereas those who had a longer-than-average hospital stay rated their recovery as slow. Patients who readmitted within 30days after discharge in fast recovery group was reclassified as slow recovery group. Analyses of clinicopathological characteristics of categorical variables and continuous variables were conducted using the chi-square test and t-test, respectively. A multivariable analysis with Cox proportional hazards model was used to compare risk factors associated with postoperative hospital day including NLR, AGR, albumin, BMI and sarcopenia. We conducted an analysis including variables that have been proven to be related to the immune system or recovery in previous studies or that are suspected to be clinically relevant. Based on these analyses, we established nomogram using independent variables mentioned above to predict recovery. P-values < 0.2 were considered statistically significant in univariate analysis and P-values <0.05 were considered statistically significant in multivariate analysis. All statistical analyses were conducted using IBM SPSS Statistics ver. 21.0. (IBM Co., Armonk, NY, USA) and R software (version 4.0.5).

3. Results

(1) Retrospective cohort study

1. Risk analysis related with recovery in multicenter cohort

1) Clinicopathologic characteristics of multicenter cohort

Of 10,271 patients, the mean age was 63.3 (±12.2) years and 3315 (32.3%) were above 70 years old. 5996 (58.4%) were male and most of them, 7102 (69.1%) were classified as ASA classification II. The mean f/u period was 29.4 (±13.0) months, and 900 (8.8%) had recurrence in that period. About 20% of patients experienced post-operative complications such as ileus, urinary discomfort, wound problems

and so on. (1705, 19.5%), and 250 (3.7%) readmitted within 30 days after discharge. The average hospital stay was 7.8 (±4.9) days and slow-recovery group included 3191 patients who discharged after 8 days of operation and 189 patients who discharged within 7 days of operation, but readmitted within 30 days. The proportion of patients who recovered quickly was statistically significantly lower in the elderly group (35.3% vs. 30.8%, p<0.001)

In the elderly group, the mean age was 76.8 (±5.1) years and 1838 (55.4%) were male. 547 (20.5%) of them had postoperative complications, and 67 (3.6%) of them readmitted within 30 days after discharge. The mean hospital stay was 8.0 (±5.4) days, and 2122 (64.0%) was categorized as fast-recovery group.

2) Associated factors with short-term postoperative recovery in colorectal cancer above 70 years old (multicenter data)

In multicenter data, ASA classification was associated with postoperative recovery in elderly patients (OR 0.70; 95%CI, 0.60-0.82, P <0.001). Furthermore, it was found that there was a correlation between the clinical stage and recovery, with the higher the clinical T (cT) and N (cN) stages, the later the recovery occurred (cT, OR 0.69; 95%CI, 0.56-0.85, P <0.001; cN, OR 0.69; 95%CI, 0.58-0.82, P <0.001, respectively) (Table 1).

Table 1. Univariate and multivariate analysis of risk factors for recovery in elderly patients

	Recovery			
	Univariate		**Multivariate**	
	OR (95%Cl)	**p-value**	**OR (95%Cl)**	**p-value**
preoperative BMI				NA
<18.5	1 (Reference)		NA	
18.5-24.9	1.01 (0.94-1.10)	0.7348	NA	
≥25.0	1.04 (0.96-1.13)	0.3382	NA	
ASA classification		<0.001		<0.001
1,2	1 (Reference)		1 (Reference)	
≥3	0.92 (0.89-0.96)		0.70 (0.60-0.82)	
cT		<0.001		<0.001
0-2	1 (Reference)		1 (Reference)	

3-4	0.91 (0.87-0.96)		0.69 (0.56-0.85)	
cN		<0.001		<0.001
0	1 (Reference)		1 (Reference)	
1,2	0.92 (0.88-0.96)		0.69 (0.58-0.82)	

Odds ratio was calculated by multivariable analysis which were significant on univariable analysis
Comparisons that were not significant on univariable analysis did not undergo multivariable analysis
BMI, body mass index; ASA, American society of anesthesiologists; c, clinical stage

3) Risk factors associated with short-term oncologic outcomes in colorectal cancer above 70 years old

In multivariable analysis, recovery status, pathologic T, N (pT, pN) stage and perineural invasion (Pni) was associated with RFS in elderly group (Table 2). Patients who were discharged within 7 days and were not readmitted within 30days were at lower risk of recurrence (HR 0.65; 95%CI, 0.52-0.82, P <0.001). Pathologic stage was significantly associated with recurrence, showing that the higher the pT, N stage, the higher the risk of recurrence (pT stage; HR 1.73; 95%CI, 1.18-2.55, P <0.001; cT; HR 2.19; 95%CI, 1.68-2.85, P <0.001). Additionally, patients with perineural invasion were associated with high recurrence (HR 1.32; 95%CI, 1.03-1.70, P <0.029)

Table 2. Multivariable analysis of risk factors for recurrence free survival in elderly patients

	Recurrence			
	Univariable		**Multivariable**	
	HR (95%Cl)	**p-value**	**HR (95%Cl)**	**p-value**
preoperative BMI				NA
<18.5	1 (Reference)		NA	
18.5-24.9	0.95 (0.54-1.67)	0.856	NA	
≥25.0	0.75 (0.42-1.35)	0.338	NA	
Recovery		<0.001		<0.001
Slow	1 (Reference)		1 (Reference)	
Fast	0.61 (0.48-0.77)		0.65 (0.52-0.82)	
pT		<0.001		0.005
0-2	1 (Reference)		1 (Reference)	
3-4	2.84 (1.98-4.08)		1.73 (1.18-2.55)	
pN		<0.001		<0.001
0	1 (Reference)		1 (Reference)	

1,2	2.86 (2.25-3.64)		2.19 (1.68-2.85)	
Lvi		<0.001		0.417
No	1 (Reference)		1 (Reference)	
Yes	1.79 (1.42-2.26)		1.77 (1.12-2.80)	
Pni		<0.001		0.029
No	1 (Reference)		1 (Reference)	
Yes	2.02 (1.60-2.54)		1.32 (1.03-1.70)	

Hazard ratio was calculated by multivariable analysis which were significant on univariable analysis

Comparisons that were not significant on univariable analysis did not undergo multivariable analysis

BMI, body mass index; cT, clinical T; cN, clinical N; p, pathologic stage Lvi, lymphovascular invasion; Pni, perineural invasion

2. Risk analysis of colorectal cancer above 70 years old (our center)

Of 1382 patients, 252 (18.2%) were above 70 years old and the mean age was 59.0 (±10.9) years. Sarcopenia was more identified in elderly group (age ≥ 70 years) than non-elderly group (age < 70 years) (84.9% vs 64.4%, p<0.001). In elderly group, 156 (61.9%) was male and mean age was 74.7 (±3.8) years. Mean of hospital stay was 10.4 (±7.6) days and, of the patients discharged earlier than the average hospital stay, 4 were readmitted within 30 days after discharge. Of 252 patients, 182 (72.2%) was categorized as fast-recovery group.

1) Associated factors with short-term postoperative recovery

In multivariable analysis, NLR, albumin and sarcopenia were associated with recovery after operation in elderly patients. (NLR; OR 0.52; 95%CI, 0.28-0.97, P=0.041; albumin; OR 2.01; 95%CI, 1.06-3.79, P=0.032; sarcopenia; OR 0.44; 95%CI, 0.21-0.94, P=0.034). Based on the results of multivariate analysis, significant variables were used to formulate the nomogram for possibility of recovery after operation for elderly patients. We constructed a prediction nomogram model of recovery (Figure 4). A summary of the point value of each variable used to compute the final score is provided. The points per unit of linear predictor is 115.855 and linear predictor units per point is 0.008631514. To begin, a vertical line was constructed to correspond to a certain score in the prediction of recovery based on the value of each variable. Patients with NLR less than 3.0 points had 76 points, with albumin

level more than 3.5g/L had 87 points, and without sarcopenia had 100 points. Then, vertical line on total points, which is the sum of three points you read on the points scale can be used to read the possibility of recovery. If patients had total 25 points, the possibility of recovery is 50%, and 75 points with 60%, 129 points with 70%, and 195 points with 80%.

