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Defining the Term "Elderly" in the Field of Surgery: A Retrospective Study Regarding the Changes in the Immunoinflammatory Indices During the Immediate Perioperative Period of the Elective Uncomplicated Laparoscopic Cholecystectomy

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Backgrounds: The term "elderly" seems to have been used as "vulnerable to various stresses" but not well defined. To define the "elderly", we investigated whether the increased age causes unfavorable changes in several immunoinflammatory indices that indicate the increased vulnerability in the surgical field.

Patients and Methods: One-hundred forty-two patients undergoing an elective-uncomplicated laparoscopic cholecystectomy (within 60 min and without intraoperative-cholangiography, bile spillage, or open conversion) were retrospectively investigated. Before surgery, immediately after surgery, and on postoperative day (POD)1, whether the patient age correlated the following variables was examined: neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-C-reactive-protein ratio (LCR), C-reactive-protein-to-albumin ratio (CAR), and others.

Results: The immunoinflammatory indices most unfavorably changed on POD1. The age correlated neither lymphocyte-to-monocyte ratio nor platelet-to-lymphocyte ratio on POD1, when NLR, LCR, and CAR showed the significant correlation with the age. Multiple regression analyses determined the following variables as the independent determinants of these 3 indices on POD1: age, intraoperative minimum body temperature ≥ 35.5°C (IntMinBT ≥ 35.5°C), maximum heart rate during POD0-1 (MaxHR) for NLR; age and IntMinBT ≥ 35.5°C for LCR; and age and MaxHR for CAR. The threshold of "elderly" was determined as 102-year-old for NLR, 94-year-old for LCR, and 97-year-old for CAR.

Conclusions: The increased age causes the unfavorable changes in early postoperative immunoinflammatory indices after the uncomplicated laparoscopic cholecystectomy. Thus, the term "elderly" can be rephrased by the term "vulnerable to various surgical stresses." The thresholds for "elderly" defined herein seem impractical. Namely, the increased vulnerability caused by the aging seems modified by the individual surgical procedures.

With the refined surgical techniques, surgeons' experiences and surgical devices, the indications of surgery for various conditions have continued to expand.[1–4] Notably, the upper limit of the age for various surgical procedures has continued to rise. Although the aging appears to arise some demerits, the high age has been no longer a contraindication for almost all kinds of surgery.[1–6] In these studies, the threshold of "elderly" was defined as the age of 70 to 80 years.[1,2,5–7] The surgical procedures in these studies were generally considered challenging to the "elderly" patients. However, the authors concluded that the surgical procedures in their studies were acceptable for the "elderly" patients because their comparisons showed no difference or only trivial difference between the "elderly" and the other patients in the outcomes, such as postoperative complications, length of hospital stay, survival outcomes, or alike. In other words, because the term "elderly" has tended to be used as "vulnerable to various stresses" in the field of surgery, the authors conducted these studies to demonstrate the acceptability of their surgical procedures for those "vulnerable" patients. However, the definitions for "elderly" in these studies are still controversial and lack logical backgrounds.

Recently, several immunoinflammatory indices, including neutrophil-to-lymphocyte ratio (NLR),[8–10] lymphocyte-to-monocyte ratio (LMR),[11] platelet-to-lymphocyte ratio (PLR),[9] lymphocyte-to-C-reactive-protein ratio (LCR),[12] and C-reactive-protein-to-albumin ratio (CAR),[13,14] have been reportedly associated with non-oncological short-term and long-term-survival outcomes of various kinds of surgery. Although both the older age and the immunoinflammatory indices have been used as the indicators of the vulnerability to the surgical stresses, the correlation between these 2 elements remains unknown.[8–14]

In the present study, we hypothesized that unfavorable perioperative immunoinflammatory responses correlate with the age of the patient, and that the immunoinflammatory indices can be used to define the term "elderly" in the surgical field instead of just using a certain cut-off value of the age as the threshold of the "elderly." To verify our hypothesis, we examined (1) whether the increased age causes the unfavorable changes in the above-mentioned indices in the perioperative period in nononcological surgery, (2) whether there is a

significant changing point of the immunoinflammatory indices that can be used as a threshold of the "elderly."

