Comparison of Nutritional/Inflammatory Scores as a Preoperative Predictor of Short-Term Surgical Risks in Hepatectomy for Colorectal Metastasis

Ryosuke Umino^{1#}; Junichi Shindoh^{1,2#*}, Yuta Kobayashi¹, Miho Akabane¹, Kazutaka Kojima¹, Satoshi Okubo¹, Masaji Hashimoto¹

¹Hepatobiliary-pancreatic Surgery Division, Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan

²Okinaka Memorial Institute for Medical Disease, Tokyo, Japan

***Corresponding author:**

Junichi Shindoh M.D., Ph.D.
Department of Gastroenterological surgery, Toranomon Hospital
2-2-2 Toranomon, Minatoku
Tokyo 105-8470, Japan
Tel: +81-3-3588-1111
E-mail: shindou-ty@umin.ac.jp

[#]RU, JS and YK equally contributed to this work

ABSTRACT

Background: Various nutritional/inflammatory scores reportedly correlate with surgical outcomes of abdominal surgery, while it remains inconclusive which one is the best in prediction of short-term surgical outcomes of patients with colorectal liver metastasis (CLM).

Methods: Clinical records of 367 hepatectomies for 267 patients with CLM were retrospectively reviewed. Preoperative nutritional/inflammatory status was determined using 14 reported nutritional/inflammatory scores and predictive powers of these scores for short-term surgical outcomes were compared.

Results: In receiver operating characteristics curve analysis, controlling nutritional status (CONUT) score showed the highest performance in prediction of major postoperative morbidity (area under the curve [AUC], 0.650) among the tested scores and similar tendency was also confirmed in prediction of global postoperative morbidity (AUC, 0.622). Multivariate analysis confirmed that the CONUT score showed significant correlation with both global morbidity (odds ratio [OR], 1.29; 95% CI, 1.11-1.49, $P=0.001$) and major morbidity (OR, 1.31; 95% CI, 1.08-1.60; $P=0.006$). When preoperative degree of malnutrition was classified into normal, light, and moderate according to the original CONUT scoring system, short-term surgical outcomes were well stratified as follows: any morbidity, 21.8% vs. 35.1% vs. 51.9% ($P=0.001$); major morbidity, 6.2% vs. 11.7% vs. 29.6% ($P=0.002$); and postoperative hospital stay, 11 days vs. 11 days vs. 12 days ($P=0.006$).

Conclusions: The CONUT score could be a simple and reliable predictor of short-term surgical outcomes of patients undergoing hepatectomy for CLM.

Key words: CONUT score, colorectal liver metastasis, surgery, nutrition

INTRODUCTION

Aggressive surgical approach including perioperative chemotherapy and repeat hepatectomy has increasingly been used in the field of colorectal liver metastases (CLM) because prolonged cancer-free interval achieved through a multidisciplinary treatment approach is reportedly correlated with better survival outcomes of patients with CLM (1). With advances in perioperative

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management and surgical techniques, the complexity of liver surgery has increased over time (2,3) and more and more poor-risk patients are becoming surgical candidates. In such context, adequate risk assessment and preemptive management are required to avoid unnecessary postoperative morbidities in the era of enhanced recovery after surgery (ERAS).

Conventionally, presence of co-morbidities, performance status, hepatic functional reserve, (4) degree of hepatectomy, (5,6) cycles of preoperative chemotherapy, (5,7) chemotherapy-associated liver injury, (8) number of hepatectomy, (9,10) operation time, blood loss, etc. have been thought to be risk factors for postoperative morbidities after hepatectomy for CLM. In addition to these, recent studies have reported that preoperative nutritional/inflammatory status is also predictive of short-term surgical outcomes in patients undergoing liver surgery (11-13).

Although various nutritional/inflammatory scores have been reported to be associated with surgical outcomes of patients undergoing major abdominal surgery, (14-17) their predictive powers for postoperative morbidities have not yet been adequately compared so far. Therefore, this study sought to investigate the predictive powers of reported nutritional/inflammatory scores for short-term outcomes of patients undergoing hepatectomy for CLM, and tried to clarify the best assessment tool for preoperative surgical risk prediction in the era of aggressive surgical approach.

METHODS

Study population

From a prospective database maintained by the Department of Gastroenterological Surgery, Toranomon Hospital, a total of 367 hepatectomies for 267 patients with CLM performed between April 2008 and December 2018 were identified. Clinicopathological data of these 367 consecutive hepatectomies were retrospectively reviewed for analysis.