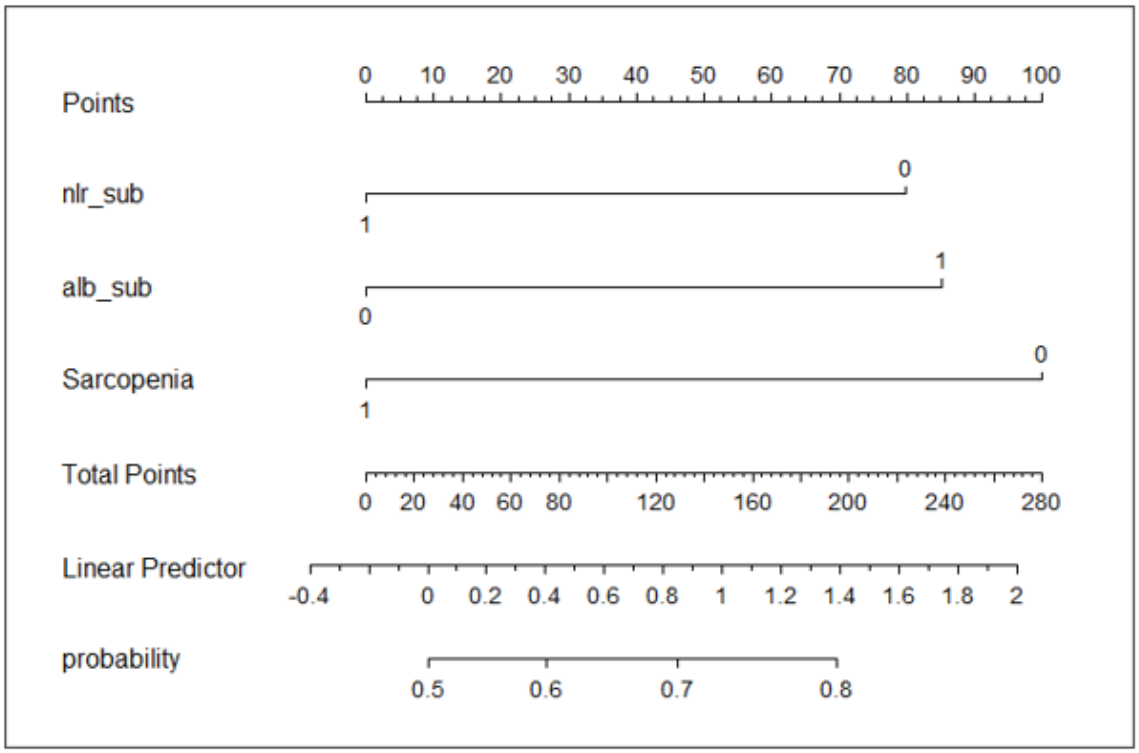
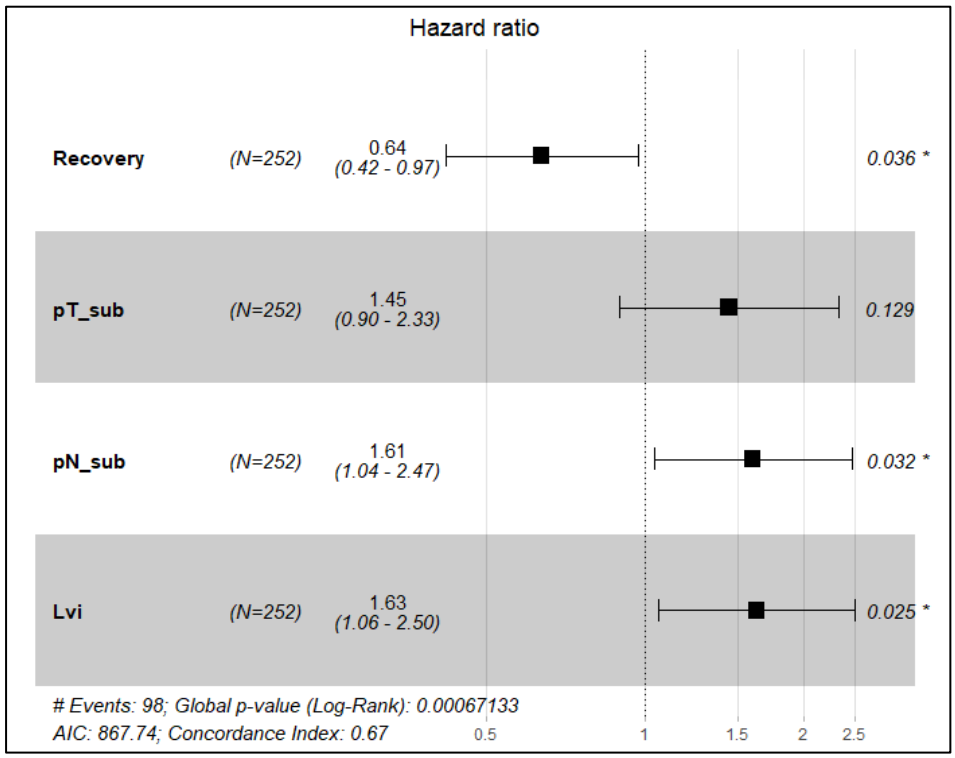


Figure 4. Nomogram to estimate the possibility of recovery; nlr, neutrophil- lymphocyte ratio; sub, subgroup; alb, albumin;

2) Risk factors associated with oncologic outcomes in colorectal cancer above 70 years old

In multivariable analysis, pathologic N stage was associated with OS and RFS. (OS; HR 1.61; 95%CI, 1.04-2.47; P=0.032, RFS; HR 2.24; 95%CI, 1.31-3.84; P=0.003). Fast recovery represented by shorter hospital stay without readmission within 30 days after discharge and lymphovascular invasion were associated with OS (HR 0.64; 95%CI, 0.42-0.97; P=0.036 HR 1.63; 95%CI, 1.06-2.50; P=0.004, respectively). Additionally, Albumin-globulin ratio and pathologic T stage was associated with RFS (HR 0.56; 95%CI, 0.33-0.97; P=0.038, HR 3.08; 95%CI, 1.44-6.59; P=0.004, respectively). Meanwhile, Sarcopenia was also not associated with both OS and RFS (Figure 5)

(A)



(B)

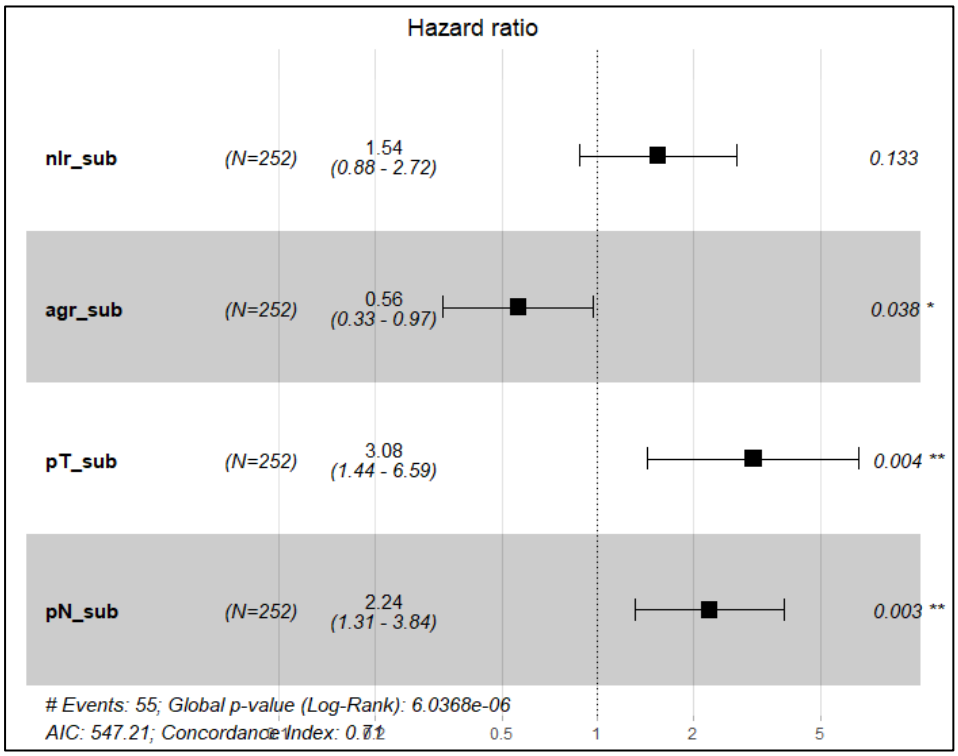


Figure 5. Forest plot of hazard ratio for death (A) and recurrence (B), pT, pathologic T stage; sub, subgroup; pN, pathologic N stage; Lvi, lymphovascular invasion; nlr, neutrophil lymphocyte ratio; agr, albumin-globulin ratio

(2) Prospective pilot cohort

1) Clinicopathological features of colon cancer (elderly vs non elderly)

Of 40 patients, 24 (60.0%) were male and the mean age was 66.3 (±13.0) years old. About 60% of all patients had more than one comorbidity. (62.5%, 25 patients). The mean hospital day was 5 days most of all discharged within 5 days (85%, 34 patients).