PATIENTS AND METHODS

Between January 2016 and December 2018, an elective laparoscopic cholecystectomy (LC) was performed for 228 patients at our institution. The uncomplicated LC (U-LC) was used as the representative minimally invasive laparoscopic surgery in this study. The U-LC was defined as the elective LC with operation time of < 60 minutes, and without bile spillage, intraoperative cholangiography, or open conversion. Intraoperative cholangiography might have caused cholangitis and/or inflammation due to bile outflowing from the slit of the cystic duct. Thus, patients receiving intraoperative cholangiography were excluded. As a result, 142 of the 228 patients undergoing an elective LC were enrolled. This retrospective study was approved by the Institutional Review Board (IRB) of the Yokohama Ekisaikai Hospital (IRB approval No. was YEH-19-S-01) and was the HIPAA compliant.

The following variables were prospectively collected and retrospectively analyzed: patient age, sex, height (cm), body weight (kg), body mass index, comorbidity, the original Charlson Comorbidity Index (without including the age as the determinant) (CCI),[15] the modified Frailty Index (mFI),[4] use of the steroid, diagnosis indicated for LC, preoperative laboratory data, intraoperative findings [operation time, blood loss, intraoperative minimum body temperature (°C) (IntMinBT)], laboratory data examined immediately after surgery and on postoperative day (POD)1, maximum heart rate (MaxHR) [beats per minute (BPM)] during POD0-1, maximum body temperature (MaxBT) (°C) during POD0-1, and clinical courses. Immunoinflammatory indices were calculated as following: NLR = (neutrophil count)/(lymphocyte count),[8–10] LMR = (lymphocyte count)/(monocyte count),[11] PLR = (platelet count)/(lymphocyte count),[9] LCR = (lymphocyte count)/(serum C-reactive-protein [mg/dL]),[12] and CAR = (serum C-reactive-protein [mg/dL])/plasma albumin level [g/dL]).[13,14] These indices were calculated in the preoperative period, immediately after surgery (POD0), and on POD1.

The correlation between the age and these indices was investigated at each time point. In previous studies, the larger the value, the more severe the vulnerability to surgical stresses in NLR,[8–10] LMR,[11] and CAR,[13,14] or the smaller the value, the more severe the vulnerability in PLR[9] and LCR.[12] Among the indices that were significantly correlated with the age, the time point at which the value of the index was maximum (NLR, LMR, CAR) or minimum (PLR, LCR) was selected and whether or not the age was an independent determinant of the index was assessed by the multivariate analysis on the selected time point. In addition, whether changes in these indices affected the clinical course was evaluated.

Statistical Analyses

Data were expressed as median (range) and number (%). Correlation coefficient (r) between the age and the above-mentioned immunoinflammatory indices were assessed using the Spearman rank correlation coefficient. Continuous variables were compared using the Man-Whitney U test for unpaired comparisons and the McNemar test for paired comparisons. Categorical variables were compared using the Fischer exact probability test. Whether the aging was an independent determinant of the above-mentioned immunoinflammatory indices was assessed by the multiple regression analysis with the analysis of variance including variables univariately correlated with the above-mentioned immunoinflammatory indices. To avoid the confounding skews,

variables that correlated each other were alternately entered into each model of the multivariate analyses one by one. In other words, variables that showed the significant correlations with the age were not entered into the multivariate models. The model showing the greatest r^2 value of the analysis of variance was adapted. The term "elderly" was defined as follows. First, the cut-off values for the incidence of postoperative complications of the immunoinflammatory indices, which were independently correlated with the age, were determined using a receiver operating characteristics curve analysis. Then, the cut-off value of each index was entered into the equation of the multiple regression model. Subsequently, the threshold of the age was calculated when parameters other than the age were fixed to be the standard values. This threshold of the age was defined as the threshold of the "elderly." A 2-tailed P-value < 0.05 was accepted as significant. Statistical analyses were performed with the software program SPSS version 23 (IBM, Armonk, NY).