Indication of surgery for colorectal liver metastases and assessment of short-term surgical outcomes

Our indication criteria for surgical resection of CLM has been reported elsewhere (18). Briefly, preoperative hepatic functional reserve was assessed using indocyanine green (ICG) clearance test in addition to general blood examinations. Based on the volumetry of future liver remnant, curative surgical maneuver is

planned to fulfill estimated ICG clearance rate of full-functioning future liver remnant of ≥ 0.05 .

Severity of postoperative morbidity was determined according to the Clavien-Dindo classification (19) and grade IIIa or greater complication was classified as major morbidity.

Assessment of preoperative nutritional status

Preoperative nutritional status was determined by following 14 nutritional/hepatic functional scores/grades using blood samples obtained within one week before surgery: Glasgow prognostic score (GPS), (20) modified GPS (mGPS), (21) Onodera's prognostic nutritional index (PNI), (22) controlling nutritional status (CONUT) score, (23) Naples prognostic score (NPS), (24) neutrophil-lymphocyte ratio (NLR), (25) platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), albumin-bilirubin (ALBI) score/grade, (26) albumin-indocyanine green evaluation (ALICE) score/grade, (27) and platelet-albumin (PAL) score/grade (28) (see *table S1* for details of calculation).

Statistical analysis

Statistical analysis was performed using the JMP software (version 14; SAS Institute Inc., Cary, NC) or the IBM SPSS software (Ver 26.0 SPSS Inc., Chicago, IL). Continuous values were expressed as the median (range) and were compared using the Wilcoxon's rank-sum test. Categorical variables were expressed as the number (%) and were compared using the Fisher exact test or the chi-squared test, as appropriate. The most appropriate nutritional score for preoperative surgical risk assessment was determined among the 14 tested nutritional scores using the receiver operating characteristic (ROC) curve analysis for global and major postoperative morbidities. Then, its correlation with the short-term surgical outcomes was investigated with a multivariate analysis using logistic regression model with backward selection. To prevent overfitting, only factors that showed a statistically significant association with postoperative morbidities with P values > 0.1 were included in the final model.

RESULTS

Baseline characteristics

The baseline characteristics of the study population are summarized in *table 1*. Median age was 63 and 67.8% of the patients were male. Of the 367 hepatectomies,

Table S1 - Nutritional/inflammatory scoring systems

Glasgow prognostic score (GPS)
0 point: CRP $\leq$ 1.0 mg/dL and albumin $\geq$ 3.5 g/dL
1 point: CRP $>$ 1.0 mg/dL or albumin $<$ 3.5 g/dL
2 points: CRP $>$ 1.0 mg/dL and albumin $<$ 3.5 g/dL
Modified Glasgow prognostic score (mGPS)
0 point: CRP $\leq$ 1.0 mg/dL
1 point: CRP $>$ 1.0 mg/dL and albumin $\geq$ 3.5 g/dL
2 points: CRP $>$ 1.0 mg/dL and albumin $<$ 3.5 g/dL
Onodera's prognostic nutritional index (PNI)
$[10 \times \text{albumin (g/dL)}] + [0.005 \times \text{lymphocyte (/mm}^3\text{)}]$
Controlling nutritional status (CONUT) score
Albumin score
$\geq$ 3.5 g/dL (0 point), 3.00-3.49 (2 point), 2.50-2.99 (4 points), $<$ 2.5 (6 points)
Lymphocyte score
$\geq$ 1600 /mm ³ (0 point), 1200-1599 (1 point), 800-1199 (2 points), $<$ 800 (3 points)
Cholesterol score
$\geq$ 180 mg/dL (0 point), 140-179 (1 point), 100-139 (2 points), $<$ 100 (3 points)
Naples prognostic score (NPS)
Albumin score: $\geq$ 4 g/dL (0 point), $<$ 4.0 (1 point)
Cholesterol score: $>$ 180 mg/dL (0 point), $\leq$ 180 (1 point)
Neutrophil-lymphocyte ratio: $>$ 2.96 (0 point), $\leq$ 2.96 (1 point)
Lymphocyte-monocyte ratio: $>$ 4.44 (0 point), $\leq$ 4.44 (1 point)
Albumin-bilirubin (ALBI) score
$0.66 \times \log_{10}[\text{bilirubin } (\mu\text{mol/L})] - 0.085 \times \text{albumin (g/L)}$
cut-off value: -2.60 and -1.39 for grading
Albumin-indocyanine green evaluation (ALICE) score
$0.663 \times \log_{10}[\text{ICG-R15 } (\%)] - 0.0718 \times \text{albumin (g/L)}$
cut-off value: -2.20 and -1.39 for grading
Platelet-albumin (PAL) score
$-0.777 \times \text{albumin (g/dL)} - 0.575 \times \log_{10}[\text{platelet count } (10^3/\text{mm}^3)]$
cut-off value: -3.77 and -3.04 for grading