The entire number of patients was divided into elderly and non-elderly groups based on the age of 70, and 20 patients were assigned each. The mean age was 55.5 (±8.4) years old in non-elderly group, and 77.2 (±5.3) in elderly group. The proportion of male was higher in the non-elderly group, (70.0% vs. 50.0%), as was the proportion with lower ASA classification scores (95.0% vs. 85.0%), although both were not statistically significant. (P=0.333, P=0.468, respectively). Patients with comorbidities were more in elderly group (90.0% vs. 35.0%, P=0.004), especially with 3 or more comorbidities significantly (25.0% vs. 10.0%, P=0.004) (Table 3).

Table 3. Demographic and clinicopathologic characteristics of patients aged <70 and ≥70 years in the study population

	Age		
	Non-elderly (n=20)	**Elderly (n=20)**	**p-value**
Sex			0.333
Male	14 (70.0%)	10 (50.0%)	
Female	6 (30.0%)	10 (50.0%)	
Age (year)			<0.001
Mean ± SD	55.5 ± 8.4	77.2 ± 5.3	
Tumor location*			
Right colon	6 (30.0%)	10 (50.0%)	
Left colon	2 (10.0%)	10 (50.0%)	
Approach			0.468
Laparoscopy	18 (90.0%)	20 (100.0%)	
Robot	2 (10.0%)	0 (0.0%)	
preoperative BMI			0.584
<18.5	1 (5.0%)	0 (0.0%)	
18.5-24.9	13 (65.0%)	13 (65.0%)	
≥25.0	6 (30.0%)	7 (35.0%)	
ASA classification			0.598
1,2	19 (95.0%)	17 (85.0%)	

3,4	1 (5.0%)	3 (15.0%)	
No. of comorbidities			0.004
0	13 (65.0%)	2 (10.0%)	
1	2 (10.0%)	8 (40.0%)	
2	3 (15.0%)	5 (25.0%)	
3+	2 (10.0%)	5 (25.0%)	

BMI, body mass index; ASA, American society of anesthesiologists; No, number;
*Right colon: cecum, ascending colon, hepatic flexure proximal transverse colon; Left colon: splenic flexure, sigmoid colon

2) Association of recovery factor between elderly and non-elderly patients and risk factors for recovery in elderly patients

There was no significant difference in clinicopathologic characteristics associated with recovery between non-elderly and elderly-groups (Table 4). The elderly had a larger prevalence of sarcopenia, however, it was not statistically significant (45.0% vs. 30.0%, P=0.514). The proportion of patients who recovered quickly was the same in both groups, as the proportion of patients who had an EQ-5D score higher than average. There were eight patients with postoperative complications; Three of them had ileus, so the diet was progressed slowly, and one of them vomited and had a L-tube inserted. Two of them experienced wound problems and two had chyle leakage treated with low long chain triglycerides diet. One had an CT scan because of a persistent high body temperature; there was no particular abnormalities at the surgery site, but therapeutic antibiotics were started to manage the infection. Patients with postoperative complications were more common in elderly group, however it was not statistically significant (25.0% vs. 15.0%, P=0.747).

Table 4. Clinicopathologic characteristics associated with recovery of patients aged <70 and ≥70 years in the study population

	Age		
	Non-elderly (<70 years) (n=20)	**Elderly (≥70 years) (n=20)**	**p-value**
NLR			0.230
<3.0	20 (100.0%)	17 (85.0%)	
≥3.0	0 (0.0%)	3 (15.0%)	
AGR			0.340
<1.2	7 (35.0%)	11 (55.0%)	
≥1.2	13(65.0%)	9 (45.0%)	

Albumin			0.658
<3.5	2 (10.0%)	4 (20.0%)	
≥3.5	18 (90.0%)	16 (80.0%)	
Sarcopenia			0.514
No	14 (70.0%)	11 (55.0%)	
Yes	6 (30.0%)	9 (45.0%)	
Recovery			1
Slow	3 (15.0%)	3 (15.0%)	
fast	17(85.0%)	17(85.0%)	
Postoperative complication			0.747
No	17 (85.0%)	15 (75.0%)	
Yes	3 (15.0%)	5 (25.0%)	
EQ-5D (preoperative)			1
<0.92	5 (25.0%)	5 (25.0%)	
≥0.92	15 (75.0%)	15 (75.0%)	
pT			0.747
0-2	9 (45.0%)	7 (35.0%)	
3-4	11 (55.0%)	13 (65.0%)	
pN			0.747
0	13 (65.0%)	11 (55.0%)	
1,2	7 (35.0%)	9 (45.0%)	

NLR, neutrophil-lymphocyte ratio; AGR, albumin-globulin ratio; EQ-5D, EurQol-5dimension; p, pathologic stage

In overall cohort, ASA classification, albumin, and cT stage was associated with recovery, respectively in univariable analysis (OR: 0.13; 95% CI, 0.01-1.15, P=0.066; OR: 3.75; 95% CI, 0.51-27.50, P=0.196, OR: 0.20,95% CI, 0.02-1.90, P=0.161, respectively). However, it was not statistically significant in multivariable analysis (OR: 0.08; 95% CI, 0.01-1.10, P=0.06; OR: 1.58; 95% CI, 1.17-1.36, P=0.175, OR: 0.14, 95% CI, 0.01-1.78, P=0.129, respectively). NLR, AGR and cN stage was not associated with recovery and sarcopenia was not either. In elderly group, ASA classification was the only risk factor for recovery in univariable analysis, while the others had no significant effects (Table 5). Sarcopenia was not associated with recovery in either the overall or elderly cohort. (P=0.624 and P=0.662)

Table 5. Univariate and multivariate analysis of risk factors for hospital day in elderly patients

	Recovery		
	Univariate		
	OR	**(95%Cl)**	**p-value**
NLR			0.358
<3.0	1 (Reference)		
≥3.0	0.27	0.02-4.46	
preoperative BMI			0.996
<18.5	1 (Reference)		
18.5-24.9	NA	NA	
≥25.0	NA	NA	
AGR			0.662
<1.2	1 (Reference)		
≥1.2	1.78	0.13-23.52	
Albumin			0.539
<3.5	1 (Reference)		
≥3.5	2.33	0.16-34.89	
Sarcopenia			0.662
No	1 (Reference)		
Yes	0.56	0.04-7.44	
ASA classification			0.030
1,2	1 (Reference)		
3,4	0.03	0.00-0.72	
cT			0.996
0-2	1 (Reference)		
3-4	0	0-Inf	
cN			0.662
0	1 (Reference)		
1,2	0.56	0.04-7.44	

Odds ratio was calculated by univariable analysis

Comparisons that were not significant on univariable analysis did not undergo multivariable analysis

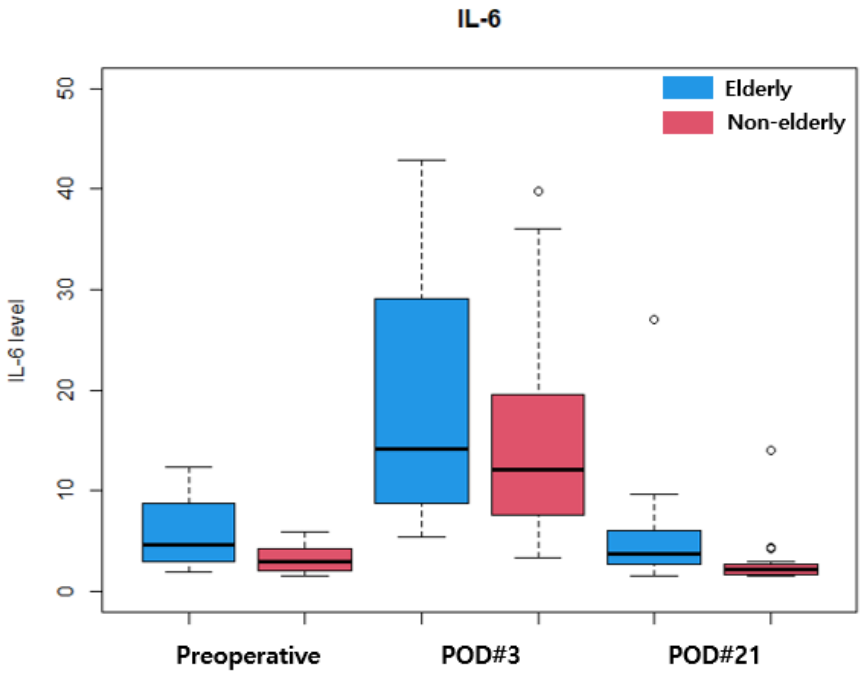
NLR, neutrophil-lymphocyte ratio; BMI, body mass index; ASA, American society of anesthesiologists; AGR, albumin-globulin ratio; c, clinical stage

The nomogram in the previous retrospective data was established based on the independent risk factors. In the prospective data seeing, under the Receiver Operating Characteristic (ROC) curve (AUC) was 0.607 by external validation, showing poor discrimination.