RESULTS

Patient Characteristics—Preoperative, Intraoperative, and Postoperative Findings

Patient characteristics, preoperative, intraoperative, and postoperative findings are summarized in Table 1. The patients'

TABLE 1. Characteristics of the Patients

Variables	Data, n (%)
Demographics	
Age at surgery (y)	60 (21-85)
Sex (M/F)	74/68
Disease	
Gallstone	127 (89.4)
Gallbladder polyp	8 (5.6)
Adenomyomatosis	7 (5.0)
Comorbidity	
Hypertension	64 (45.1)
Hyperlipidemia	41 (28.9)
Vascular diseases	24 (16.9)
Diabetes	20 (14.1)
COPD	8 (5.6)
Charlson Comorbidity Index	1 (0-7)
Modified Frailty Index	1 (0-5)
Height (cm)	162 (140-186)
Body weight (kg)	60.7 (38-115)
BMI	23.5 (15.6-42.8)
Intraoperative variables	
Operation time (min)	47 (41-59)
Bleeding (mL)	5 (1-50)
Intraoperative minimum BT (°C)	35.9 (34.1-37.1)
Postoperative variables	
Maximal heart rate on postoperative day 0 to 1 (/min)	82 (62-127)
Maximal BT on postoperative day 0 to 1 (°C)	37.7 (36.9-39.5)
Postoperative complications	9 (6.3)
Clavien-Dindo grade I	4 (2.8)
Wound exudate	2
Wound bleeding	2
Clavien-Dindo grade II	5 (3.5)
Bowel paralysis	2
Paroxysmal atrial fibrillation	1
Pneumonia	1
Acute pancreatitis	1
Length of postoperative stay (d)	2 (0-7)

BMI indicates body mass index; BT, body temperature; COPD, chronic obstructive pulmonary disease.
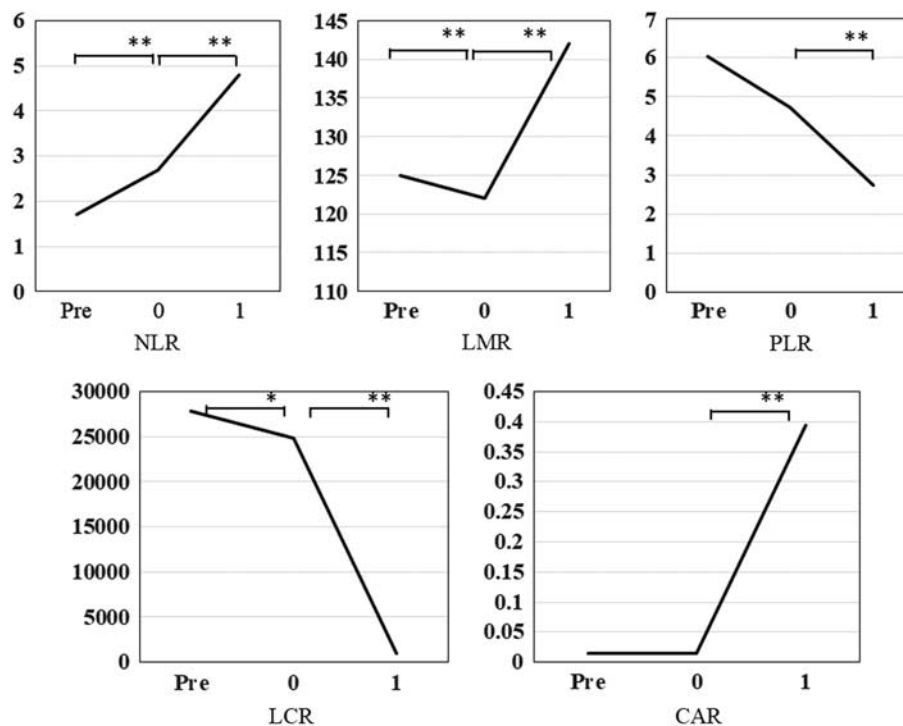
FIGURE 1. Chronological changes in the immunoinflammatory indices These line graphs indicate the chronological changes in the inflammatory indices: neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-C-reactive-protein ratio (LCR), and C-reactive-protein-to-albumin ratio (CAR). In NLR, LMR, and LCR, the value of each index was significantly different from the prior value (**$P < 0.001$ and *$P = 0.003$). In PLR and CAR, the value immediate after surgery (the horizontal axis label "0") was not significantly different from the preoperative value (the horizontal axis label "Pre"). However, the value on postoperative day 1 (the horizontal axis label "1") was significantly different from the value immediate after surgery in PLR and CAR.