Table 1 - Baseline characteristics

Age, y	63 (31-88)
Male	249 (67.8)
ASA-PS, class1/ 2/ 3	160 (44.4)/ 182 (50.6) / 18 (5.0)
Number of hepatectomy	
1	267 (72.8)
2	74 (20.2)
3	17 (4.6)
4	7 (1.9)
5	2 (0.5)
Number of tumor	2 (1-83)
Maximum size of tumor (mm)	23 (5-155)
Preoperative chemotherapy	121 (33.0)
Albumin (g/dL)	3.8 (2.3-4.9)
Total bilirubin (mg/dL)	0.8 (0.2-7.3)
Total cholesterol (mg/dL)	196 (64-399)
C-reactive protein (mg/dL)	0.1 (0-14.3)
Prothrombin activity (%)	96 (63-138)
White blood cell (/mm ³)	5.2 (2.8-14.9)
Neutrophil (%)	58.8 (19.0-87.5)
Lymphocyte (%)	29.4 (5.0-59.0)
Monocyte (%)	6.4 (0.5-20.0)
Platelet count (104/mm ³)	20.0 (1.4-52.2)
ICG-R15 (%)	9.8 (0.9-81.3)
Major hepatectomy	78 (21.2)
Laparoscopic approach	30 (8.2)
Operation time (min)	175 (47-1159)
Estimated blood loss (mL)	352 (0-7359)
Transfusion	24 (6.5)
Any morbidity	110 (29.9)
Major morbidity	40 (10.9)

Figures represent median (range) or number (percentage) unless indicated. Abbreviations. ASA-PS class, American society of anesthesiologists physical status class, ICG-R15, indocyanine green retention rate at 15 minutes.

267 (72.8%) cases were initial hepatectomy and the remaining 100 (27.2%) cases were repeat hepatectomies for recurrence or 2-stage approach for remaining tumors. Preoperative chemotherapy was used in 121 (33.0%) cases and major hepatectomy was selected in 78 (21.2%) cases. Median operation time was 175 minutes and estimated blood loss was 352 mL. Incidences of any morbidity and major morbidity (i.e., Clavien-Dindo $\geq$ IIIa) were 29.9% and 10.9%, respectively.

Preoperative nutritional / inflammatory scores and its performance in prediction of postoperative morbidities

Area under the curves (AUCs) in the ROC analysis for the tested 14 scores are summarized in *table 2*. For prediction of any postoperative morbidity, ALICE score (AUC 0.633), PAL score (AUC 0.631), ALBI score (AUC 0.627), PNI (AUC 0.623), and CONUT score (AUC 0.622)

showed good performance compared to the other nutritional/inflammatory scores. For major morbidity, CONUT score (AUC 0.650) showed the highest performance among the 14 scores, followed by PAL score (AUC 0.646), PNI (AUC 0.643), ALICE score (AUC 0.639), and GPS (AUC 0.633).

Given these results and clinical usability without complex calculation such as logarithm, CONUT score was selected as the best scoring system for predicting both global and major postoperative morbidities in patients undergoing hepatectomy for CLMs.