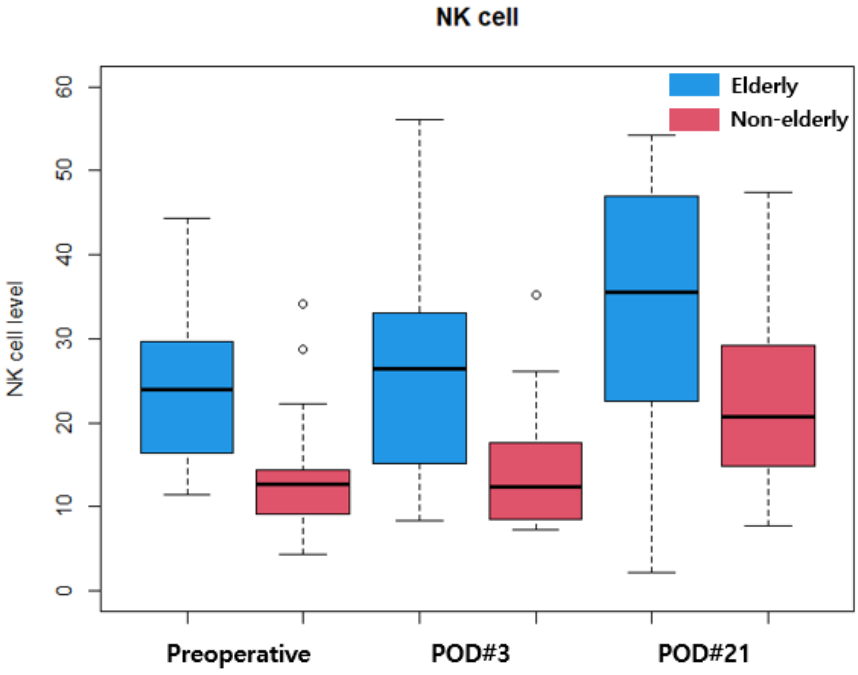
3) Association of immunologic factors between elderly and non-elderly patients and risk factors for recovery in elderly patients

In overall cohort, the average of IL-6 level tended to be high in the elderly group than non-elderly group when comparing the level of two groups (Figure 6). The average of preoperative IL-6 level was significantly higher in the elderly group than non-elderly group (6.055 vs. 3.230, P=0.002). The elderly group had higher mean values for both the IL-6 level on the postoperative day 3 (POD#3) and postoperative day 21 (POD#21), however, there was no statistically significant difference (POD#3: 18.070 vs. 14.625, P=0.332, POD#21: 13.320 vs. 2.920, P=0.2127). In the case of NK cell, the elderly group exhibited a generally higher total NK cell level. Compared to non-elderly group, the average NK cell value of the elderly group was higher in all preoperative, postoperative day 3, and postoperative day 21, and all of these differences were statistically significant (Preoperative day: 24.375 vs. 13.765, P <0.001, POD#3: 25.670 vs. 14.460, P=0.001, POD#21: 34.161 vs. 22.215, P=0.005). TNF-alpha also showed a higher average value in the elderly group, although there was no discernible difference in the numerical value and not significant statistically. Furthermore, irrespective of the time of blood collection, there was no statistically difference in both preoperative, postoperative day3, and postoperative day 21. (Preoperative day: 1.332 vs. 1.156, P <0.200, POD#3: 1.423 vs. 1.178, P=0.137, POD#21: 1.232 vs. 1.004, P=0.057).

(A)


IL-6
Elderly
Non-elderly
IL-6 level
0
10
20
30
40
50
Preoperative
POD#3
POD#21

(B)


NK cell
Elderly
Non-elderly
NK cell level
0
10
20
30
40
50
60
Preoperative
POD#3
POD#21

(C)

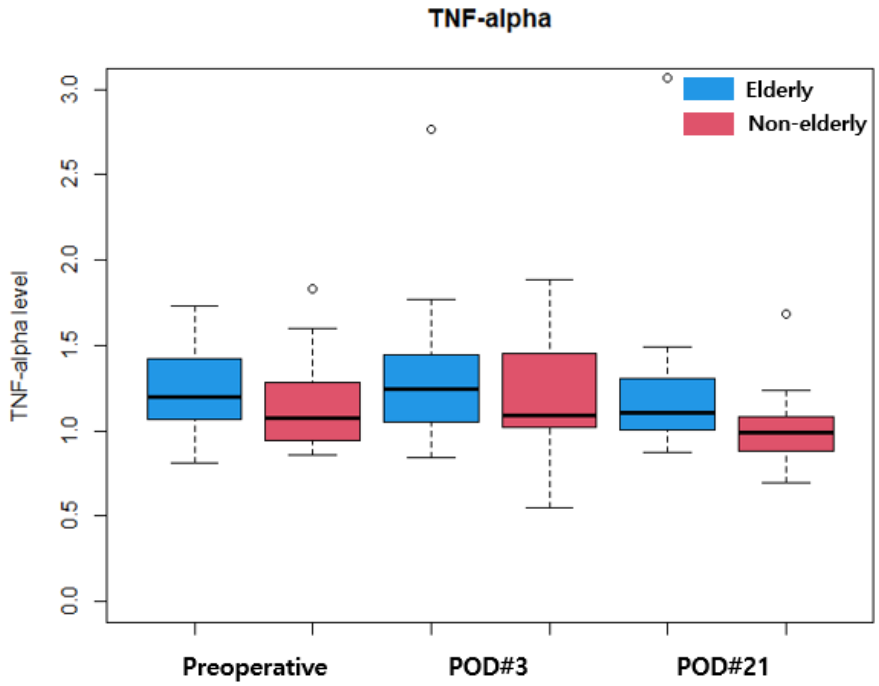


Figure 6. Box plot comparing the mean value between the elderly group and the non-elderly group in chronological order. (A) interleukin 6 level (B) NK cell level (C) TNF alpha level; IL-6, interleukin-6; NK cell, natural killer cell; TNF-alpha, tumor necrosis factor- alpha

In overall cohort, IL-6 level at POD#3 and TNF-alpha level at POD#3 was associated with recovery in univariable analysis (OR: 0.95, 95% CI, 0.89-1.02, P=0.189 and OR: 0.16, 95% CI, 0.02-0.99, P=0.049). Additionally, TNF-alpha level at POD#3 was associated with recovery in multivariable analysis (OR: 0.16, 95% CI, 0.02-0.99, P=0.049). However, there were no significant variables associated with recovery among the immunologic factors in elderly patients regardless of the type of immunologic factor or the timing of blood collection (Table 6).

Table 6. Univariate and multivariate analysis of risk factors among cytokines for hospital day in elderly patients

	Recovery		
	Univariate		
	OR (95%CI)	**95% CI**	**p-value**
Preoperative lab			
IL-6	0.8	0.55-1.17	0.259

NK cell	0.99	0.86-1.13	0.857
TNF-alpha	0.86	0.08-9.06	0.897
POD#3 lab			
IL-6	0.97	0.88-1.08	0.596
NK cell	0.99	0.89-1.09	0.782
TNF-alpha	0.21	0.04-1.27	0.089
POD#21 lab			
IL-6	1.06	0.75-1.50	0.727
NK cell	0.99	0.89-1.09	0.782
TNF-alpha	1.46	0.05-39.09	0.821

Odds ratio was calculated by univariable analysis

Comparisons that were not significant on univariable analysis did not undergo multivariable analysis

IL-6, interleukin-6; NK cell, natural killer cell; TNF-alpha, tumor necrosis factor alpha

4) Association between recovery factors and sarcopenia & between immunologic factors and sarcopenia

Among the variable that were thought to be clinically related to recovery, there were no variables showing differences according to the presence or absence of sarcopenia in overall cohort. Likewise, in the elderly group, none of the variables considered clinically related to recovery showed significant differences based on the presence or absence of sarcopenia. Even, there was a numerically higher proportion of patients who recovered quickly among patients with sarcopenia; however, the difference was not statistically significant and there was actually only one difference when comparing the number of patients concerned (Table 7).

