INTRODUCTION

Colorectal cancer is the second most common cause of cancer death worldwide, following lung cancer [1]. The worldwide population is aging, and the incidence of cancer is rapidly growing. Older patients show biological heterogeneity regarding comorbidity, physical capacity, cognitive faculty, and mental health impairments. Frailty is considered to be a phenotype of decreased physiological reserves and impaired resistance to stressors [2]; it influences the morbidity and mortality in older patients with colorectal cancer [3]. Frailty assessment tools have been developed to identify subsets of older patients that may be at risk of adverse outcomes after surgery, including the Kihon Checklist (KCL).

KCL was established by the Japanese Ministry of Health, Labor, and Welfare to identify whether individuals ≥65 years old might require medical care or social support. It is composed of 25 self-reported responses to questions. KCL was validated by a score ≥8 of the total 25 questions equating to frailty defined by the Cardiovascular Health Study criteria set by Fried et al [2,4], and it is now being accepted for frailty screening worldwide [5–7]. KCL screening meets almost all aspects of geriatric assessment: physical function, social activities,
nutrition, cognition, and psychological status, so it has been suggested to be suitable for use in geriatric research. We previously reported that preoperative frailty assessed by KCL was significantly associated with postoperative complications in older patients with colorectal cancer [8]. Many researchers have shown a preoperative subset of frail patients to be a risk factor for not only worse postoperative outcomes but also decline in functional status or quality of life [3,9-11]. To our knowledge, however, pre- and postoperative status of frailty in older patients with colorectal cancer has not been widely examined.

In this multicenter cohort, we prospectively analyzed perioperative evaluation of frailty using KCL assessment and predictors of postoperative change of frail status in older patients who underwent elective surgery for colorectal cancer.

METHOD

Study Design and Participants. This multicenter cohort study was prospectively managed by the Second Department of Surgery at Wakayama Medical University Hospital (WMUH). It was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the ethics committees of all participating institutions (approval number 1975; WMUH). It was registered to UMIN-CTR, registration number UMIN000026689.

Included in this study were consecutive patients aged ≥ 65 years for whom elective colorectal cancer surgery was planned between May 2017 and December 2018. Eligible patients were recruited from WMUH and 8 affiliated tertiary hospitals [8]. Written informed consent was obtained from all participating patients prior to our enrollment.

Frail Scoring. We evaluated the status of frailty based on a validated scoring system, KCL, a patient-reported questionnaire (Table 1). KCL questionnaire was divided into 7 domains: instrumental (3 questions), social (4 questions), activities of daily living and physical function (5 questions), nutritional status (2 questions), oral function (3 questions), cognitive function (3 questions), and depressive mood (5 questions). As previously reported, a total score ≥ 8 was considered as being a state of frailty and score ≤ 7 was classified as prefrail or robust in conformity to the Cardiovascular Health Study criteria [4]. In this cohort, patients with a KCL score ≥ 8 were regarded as "frail," whereas those scoring ≤ 7 as were regarded as "nonfrail."

Eligible patients answered KCL within 14 days before surgery and 1 month after surgery, a reflection of the perioperative course and events. They answered KCL questionnaire at the outpatient clinic or in hospital during the study period by themselves.

Data Collection. We collected the following data: age, sex, body mass index (BMI), comorbidity (history of cerebrovascular disease, chronic respiratory disease, myocardial disease, orthopedic lower limb disease, hypertension, diabetes mellitus, use of anticoagulant agent, and malignancy), American Society of Anesthesiologists score, and performance status (PS) score. We also retrieved other variables of preoperative biochemical blood examination (hemoglobin, serum concentration of albumin, surgical findings [operation time, blood loss, history of laparotomy, and laparoscopic versus open approach], and postoperative factors [complications or mortality within 30 days, delirium, and final TNM staging]). According to WHO criteria [12], anemia was defined as hemoglobin levels ≤ 13.0 g/dl in men or ≤ 12.0 g/dl in women, and hypoalbuminemia was set as serum albumin levels ≤ 3.5 g/dl. Finally, we investigated length of hospital stay and 30-day mortality.

We retrieved case registration and all data from the 8 participating hospitals with electronic data capturing system.

Statistical Analysis. Differences between postoperative "Change frail" group and "Stay nonfrail" group were analyzed using Mann–Whitney test or χ² test. In all variables with a P value < .05 in univariate analysis, multivariable logistic regression models were adopted to calculate odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All analyses were performed using JMP Version 14 (SAS Institute Inc, Cary, NC).

RESULTS

There were 521 patients identified within our study period. As our previous report [8], 500 patients were assessed, and 21 patients were excluded from our examination. Five patients (1.0%) died within 30 days after surgery: 3 of cancer progression, 1 from severe pneumonia,
and 1 from multiple organ failure during the study period. Consequently, 495 patients were subject to pre- and postoperative analyses of frail status.