Short-term outcomes according to the undernutrition grade based on the CONUT score

When stratifying the study cohort according to the undernutrition grade of the CONUT score defined in the original report (23), 179 (49.7%) cases were classified as

Table 2 - Predictive powers of nutritional/inflammatory scores for postoperative morbidities

Any morbidity	AUC
Categorical variable systems	
CONUT score	0.622
GPS	0.603
PAL grade	0.587
ALICE grade	0.582
NPS	0.575
ALBI grade	0.566
modified GPS	0.501
Continuous variable systems	
ALICE score	0.633
PAL score	0.631
PNI	0.623
ALBI score	0.618
LMR	0.605
PLR	0.547
NLR	0.541
Major morbidity	
Categorical variable systems	
CONUT score	0.650
GPS	0.633
PAL grade	0.622
ALICE grade	0.575
ALBI grade	0.571
NPS	0.556
modified GPS	0.519
Continuous variable systems	
PAL score	0.646
PNI	0.643
ALICE score	0.639
ALBI score	0.626
LMR	0.560
PLR	0.550
NLR	0.527

Abbreviations. AUC, area under the curve; GPS, Glasgow prognostic score, PNI, prognostic nutritional index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; NPS, Naples prognostic score. See Supplemental Table for details.

normal (CONUT score 0-1), 154 (42.8%) were classified as light (CONUT score 2-4), and 27 (7.5%) were classified as moderate (CONUT 5-8), excluding 7 cases missing total cholesterol values before surgery.

Table 3 summarized the patient characteristics and short-term surgical outcomes according to the CONUT undernutrition grade. Number and maximum diameter of tumor increased and the proportion of patients who received preoperative systemic therapy tended to be higher as the undernutrition grade got advanced. Higher proportion of patients who presented advanced CONUT score required open major hepatectomy. Incidences of any morbidity and major morbidity were well correlated with these undernutrition grade. However, there was no statistical difference regarding the other liver-related morbidities including bile leak, refractory ascites/pleural effusion, wound infection, bleeding, or postoperative hepatic insufficiency, except for abdominal abscess. The length of hospital stay also

showed significant correlation with the CONUT score as follows: normal, 11 days (interquartile range [IQR], 8-15 days); light, 11 days (IQR, 9-17 days); and moderate, 12 days (IQR, 11-28 days) ($P=0.006$).

In multivariate analysis, CONUT score showed significant correlation with any morbidity (odds ratio [OR], 1.29; 95% CI, 1.11-1.49; $P=0.001$) and major morbidity (OR, 1.31; 95% CI, 1.08-1.60; $P=0.006$) independent from tumor factors, extent of hepatectomy, or preoperative chemotherapy. For surgical site infection, while preoperative chemotherapy and prolonged operation time were identified as independent risk factors, the CONUT score showed no significant correlation with SSI (table 4).

DISCUSSION

This study analyzed the influence of preoperative nutritional/inflammatory status on short-term surgical outcomes in patients undergoing hepatectomy for CLM. Comparison of various nutritional/inflammatory scores revealed that CONUT score, simply scored using the three variables: albumin, lymphocyte, and cholesterol, shows the best performance in prediction of postoperative morbidities. Multivariate analysis confirmed that CONUT score is associated with increased risk of both global and major morbidities, and the undernutrition grade based on the CONUT score was predictive of postoperative morbidity rates and length of hospital stay.

A glowing attention has recently been paid on nutritional status of patients undergoing treatment for cancers (29). An increased systemic immune-inflammatory response by host-tumor interaction is reportedly associated with progressive nutritional decline and may deteriorate anti-tumor immune response which results in poor oncological outcomes (30). Therefore, several studies have been conducted to establish a new evaluation method for nutritional/inflammatory status to improve treatment outcomes for cancer patients. McMillan et al. were the first to show that the GPS, calculated by only two factors (i.e., serum levels of C-reactive protein and albumin), sensitively predicts survival outcomes of patients independent of the oncological stage or performance status (31). Josse et al. reported the importance of evaluation of inflammatory status and showed that preoperative NLR is associated with a risk of anastomotic leakage among patients undergoing resection of colorectal cancer (16). Similar studies using various scoring systems have been reported elsewhere (14, 15, 17). Because adequate assessment of preoperative

Table 3 - Baseline characteristics and surgical outcomes according to the CONUT undernutrition grade