Table 7. Association between recovery factors and sarcopenia in elderly patients

	Sarcopenia		
	No (n=11)	**Yes (n=9)**	**p-value**
NLR			1
<3.0	9 (81.8%)	8 (88.9%)	
≥3.0	2 (18.2%)	1 (11.1%)	
preoperative BMI			1
<18.5	0 (0.0%)	0 (0.0%)	
18.5-24.9	7 (63.6%)	6 (66.7%)	
≥25.0	4 (36.4%)	3 (33.3%)	
AGR			1

<1.2	6 (54.5%)	5 (55.6%)	
≥1.2	5 (45.5%)	4 (44.4%)	
Albumin			0.432
<3.5	1 (9.1%)	3 (33.3%)	
≥3.5	10 (90.9%)	6 (66.7%)	
ASA classification			1
1,2	9 (81.8%)	8 (88.9%)	
3,4	2 (18.2%)	1 (11.1%)	
Recovery			1
0	2 (18.2%)	1 (11.1%)	
1	9 (81.8%)	8 (88.9%)	
cT			1
0-2	4 (36.4%)	3 (33.3%)	
3-4	7 (63.6%)	6 (66.7%)	
cN			0.203
0	5 (45.5%)	4 (44.4%)	
1,2	6 (54.5%)	5 (55.6%)	

Hazard ratio was calculated by multivariable analysis which were significant on univariable analysis

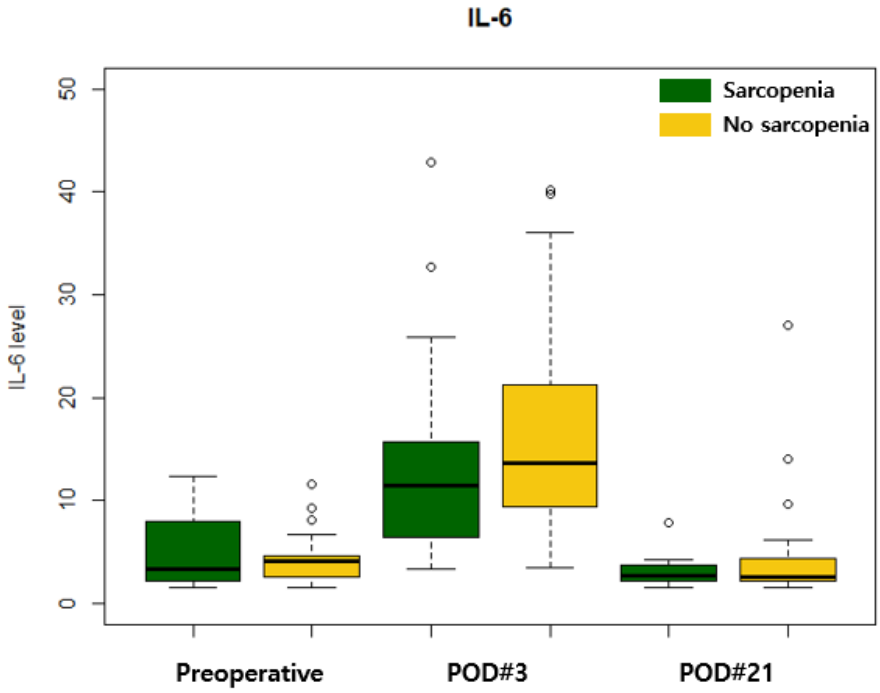
Comparisons that were not significant on univariable analysis did not undergo multivariable analysis

NLR, neutrophil-lymphocyte ratio; BMI, body mass index; AGR, albumin-globulin ratio; ASA, American society of anesthesiologists; c, clinical stage

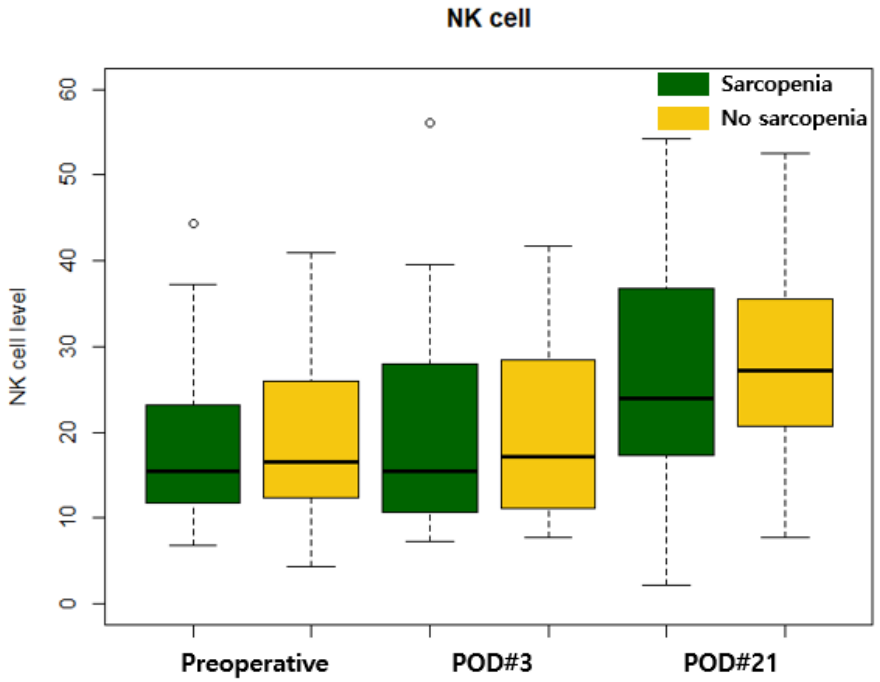
There were no statistically significant variables in the distribution of immunologic factors related with sarcopenia including IL-6 and NK cell regardless of the timing of blood sampling; preoperative, POD#3 and POD#21 (Figure 7). In IL-6, preoperative value was higher in patients with sarcopenia, however, postoperative value was higher in patients without sarcopenia in both POD#3 and POD#21. Not every difference was statistically significant, though (Preoperative day: 5.047 vs. 4.400, P=0.513, POD#3: 14.427 vs. 17.500, P=0.403, POD#21: 3.093 vs. 11.136, P=0.213). In NK cell, the average of level was higher in patients with sarcopenia whatever the time. Yet, a statistically significant difference was not shown in this variable either (Preoperative day: 19.133 vs. 19.032, P=0.976, POD#3: 21.133 vs. 19.440, P=0.663, POD#21: 28.295 vs. 18.124, P=0.971). In TNF-alpha, the average of level was higher in patients with sarcopenia at preoperative, and postoperative 21th day, and higher in patients without sarcopenia at postoperative 3rd day. Likewise, there were no statistically significant differences in these outcomes (Preoperative day: 1.256 vs. 1.229, P=0.841, POD#3: 1.256 vs. 1.327, P=0.679,

POD#21: 1.165 vs. 1.090, P=0.549).

(A)



(B)



(C)

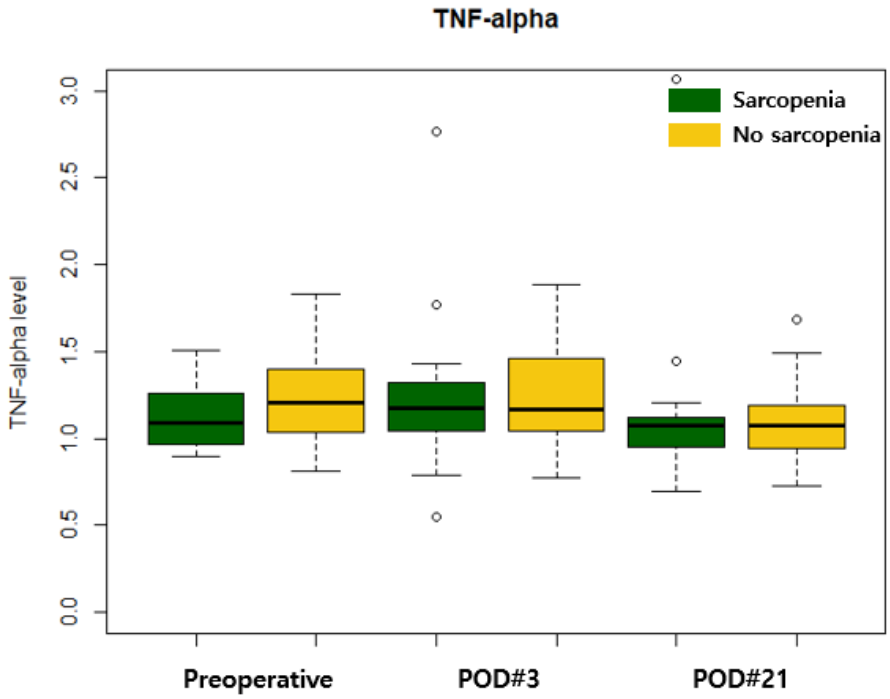


Figure 7. Box plot comparing the mean value of immunologic factors between the sarcopenia group and No sarcopenia group in chronological order. (A) interleukin 6 level (B) NK cell level (C) TNF alpha level; IL-6, interleukin-6; NK cell, natural killer cell; TNF-alpha, tumor necrosis factor-alpha

In overall cohort, irrespective of the sort of immunologic factor or the time of blood collection, there were no significant factors related to recovery among the immunologic factors in overall cohort. Similarly, no factors were shown to be significantly relevant in the elderly group (Table 8).