age ranged 21 to 85 years with a median of 60. There were 74 men and 68 women. The most prevalent comorbidity was hypertension (64/142, 45.1%). The CCI ranged 0 to 7 with a median of 1 and the mFI ranged 0 to 5 with a median of 1. The steroid was not used in any patients.

Chronological Changes in the Immunoinflammatory Indices and the Correlation Between the Age and Each Immunoinflammatory Index

Chronological changes in the immunoinflammatory indices are shown in Figure 1. In NLR, LMR, and LCR, the value on each time point significantly differed from the prior time point. In PLR and CAR, the value on POD0 was not significantly different from the preoperative value. However, the values of PLR and CAR on POD1 significantly differed from those on POD0. All indices showed the maximum (NLR, LMR, and CAR) or minimum (PLR and LCR) values on POD1. The correlations between the age and these immunoinflammatory indices are shown in Figures 2 and 3. Basically, these indices showed significant correlation with the age at most measured time points [(index); (in the preoperative period); (POD0); (POD1)—NLR: $r = 0.231$, $P = 0.006$; $r = 114$, $P = 0.181$; $r = 0.230$, $P = 0.006$; LMR: $r = -0.231$, $P = 0.006$; $r = -0.167$, $P = 0.047$; $r = -0.124$, $P = 0.143$; PLR: $r = -0.162$, $P = 0.054$; $r = -0,081$, $P = 0.340$; $r = -0.052$, $P = 0.540$; LCR: $r = -0.189$, $P = 0.024$; $r = -0.164$, $P = 0.050$; $r = -0.370$, $P < 0.001$; CAR: $r = 0.177$, $P = 0.035$; $r = 0.122$, $P = 0.148$; $r = 0.356$, $P < 0.001$]. NLR, LCR, and CAR on POD1 showed the significant correlation with the age.

Multivariate Analysis to Determine Whether the Age Was an Independent Determinant of the Immunoinflammatory Indices

In the univariate analyses, the age, CCI, mFI, IntMinBT $\geq 35.5°C$, MaxHR (BPM), and MaxBT (°C) were significantly correlated with NLR, LCR, and CAR on POD1. In addition, the presence of diabetes mellitus and the presence of vascular disease were significantly associated with an increased CAR on POD1. Table 2 shows the results of the multivariate analyses to determine whether the age was an independent determinant of these indices on POD1: the independent determinants were the age, IntMinBT $\geq 35.5°C$, and MaxHR for NLR on POD1, the age and IntMinBT $\geq 35.5°C$ for LCR on POD1, and the age and MaxHR for CAR on POD1. The age was included in the independent determinants of these 3 indices on POD1. The constant term of the multiple regression model for each index was -1.25 for NLR, 1.26×10^3 for LCR, and -20.0 for CAR, respectively (Table 2).

Determination of the Definition for the Term "Elderly"