In preoperative assessment, there were 164 patients (32.8%) regarded as frail, whereas there were 172 patients (34.7%) postoperatively. Of 336 preoperative "nonfrail" patients, 38 patients changed into "frail" postoperatively except for 1 mortality. The details of our study flowchart are presented in Figure 1.

Characteristics of the 500 patients who were enrolled in preoperative assessment are shown in Table 2. Median age of all patients in this study was 76 years old, ranging between 65 and 96 years. Creation of a temporary or permanent stoma was required in 100 patients (20.0%). Short-term postoperative complications were counted in 97 patients (19.4%), and the details are shown in Table 3. In examination variables, median BMI, median operation time, and median blood loss were 21.5, 220 minutes, and 25 mL, respectively. In this cohort, we set these median values as cutoff for our next analyses.

Main analysis was carried out for 335 preoperative “nonfrail” patients (KCL ≤ 7) to detect related factor of changing into postoperative "frail." According to univariate analysis, significant factors of changing frail postoperatively were PS ≥ 2 (P = .014), history of laparotomy (P = .023), open surgery (P = .006), complication (P < .001), ostomy creation (P = .023), and postoperative delirium (P = .024). In multivariate logistic regression analysis, complication (OR 2.69, 95% CI 1.19–6.09, P = .018), and ostomy creation (OR 2.32, 95% CI 1.01–5.33, P = .047) were independently related to postoperative changing frail. These results are shown in Table 4. In these 335 patients, the median KCL score of patients who suffered from complications got worse from 4.5 (preoperative assessment) to 12.8 (postoperative assessment), and that of patients who required ostomy creation worsened from 4.0 to 14.5.

**DISCUSSION**

Older patients who changed from being preoperative “nonfrail” to postoperative “frail” by KCL screening had significant relations to...
postoperative complication and ostomy creation in colorectal cancer surgery. Older patients, particularly those classified as frail, have poorer postoperative outcomes, decline of physical function, and impaired health-related quality of life (HRQL) associated with colorectal cancer [13–15]. Previous observational studies have not shown what would induce postoperative change of frail status in older patients with colorectal cancer. This is thus the first prospective study to examine predictable factors leading to change from “nonfrail” patient into postoperative “frail” patient during colorectal cancer surgery.

KCL was originally created to identify older individuals requiring health care and social support in the Japanese long-term insurance system. Several researchers have examined the validation of frailty screening, and it has been translated into English [16], Portuguese [5], Spanish [6], and Turkish [7]. We previously demonstrated that preoperative frailty screening using KCL could be useful for predicting postoperative complication in older patients with colorectal cancer [8].

There could be several reasons why the factors that predict the preoperative frail status differed from those of the postoperative status in older patients that underwent colorectal cancer surgery. Multidisciplinary intervention before surgical management or treatment decision-making might lead to prevention of postoperative frailty [3,17]. The implementation of enhanced recovery after surgery (ERAS) programs could bring favorable postoperative outcomes in patients with colorectal cancer. The ERAS program has been widely used in practice for older patients who are in a state of vulnerability or frailty [18,19]. The participating hospitals in this study treated the enrolled patients with standardized ERAS protocol and managed their reduction of organ dysfunction and length of postoperative

### Table 3

| Complication                        | Preoperative nonfrail group (n = 336) | Preoperative frail group (n = 164) | Total (N = 500) |
|-------------------------------------|--------------------------------------|-----------------------------------|-----------------|
| Surgical                            |                                      |                                   |                 |
| Bowel obstruction disorder          | 9                                    | 10                                | 19              |
| Surgical site infection             | 12                                   | 6                                 | 18              |
| Anastomotic leakage                 | 5                                    | 7                                 | 12              |
| Intra-abdominal abscess             | 6                                    | 2                                 | 8               |
| Wound dehiscence                    | 4                                    | 2                                 | 6               |
| Medical                             |                                      |                                   |                 |
| Cardiopulmonary event               | 9                                    | 11                                | 20              |
| Urinary tract disorder              | 3                                    | 4                                 | 7               |
| Cerebrovascular event               | 0                                    | 1                                 | 1               |
| Other                               | 2                                    | 4                                 | 6               |
| Total                               | 50                                   | 47                                | 97              |