Table 8. Univariate and multivariate analysis of risk factors among cytokines for hospital day in elderly patients

	Sarcopenia		
	Univariate		
	OR (95%Cl)	95% CI	p-value
Preoperative lab			
IL-6	1.16	0.88-1.52	0.291
NK cell	0.96	0.87-1.07	0.496
TNF-alpha	2.8	0.29-26.98	0.374
POD#3 lab			
IL-6	1	0.93-1.08	0.984

NK cell	1.01	0.94-1.09	0.756
TNF-alpha	1.22	0.30-4.92	0.785
POD#20 lab			
IL-6	0.81	0.52-1.25	0.346
NK cell	0.99	0.93-1.06	0.824
TNF-alpha	3.02	0.24-38.48	0.396

Odds ratio was calculated by univariable analysis

Comparisons that were not significant on univariable analysis did not undergo multivariable analysis

IL-6, interleukin-6; NK cell, natural killer cell; TNF-alpha, tumor necrosis factor alpha

5) Differences of EQ-5D-3L according to age and recovery

The proportion of patients with higher pre-operative EQ-5D-3L index value was more common in fast recovery group (64.7% vs. 33.3%) for elderly cohort, while the proportion of patients with higher post-operative EQ-5D-3L index value was similar in lower post-operative EQ-5D-3L index value (67.6% vs.66.7%) in overall cohort. However, neither was statistically significant (P=0.701 and P=1.000, respectively). In elderly group, patients in the fast recovery group had a larger proportion of patients with higher pre-operative EQ-5D-3L index (64.7% vs. 33.3%), and as well as a higher proportion of patients with higher post-operative EQ-5D-3L index (88.2% vs. 33.3%). However, it was also not significant statistically (P=0.701, P=0.159, respectively)

Postoperative EQ-5D-3L index value showed a higher mean value in the elderly group, however, did not show a statistically significant difference (non-elderly group: 0.902, elderly group: 0.860, P=0.125) (Figure 8).

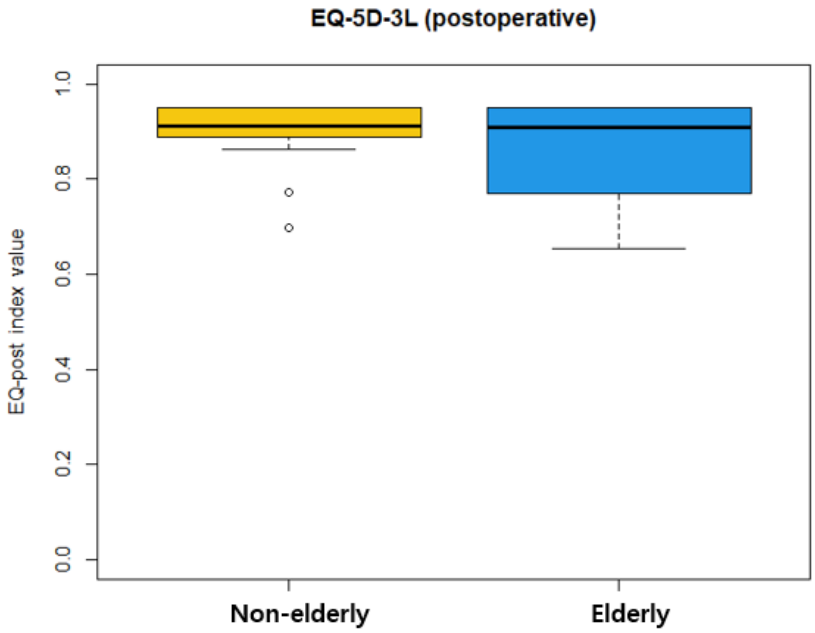


Figure 8. Box plot comparing the mean value of postoperative EQ-5D-3L index value between non-elderly group and elderly group; EQ-5D-3L, EuroQol group – 5 dimension – 3 level

In addition, the slow recovery group exhibited a lower mean value for the postoperative EQ-5D-3L index value, nevertheless, there was no statistically significant difference observed (0.869 vs. 0.883, P=0.125) (Figure 9).

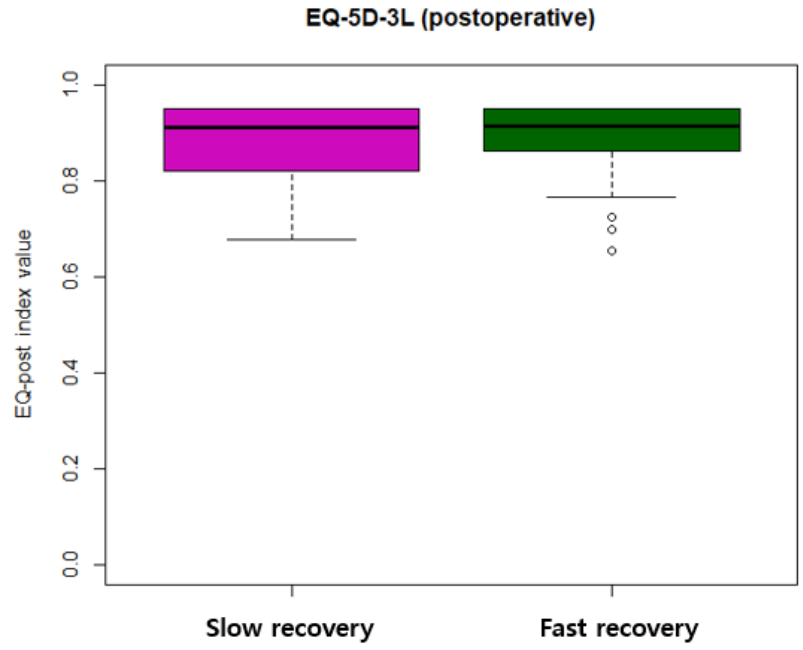


Figure 9. Box plot comparing the mean value of postoperative EQ-5D-3L index value between slow recovery group and fast recovery group; EQ-5D-3L, EuroQol group – 5 dimension – 3 level

4. Discussion

We found that NLR, albumin, and sarcopenia were associated with postoperative recovery in elderly patients and fast recovery, represented by short hospital stay without readmission within 30days after discharge was associated with OS, and associated with short-term RFS in multicenter data. In addition, ASA classification was only risk factor for recovery. Elderly patients showed higher mean value of IL-6 and NK cell than non-elderly patients, meanwhile, there was noticeable distinction in TNF-alpha level. Among IL-6, only preoperative IL-6 was significant statistically, however, NK cell showed significant difference irrespective of the timing of blood sampling. No significant risk factors for either recovery or sarcopenia were found among the immunological variables in prospective cohort of elderly patients. Furthermore, both the overall patient population and the elderly group patients showed a tendency toward faster recovery in those with higher postoperative EQ-5D-3L index values while there was no statistically significant difference.

Currently, the number of the elderly population is rapidly increasing worldwide, and the proportion of the elderly in cancer patients is also substantially growing [6]. This aging population also affects CRC; more than half of newly diagnosed CRC patients are 65 years or older and about 30% are 75 years or older[46, 47]. However, the relative survival of elderly patients aged 65 and up CRC patients is often worse than that of younger patients, owing to the more advanced stage at diagnosis as well as the insufficient appropriate treatment at the right moment [48]. In the elderly patients, unlike young individuals, there are numerous variables that impact recovery in addition to disease itself, such as underlying disease, performance status, comorbidities and so on [49-51]. However, without considering these distinctions, uniform treatments are presently recommended for elderly patients, just like younger patients. Therefore, it is important to identify factors that can assist in providing appropriate treatment for elderly population in accordance with the aging era.

It is difficult to describe old age precisely because it is an abstract concept with disparities across

individuals in biological and physical ages. There was a discrepancy in the definition of old age in many studies [6, 50, 52-54]. Among them, multiple studies have shown that the presence of comorbidities increases the risk of postoperative complications, especially in patients over the age of 70 [11, 55]. According to a poll conducted by the Japanese government's Cabinet office, many people consider anyone above of 70 or 75 to be elderly, with similar cutoffs adaptable for populations in other developed eastern nations [56], in addition, SIOG recommends that geriatric assessment be performed for cancer patients over the age of 70 [13]. Therefore, the criteria for the elderly was defined as 70 years of age or older in this study.