Postoperative complications were observed in 9 of the 142 patients (6.3%) [Clavien-Dindo grade I, 4 (2.8%); grade II, 5 (3.5%)]. None of the patients showed Grade III or more severe complications. The median length of postoperative hospital stay was 2 days (range, 0 to 7 d) (Table 1). NLR, LCR, and CAR were significantly different between patients with and without complications (with vs. without
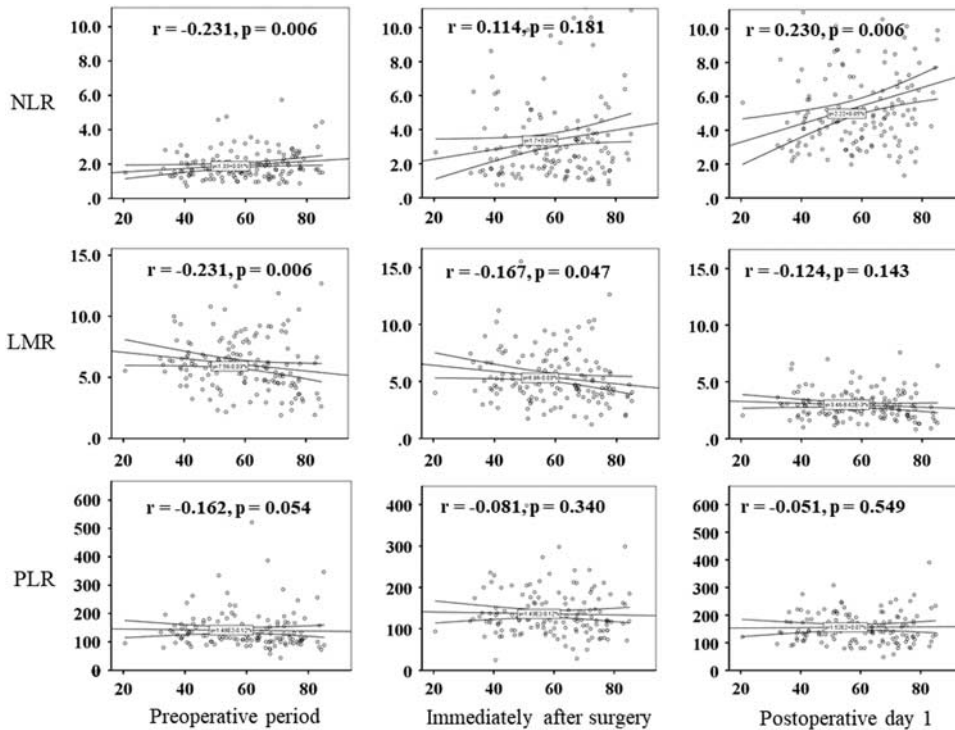
FIGURE 2. Correlation between the age and neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), or platelet-to-lymphocyte ratio (PLR). NLR was significantly correlated with the age in the preoperative period and on postoperative day 1 (POD1), but not correlated with age immediately after surgery. LMR showed the significant correlation with the age in the preoperative period and immediately after surgery, but not on POD1. PLR was not correlated with the age on any time points.

complications; NLR, 6.23 vs. 4.68, $P = 0.019$; LCR, 405 vs. 942, $P = 0.047$; CAR, 0.669 vs. 0.378, $P = 0.024$).

The cut-off value of each index on POD1 for the grade I-II complications was determined to be 6.49 for NLR, 409 for LCR, and 1.04 for CAR by the receiver operating characteristics curve analysis. Parameters of the multiple regression model other than the age for each index were fixed as the median value of the present analysis: MaxHR, 82 BPM; IntMinBT, 35.9°C. From these

cut-off values and fixed parameters, the threshold of the "elderly" was determined as the following: 102-year-old for NLR, 94-year-old for LCR, and 97-year-old for CAR, respectively.

DISCUSSION

The present study revealed that the increased age significantly correlated the unfavorable changes in early
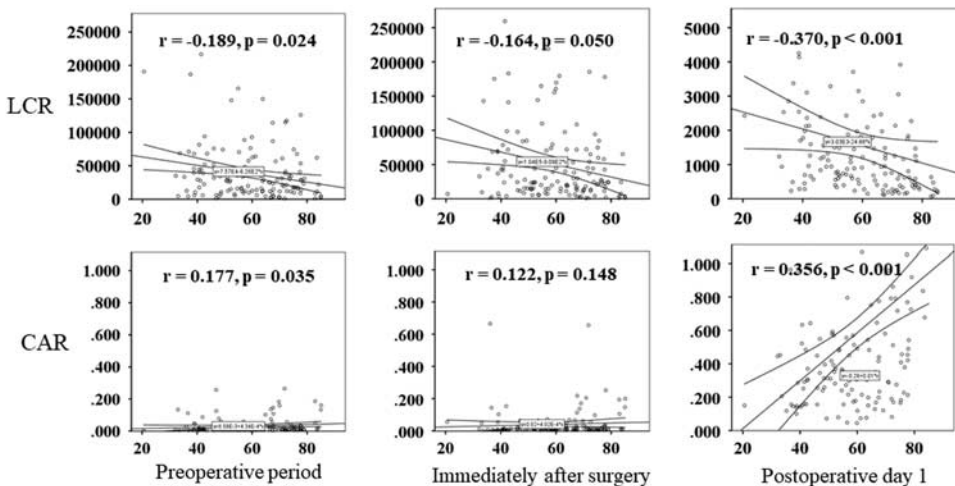
FIGURE 3. Correlation between the age and lymphocyte-to-C-reactive-protein ratio (LCR) or C-reactive-protein-to-albumin ratio (CAR). LCR was significantly correlated with the age in the preoperative period and on postoperative day 1 (POD1), but not correlated with age immediately after surgery. CAR showed the significant correlation with the age in the preoperative period and on POD1, but not immediately after surgery.