### Table 4

| Variables                          | Univariate analysis | Multivariate analysis |
|------------------------------------|---------------------|-----------------------|
|                                   | Change frail (n = 38) | Stay nonfrail (n = 297) | P value | OR (95% CI) | P value |
| Sex                                |                      |                       |         |             |         |
| Female                             | 16                   | 115                   | .687    |             |         |
| Male                               | 22                   | 182                   |         |             |         |
| BMI                                |                      |                       |         |             |         |
| <21.5                              | 16                   | 124                   | .967    |             |         |
| ≥21.5                              | 22                   | 173                   |         |             |         |
| Cerebrovascular disease            |                      |                       |         |             |         |
| Yes                                | 3                    | 22                    | .914    |             |         |
| No                                 | 35                   | 264                   |         |             |         |
| Chronic respiratory disease        |                      |                       |         |             |         |
| Yes                                | 3                    | 33                    | .547    |             |         |
| No                                 | 35                   | 264                   |         |             |         |
| Myocardial disease                 |                      |                       |         |             |         |
| Yes                                | 2                    | 39                    | .164    |             |         |
| No                                 | 36                   | 258                   |         |             |         |
| Orthopedic disease                 |                      |                       |         |             |         |
| Yes                                | 4                    | 20                    | .393    |             |         |
| No                                 | 34                   | 277                   |         |             |         |
| History of malignancy              |                      |                       |         |             |         |
| Yes                                | 5                    | 30                    | .562    |             |         |
| No                                 | 33                   | 267                   |         |             |         |
| Hypertension                       |                      |                       |         |             |         |
| Yes                                | 23                   | 168                   | .642    |             |         |
| No                                 | 15                   | 129                   |         |             |         |
| Diabetes mellitus                  |                      |                       |         |             |         |
| Yes                                | 9                    | 61                    | .653    |             |         |
| No                                 | 29                   | 236                   |         |             |         |
| Anticoagulant therapy              |                      |                       |         |             |         |
| Yes                                | 5                    | 57                    | .367    |             |         |
| No                                 | 33                   | 240                   |         |             |         |
| ASA                                |                      |                       |         |             |         |
| 3, 4                               | 7                    | 59                    | .833    |             |         |
| 1, 2                               | 31                   | 238                   |         |             |         |
| PS                                 |                      |                       |         |             |         |
| 2, 3, 4                            | 2                    | 2                     | .014    | 7.71        | .070    |
| 0, 1                               | 36                   | 295                   |         | (0.84-70.38)|         |
| Anemia                             |                      |                       |         | .785        |         |
| Yes                                | 8                    | 57                    |         |             |         |
| No                                 | 30                   | 240                   |         |             |         |
| Hypoalbuminemia                    |                      |                       |         |             |         |
| Yes                                | 5                    | 24                    | .295    |             |         |
| No                                 | 33                   | 273                   |         |             |         |
| Tumor location                     |                      |                       |         | .848        |         |
| Colon                              | 25                   | 200                   |         |             |         |
| Rectum                             | 13                   | 97                    |         |             |         |
| History of laparotomy              |                      |                       |         | .023        | .054    |
| Yes                                | 14                   | 61                    |         | 2.16        |         |
| No                                 | 24                   | 236                   |         | (0.99-4.73)|         |
| Surgical approach                  |                      |                       |         | .006        | .067    |
| Open                               | 8                    | 22                    |         | 2.49        |         |
| Lap                                | 30                   | 275                   |         | (0.94-6.62)|         |
| Operation time (min)               |                      |                       |         |             |         |
| ≥220                               | 18                   | 155                   | .576    |             |         |
| <220                               | 20                   | 142                   |         |             |         |
| Blood loss (mL)                    |                      |                       |         | .292        |         |
| ≥25                                | 22                   | 145                   |         |             |         |
| <25                                | 16                   | 152                   |         |             |         |
| Complication                       |                      |                       |         |             |         |
| Yes                                | 13                   | 37                    | .001    | 2.69        | .018    |
| No                                 | 25                   | 255                   |         | (1.19-6.09)|         |
| Ostomy creation                    |                      |                       |         | .023        | .047    |
| Yes                                | 12                   | 49                    |         | 2.32        |         |
| No                                 | 26                   | 248                   |         | (1.01-5.33)|         |
| Delirium (postoperative)           |                      |                       |         |             |         |
| Yes                                | 5                    | 13                    | .024    | 2.40        | .159    |
| No                                 | 33                   | 284                   |         | (0.72-8.02)|         |

ASA, American Society of Anesthesiologists score; Lap, laparoscopic surgery; Open, open surgery.

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In conclusion, patient-reported KCL assessment could distinguish impairments of older patients with colorectal cancer. Further study of optimal intervention or assessment, not only KCL, is necessary to prevent postoperative worse outcome and prognosis in older patients with colorectal cancer.

**Author Contribution**

Conception and design of this study: KT, KM, and HY
Acquisition of data: KT, YF, SS, HK, NY, TH, HL, and YM
Analysis and interpretation of data: KT

**Conflict of Interest**

The authors have no conflicts of interest to declare.

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**Ethics Approval**

For this prospective multicenter study, the authors received approval of Wakayama Medical University Ethics Committee following ethical guidelines for medical and health research involving human subjects.

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