The term 'recovery' refers to the return to their original condition. Patients are particularly concerned about this before surgery, expecting to return to their pre-surgical condition as soon as possible. There are various factors that influence postoperative recovery, including the patient's whole-body condition, underlying diseases, and immune-related blood sample levels before surgery. Postoperative recovery is so complex to define with various dimensions including physical, psychological social and so on. Furthermore, assessing the patient as having recovered well or rapidly is ambiguous because subjective opinion is included. Each studies used different indicators such as length of hospital stay, number of complications, or specific symptoms including pain, nausea to assess postoperative recovery. The systemic review by Neville et al. showed that length of stay was common primary outcome of postoperative recovery in many studies[57]. It is used to represent postoperative recovery since approval of discharge by hospital implies a minimal level of physiological and functional recovery. In addition, meta-analysis of randomized trials by Liang LV et al. showed enhanced recovery after surgery pathways may be able to lower the length of hospital stay following major colorectal surgery while maintaining patient safety[58]. Therefore, we utilized the 'hospital stay' as a proxy for postoperative recovery.

Recovery is influenced by a variety of factors, including age. Several studies have found that immunologic variables have a role in recovery as well. Among them, IL-6 is a an inflammatory cytokine that has been related to immunological modulation, hematopoiesis, and carcinogenesis [59]. Several studies studied the diagnostic and prognostic value of IL-6 [23, 24, 60-63] (Table 9). Yeh K.Y et al

demonstrated that patients with serum IL-6 <10 pg/mL and soluble IL-6 receptor > 800 pg/mL survived significantly longer, and that serum IL-6 level was significant predictive factors for 3-,5- and 10-year overall survival in CRC [23]. Shiga K et al. showed that CRC patients with high IL-6 levels (IL-6 ≥ 6.3 pg/mL) had a worse OS rate than those with low levels of IL-6 levels [63]. Moreover, Jinming Xu et al systematically reviewed 16 studies on IL-6 and reported that high serum IL-6 level was shown to be adversely related to overall survival (OS) (HR 1.76; 95%CI, 1.42-2.19; P <0.001) and disease-free survival (DFS) (HR 2.97; 95%CI, 1.76-5.01; P <0.001). Additionally, CRC patients with higher serum IL-6 levels showed a worse OS (P=0.0027) and DFS (P<0.001) [64].

Table 9. Association between IL-6 and oncologic outcomes in colorectal cancer

Nation	Year	Analysis	End point	Cut-off (pg/mL)	Hazard ratio (95% CI) or results
Italy [60]	2000	ELISA kit	Overall survival	10	RR: 1.82
Greece [22]	2005	ELISA kit	Disease-free survival	8	IL-6 ≥8: reduced disease-free survival
Taiwan [23]	2010	ELISA kit	Overall survival	10	IL-6 ≤10: HR 0.403 (0.132-0.810)
Japan [61]	2013	Quanti Glo Human IL-6 Immunoassay	Overall survival	2.41	HR: 4.1 (1.23-13.981)
Korea [24]	2013	ELISA kit	Disease free survival	9	IL-6 ≥9: reduced disease-free survival
Japan [65]	2014	ELISA kit	Overall survival	2	HR: 4.21 (1.289-13.756)
Austria [62]	2014	xMAP technology	Overall survival	N/A	HR: 2.27 (1.227-4.371)
Japan [63]	2016	Cheminolucent immunoassay	Overall survival Disease-free survival	6.3	IL-6 ≥6.3: reduced overall survival, Reduced disease-free survival

IL-6, Interleukin-6; HR, Hazard ratio, Xmap technology: technology developed by Luminex (Riverside, CA)
ELISA: enzyme-linked immunosorbent assay

TNF-alpha is pro-inflammatory cytokine produced by activated monocytes/macrophages and tumor cells [25] and is important in immune system maintenance and homeostasis, inflammation, and host defense [26]. Noyko Stanilov et al found that, when compared to monocytes isolated from healthy individuals, monocytes from CRC patients produced significantly higher levels TNF-alpha (1926±690 pg/mL vs. 1465±771 pg/mL, P=0.034), and TNF-alpha production increased with the stage, since monocytes from patients with advanced cancer secreting significantly more TNF-alpha than monocytes from patients with early stage of the cancer (2298±127 pg/mL vs. 1687±780 pg/ml, P=0.041) [66]. In

addition, a further research that was published two years later from them, revealed that among patients with colorectal cancer, patients with low serum TNF-alpha level had significantly higher survival rate than those with high serum TNF-alpha level (38.4 vs 7.761 months; log ranks test, P<0.001) In subgroup analysis, TNF level was observed to be substantially higher in stage IV as compared to earlier stages of CRC and controls [25].

The NK cells are the cytotoxic lymphocytes, important component of antitumor innate immune response and perform cytotoxic functions by secreting a variety of cytokines and chemokines [67-69]. Yang-ping Tang reported that colon cancer patients with a lower level of NK cells showed shorter survival times than those with a higher level of NK cells significantly (P=0.006) and found that the proportion of NK cells to be a good predictor for the first, second, and third year of survival (AUC : 0.670, 0.674, 0.741, respectively) [21]. Sarah Nersesian et al reviewed 7 studies of NK cell infiltration of colorectal cancer involving 3432 patients and found that of the 7 studies, five showed a significantly improved overall survival in patients with high NK cell infiltration and suggested that the survival of patient with colorectal cancer has strong evidence to be influenced by NK cell infiltration [70-75].

Recovery can be impacted by immunologic factors as well as the composition of the body. Loss of muscle is one of the significant biological changes that caused by aging. Sarcopenia has been defined as a reduction in muscle mass associated with aging, but later as a result of underlying diseases, especially advanced cancer. In CRC patients, infection-related complications are a prominent concern among postoperative morbidities, and some studies have found a link between these infectious problems and preoperative malnutrition, especially represented by low muscularity [76-78]. Furthermore, low muscularity has an adverse influence on postoperative complication the survival outcome. Dolan et al evaluated the relationship between preoperative sarcopenia and oncologic outcome and showed that sarcopenia was found in 19.6% of their enrolled patients, and was associated with 30-day mortality (P=0.042) and 1-year mortality (P=0.046) [79]. Also, Jingjie Xiao et al examined the influence of preoperative muscle characteristics on postoperative recovery. They showed that patients with low SMI or low skeletal muscle radiodensity (SMD) had longer length of hospital stay (OR, 1.33; 95% CI:1.05-

1.68; OR,1.39; 95%CI, 1.131.74, respectively) and higher risks of overall mortality (HR, 1.40; 95% CI, 1.13-1.74; HR,1.44; 95% CI,1.12-1.85, respectively). In addition, patients with low SMI were also more likely to have one or more postoperative complications and had higher risk of 30-day mortality (OR, 1.31; 95% CI, 1.04-1.65; OR, 4.85; 95% CI,1.23-19.15, respectively)[35].

Therefore, in this study, based on the existing studies mentioned above, in the process of finding modifiable factors related to recovery, the association with recovery was examined for the immune factors whose diagnostic and prognostic values were studied previously. Additionally, we attempted to find out the relationship between the preoperative sarcopenia and recovery by focusing on the fact the degree of muscle before surgery will affect postoperative recovery based on aforementioned publications.

We discovered that NLR, AGR and sarcopenia were all associated with recovery after surgery. Despite not deriving a significant AUC value from external validation, we found out significant factors identified through previous data indicated the same trend in prospective data. It was also challenging to move on to the external validation due to the small number of patients in prospective data, and if additional patients are enrolled, it is expected that meaningful results can be obtained based on the tendencies demonstrated in this study. In addition, this paper is significant since it explores further into patients' subjective opinions. Additionally, recovery, as measured by a shorter postoperative hospital stay, was associated with OS, and also associated with short-term RFS in multicenter data. It indicates that recovery, as reflected by a brief hospital stay, might affect oncologic outcomes and can be a predictive factor for oncologic outcomes. In other words, it is critical to allow patients to recover fast in order for them to have a good prognosis since not just pathology but also how well they recover is associated to future prognosis.

Furthermore, the number of elderly patients with sarcopenia was much greater than non-elderly patients in both previous data and prospective data, and sarcopenia was a significant factor for predicting recovery. It suggests that elderly patients with sarcopenia might recover more slowly after surgery, and we need to investigate ways to improve muscle mass prior to surgery, such as rehabilitation

or nutritional treatment in advance.