TABLE 2. Results of the Multivariate Analyses to Determine Whether the Age Was an Independent Determinant of the Immuoinflammatory Index on Postoperative Day 1

Variables	Partial Regression Coefficient	95% Confidence Interval	*P*
Neutrophil-to-lymphocyte lymphocyte ratio (NLR)			
Age (y)	0.044	0.010-0.084	0.018
Modified Frailty Index	−0.080	−0.581 to 0.532	0.803
Intraoperative minimum BT ($\geq 35.5°C$)	−2.16	−0.402 to 3.92	0.019
Maximum BTfrom POD0-1 (°C)	−0.217	−1.04 to 0.541	0.599
Maximum HR from POD0-1 (/min)	0.066	0.025-0.105	0.001
Lymphocyte-to-C-reactive-protein ratio (LCR)			
Age (y)	−17.4	−38.5 to −1.35	0.014
Modified Frailty Index	21.6	−238 to 357	0.895
Intraoperative minimum BT ($\geq 35.5°C$)	787	$224\text{-}1.48\times10^3$	0.047
Maximum BT from POD0-1 (°C)	−233	−848 to 510	0.552
Maximum HR from POD0-1 (/min)	−49.6	−104 to −17.3	0.055
C-reactive-protein-to-albumin ratio (CAR)			
Age (y)	0.090	0.021-0.162	0.020
With diabetes mellitus	−0.106	−0.449 to 0.199	0.518
With vascular disease	−0.108	−0.534 to 0.368	0.643
Modified Frailty Index	0.102	− 0.055 to 0.275	0.232
Intraoperative minimum BT ($< 35.5°C$)	0.220	−0.074 to 0.523	0.170
Maximum BT from POD0-1 (°C)	0.207	−0.002 to 0.415	0.062
Maximum HR from POD0-1	0.150	0.072-0.234	0.003

NLR on POD1 = −1.25+0.044×(Age [years])−2.16×(intraoperative minimum BT; 1, $\geq 35.5°C$: 0, $< 35.5°C$)+0.066×(Maximum HR [BPM]).
LCR on POD1 =1.26×10³−17.4×(Age [years])+786×(intraoperative minimum BT; 0, $\geq 35.5°C$; 1, $< 35.5°C$).
CAR on POD1 = −20.0+0.090×(Age [years])+0.150×Maximum HR.
BPM indicates beats per minute; BT, body temperature; HR, heart rate; POD, postoperative day.

postoperative immunoinflammatory indices. In addition, the age was the independent determinant for NLR, LCR, ad CAR on POD1. Among these indices that change most unfavorably on POD1, the partial regression coefficient of the age was 0.044 for NLR, −17.4 for LCR, and 0.090 for CAR, respectively (Table 2). In other words, in these 3 indices, the 1-year increase in the age leads to the change with the value of each partial regression coefficient. This indicates that the aging directly leads to the unfavorable changes in NLR, LCR, and CAR. From these indices, the threshold of the "elderly" was determined to be around the age of 94 to 102 years in this study. With regard to the LMR and PLR, the postoperative changes in monocyte or platelet count did not show the statistically significant correlation with the age unlike the other elements of the immunoin-flammatory indices examined. Thus, the age significantly correlated with neither LMR nor PLR on POD1, when the most prominent change of each index was observed.

Preoperative and early postoperative changes in the immunoinflammatory indices examined in this study have been reported to correlate significantly the short-term and long-term postoperative outcomes in various surgical procedures.[10,12–14] On the basis of these studies, it can be stated that the unfavorable change in the NLR, LCR, and CAR leads to both the increased incidence of postoperative complications and the worsened survival outcomes in various types of surgery.[8–10,12–14] In other words, these indices indicate the vulnerability to various surgical stresses. Reflecting these studies into our present findings, we consider that the aging causes the increased susceptibility to both the postoperative complications and the worsened long-term surgical outcomes.

The safety for the "elderly" patients in various surgical procedures has been vigorously reported.[1–7] With the standardization of the laparoscopic surgery in various procedures, the minimization of the surgical stresses has been reportedly brought on by the laparoscopic surgery.[1,3,4,7] Namely, these reports suggest that the laparoscopic surgery can enable the safer application of various surgical procedures to the "elderly" patients.[1,3,4,7] However, the present study demonstrated that the aging was correlated significantly with the changes in the immunoinflammatory indices toward the increased vulnerability even in patients undergoing the U-LC. We adopted the U-LC because the LC was considered literally as the minimally invasive laparoscopic surgery. The U-LC was regarded as the simplest and the least burdensome laparoscopic surgery, but had a significant unfavorable impact on changes of several immunoinflammatory indices as shown in this study. Currently, there exist various oncologic laparoscopic surgeries and their indications have continued to expand.[7] It is considered that the oncologic laparoscopic surgery easily brings more prominent changes in these immunoinflammatory indices compared with the U-LC because the oncologic laparoscopic surgery requires more complicated procedures than the U-LC does, suggesting that the oncologic laparoscopic surgery more easily leads to the increased vulnerability caused by the aging compared with the U-LC.

There are several limitations in this study. First, the thresholds of the "elderly" that were determined in this study appear impractical. The patients' age ranged from 21 to 85 years in this study. Despite this, the threshold of the "elderly" was determined as 102-year-old for NLR, 94-year-old for LCR, and 97-year-old for CAR. These thresholds of the "elderly" were calculated from the cut-off values for the grade I-II postoperative complications. It is considered that the surgical stresses caused by the U-LC were too small to cause the postoperative complications and thus these thresholds for the "elderly" might have been extremely high. This suggests that the cut-off values of these indices vary according to the magnitude of the procedures and/or diseases themselves. Second, we evaluated these indices only up

to POD1. After the LC, the length of postoperative stay usually requires a day or 2 days after surgery. Thus, we could assess these indices only up to POD1. Conversely, these immunoinflammatory indices significantly changed even in patients who were uneventfully discharged from hospital on POD1 or POD2. This may indicate that if some critical events occur, severe morbidity can easily develop in these patients because of the underlying increased vulnerability caused by the U-LC alone. Third, it was uncertain whether the U-LC was suited to the purpose of this study. The LC is the most prevalent and representative procedure of the laparoscopic surgery. Thus, we adopted the U-LC. However, the generalizability of our present findings to other surgical procedures needs to be verified in future studies.[1–7] Fourth, this study was conducted as a retrospective study. Therefore, the postoperative management of the patients might have varied according to the attending physicians. We are currently constructing a prospective database under a uniform protocol for the postoperative management.

In conclusions, our present findings suggest that the aging is the independent determinant of the unfavorable changes in several immunoinflammatory indices. The unfavorable change in the indices was most prominent on POD1 after the U-LC. From the values on POD1, the threshold of the "elderly" was determined as 102-year-old for NLR, 94-year-old for LCR, and 97-year-old for CAR. These thresholds seemed impractically high. In other words, although the aging can cause the increased vulnerability to various surgical stresses even after the U-LC, the term "elderly" should be defined according to the individual surgical procedures and/or diseases themselves.

ACKNOWLEDGMENT

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