Among immunological variables, there were no significant risk factors associated with recovery or sarcopenia. The small sample size is assumed to have impacted the fact that risk factors validated in historical data did not yield meaningful findings in prospective cohorts. However, IL-6 and NK cells were shown to be elevated in elderly patients when compared to non-elderly patient groups. Notable, there was a substantial difference in preoperative IL-6 and NK cell levels at both preoperative, POD#3, and POD#21. NK cells, in particular, were higher in the elderly group regardless of the time of blood collection, indicating that level of NK cells does not always decline in elderly patients before and after surgery. This finding suggests that, the outcome in the elderly will not always be poor considering the findings of other publications that indicate low NK cell levels are associated with a poor prognosis. It also implies that, we don't need to hesitate to provide active, supportive treatment to senior population because of the chronological age. In addition, we also surveyed a questionnaire regarding direct answers to subjective health-related quality of life that patients felt. Although not statistically significant, patients with higher postoperative EQ-5D-3L index levels in both total and elderly patients recovered faster. This is consistent with what we anticipated during the study planning stage. It is also crucial for the patient to feel subjectively during the patient's recovery, and it is significant that the approach utilized in this study can aid in the process of quantifying these subjective findings. It is also expected that if more patients are enrolled in the future, statistically significant value will be obtained.

However, sample size of prospective cohort in this study was too small to prove the power of the study. It also can increase the margin of error and compromise the internal and external validity of a study. Furthermore, the retrospective analysis with non-randomized design was used to analyze patients who received curative resection for colorectal cancer. There might have been a selection bias and some data could have been missing. However, it is meaningful that we computed a factor to predict risk of recovery from historical data and examined the variables related with recovery using multicenter data with large sample size. It may reflect the clinical practice at diverse centers, and large sample size can yield better and more reliable results with smaller margins or error and lower standards of deviation.

In addition, in this study, hospital stay was used to assess the recovery, however, the length of stay could be influenced by many non-clinical factors such as the patients' desire to be discharged, the family's circumstances, the patient's work-related problems, insurance issues and so on. Furthermore, recovery is subjective, and is not completed by discharge; the patient's situation after discharge, such as a return to daily life should be taken into account. Nevertheless, most studies analyze the recovery using the length of stay and so far, it may be claimed to be the optimal tool for reflecting recovery, and in an effort to overcome these limitations, the retrospective study included additional patients who were readmitted within 30 days after discharge to reflect the situation after discharge.

We demonstrate that sarcopenia, albumin, and neutrophil lymphocyte ratio were associated with postoperative recovery in elderly patients and the association between the oncologic outcomes and recovery was also established. We also exhibited that elderly patients tend to have higher NK cell levels and IL-6 levels, although no significant immunologic factors were found to be associated with recovery or sarcopenia. The results of the NK cell level, which were not lower in the elderly group, showed that as compared to the non-elderly group, elderly patients do not always have poor outcomes before and after surgery, and we can thus consider active treatment for them regardless of age. Consequently, prior to surgery, we have to work on enhancing the recovery-related parameters mentioned in this study, and the additional research will be required to identify whether other factors, other than the cytokines implemented in this study, or the cytokines analyzed in this study, may also have an impact on recovery.

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국문 요약

연구배경 및 목적 대장암은 전세계에서 발병률이 높은 암 중에 하나이며, 고령화 사회에서 고령환자의 비율도 증가하고 있다. 따라서, 고령 환자에게 적절한 개별화된 치료에 대한 관심도 증가하고 있다. 암 관련 염증은 암의 진행과 예후에 영향을 미치며, 이 과정에 영향을 주는 면역학적 요인과 수술 후 회복에 영향을 끼치는 면역학적 요인이 매우 중요하다. 따라서, 본 연구에서는 고령환자에서 수술 후 개별화된 치료 계획을 수립하는 데에 도움을 줄 수 있는 여러 교정가능한 요인들에 대하여 분석해보고자 하였다.

연구 방법 본 연구는 후향적 코호트 분석과 전향적 코호트 분석을 모두 시행하였으며, 후향적 연구에서는 2018년 3월부터 2020년 9월까지 전국 8개의 3차병원에서 대장암으로 근치적 절제수술을 받은 10,271 명의 환자들의 자료를 분석하였고, 추가적으로 서울아산병원에서 2005년 1월부터 2011년 11월까지 대장암으로 근치적 절제수술을 받은 1383명의 환자들의 008년 1월부터 2016년 12월까지 서울아산병원에서 수술 전 화학방사선치료와 근치적 절제수술을 받은 1535명의 환자들의 자료를 분석하였다. 후향적 연구에서는 2023년 9월부터 11월까지 서울아산병원에서 대장암으로 수술을 진행한 40명의 환자들을 모집하여 포함하였다. 고령의 기준은 70세로 잡고, 환자를 20명씩 분류하여 모집하였으며, 수술 전 복부영상검사를 진행하였다. 수술 전, 수술 후3일째, 수술 후 21일째 (첫 외래 내원 시)에 백혈구, 중성구, 알부민을 포함한 기존 혈액검사에 인터루킨-6, 자연살해세포, 종양괴사인자-알파를 포함한 면역검사를 추가해서 진행하였다. 수술 전후에 EQ-5D-3L이라는 설문지를 통해, 환자의 삶의 질에 대한 정보를 확보하였다. 수술 전 시행한 복부영상검사를 기반으로 인공지능 소프트웨어를 통해 골격근지표를 획득하여 체지방률과 성별에 따라 다른 기준을 적용하여 근감소증을 분류하였다. 일차 종결 포인트는 회복력으로 수술후부터 퇴원까지의 기간을 재원기간으로 하여, 평균 재원기간보다 빨리 퇴원하였으며 퇴원 후 30일 이내에 재입원이 없는 경우 빠른 회복을 보이는 그룹으로 분류하였다.

이차 종결 포인트는 EQ-5D-3L 설문지의 값으로 설정하였다.

연구 결과 후향적 코호트에서 중성구-림프구 비율, 알부민, 그리고 근감소증이 고령환자에서 회복과 관련 있음이 확인되었다. 중성구-림프구 비율이 낮을수록, 알부민이 높을수록, 근감소증이 없을수록 회복이 빠른 것으로 확인되었고, 또한, 재원기간으로 대표되는 환자의 회복의 정도가 빠를수록 전체 생존율이 높고, 단기간 무병생존율이 높았다. 또한, 병리학적 림프절 병기와 림프혈관 침범 역시 전체 생존율과 관련이 있었다.

전향적 코호트에서 평균 재원기간은 5일이었고, 5일이내 퇴원할 경우 회복이 빠른 그룹으로, 6일이 지나서 퇴원한 경우 회복이 느린 그룹으로 분류되었다. 전향적 코호트에서는 마취 전 신체상태가 좋지 않을수록 회복이 느렸고, 그 외에 회복에 영향을 끼치는 유의미한 인자는 확인되지 않았다. 면역검사 결과 중에서는 수술 전 인터루킨-6와 수술 전, 수술 후 3일째, 수술 후 21일째의 자연살해세포 수치가 고령 그룹에서 유의미하게 더 높은 것으로 확인되었다. 하지만, 면역 검사들 중에서 회복 또는 근감소증의 위험인자로 확인된 지표는 없었다. EQ-5D-3L 수치는 회복이 높은 환자군에서 회복이 느린 환자군에 비해 높았으나 유의미한 차이를 보이지는 않았다.

결론 본 연구에서는, 중성구-림프구 비율, 알부민 그리고 근감소증이 고령환자에서 회복에 영향을 끼치는 주요 인자임을 확인하였고, 또한, 수술 후 회복은 종양학적 결과와도 관련이 있음을 알 수 있었다. 면역검사들 중에서는 채혈 시기에 상관없이 회복 혹은 근감소증에 유의미한 영향을 주는 검사는 없었으나 고령의 환자에서 전반적으로 인터루킨-6와 자연살해세포 수치가 높게 나타나는 것을 확인할 수 있었다. 특히, 자연살해세포 수치가 고령에서 높게 나타난 것으로 보아, 고령이라고 하더라도 꼭 비고령 환자에 비해 수술 후 체내 면역지표가 감소하는 것은 아니라는 것을 알 수 있었다. 결과적으로, 고령의 환자들을 치료할 때, 본 논문에서 확인된 회복 관련 요인들을 수술전에 향상시키는 것을 고려해보아야 하고, 본 논문에서 시행한 면역 검사 또는 또다른 면역 검사들 중에

서 회복에 영향을 끼치는 요인이 있을지 추가적인 연구가 필요할 것으로 보인다.