	Normal (score 0-1) n=179 (49.7%)	Light (score 2-4) n=154 (42.8%)	Moderate (score 5-8) n=27 (7.5%)	P
Patient's characteristics				
Age, y	63 (35-85)	63 (35-88)	64 (31-83)	0.891
Gender, male/ female	127 (71.0) /52 (29.1)	105 (68.2) /49 (31.8)	14 (51.9) /13 (48.2)	0.138
ASA-PS, class1/ 2/ 3	85 (47.5) /83 (46.4) /11 (6.2)	69 (44.8) /79 (51.3) /6 (3.9)	6 (22.2) /20 (74.1) /1 (3.7)	0.174
Tumor factors				
Primary lesion, colon/ rectum	122 (68.2) /57 (31.8)	94 (61.0) /60 (39.0)	14 (51.9) /13 (48.2)	0.161
Number of tumor	2 (1-30)	2 (1-83)	3 (1-27)	0.116
Maximum size of tumor (mm)	20 (5-125)	24 (6-155)	30 (8-85)	0.005
Preoperative chemotherapy	53 (29.6)	54 (35.1)	12 (44.4)	0.244
Operative parameters				
Major hepatectomy	29 (16.2)	38 (24.7)	11 (40.7)	0.008
Laparoscopic approach	22 (12.3)	6 (3.9)	1 (3.7)	0.029
Operation time (min)	169 (47-584)	176 (70-541)	182 (60-1159)	0.370
Estimated blood loss (mL)	335 (0-2871)	373 (0-3488)	520 (50-7359)	0.043
Any morbidity (%)	39 (21.8)	54 (35.1)	14 (51.9)	0.001
Bile leak	12 (6.7)	19 (12.3)	3 (11.1)	0.293
Ascites/Pleural effusion	8 (4.5)	16 (10.4)	4 (14.8)	0.109
SSI				
Wound infection	4 (2.2)	5 (3.3)	0 (0)	0.923
Abdominal abscess	6 (3.4)	5 (3.3)	6 (22.2)	<0.001
Postoperative bleeding	1 (0.6)	2 (1.3)	0 (0)	0.829
PHI ^a	2 (1.1)	0 (0)	0 (0)	0.541
Others	12 (6.7)	13 (8.4)	6 (22.2)	0.069
Major morbidity (%)	11 (6.2)	18 (11.7)	8 (29.6)	0.002
Mortality	0 (0)	0 (0)	0 (0)	1
Hospital stay (days) ^a	11 (8-15)	11 (9-17)	12 (11-28)	0.006

Figures represent number (percentage) or median (range).

Abbreviation: SSI, surgical site infection; PHI, postoperative hepatic insufficiency; ASA-PS class, American society of anesthesiologists physical status class.

^aPostoperative hepatic insufficiency was defined as peak total bilirubin >7 mg/dL.

Table 4 - Multivariate analysis for predictors of any morbidity, major morbidity and surgical site infection

	P ^a	Coefficients ^b	SE	Wald χ^2	OR	95% CI
Any morbidity						
Preoperative chemotherapy	<0.001	1.103	0.266	17.14	3.01	1.79-5.08
Operation time >180 min	<0.001	1.009	0.260	15.04	2.74	1.65-4.57
CONUT score +1 point	0.001	0.253	0.075	11.45	1.29	1.11-1.49
Number of laparotomy +1	0.081	0.293	0.168	3.05	1.34	0.97-1.86
Major morbidity						
Blood loss >500 mL	<0.001	1.587	0.433	13.45	4.89	2.09-11.4
Preoperative chemotherapy	<0.001	1.564	0.418	14.03	4.78	2.11-10.8
CONUT score +1 point	0.006	0.273	0.099	7.61	1.31	1.08-1.60
Number of laparotomy +1	0.056	0.441	0.231	3.65	1.55	0.99-2.44
SSI^c						
Preoperative chemotherapy	0.006	1.533	0.462	11.02	4.63	1.87-11.4
Operation time >180 min	0.006	-1.446	0.524	7.60	0.24	0.08-0.66
Blood loss >500 mL	0.095	0.828	0.496	2.78	2.29	0.87-6.05
CONUT score +1 point	0.099	0.192	0.117	2.73	1.21	0.97-1.52

^aBased on likelihood test adjusted for the other factors in the final model. ^bEstimated coefficient for the variable and the associated standard error.

^cSSI included wound infection or abdominal abscess.

Abbreviations: SSI, surgical site infection; SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval;

ASA-PS class, American society of anesthesiologists physical status class.

Note. Multivariate logistic regression was applied with stepwise backward selection. Initially all the potential independent variables were included in the statistical model. Then factors that showed no or limited statistically significant association ($P > 0.1$) adjusted for the remaining factors in the model were deleted from the model in stepwise fashion. The 10 tested variables were as follows: age (>65 vs. ≤ 65), gender, ASA-PS class (≥ 2 vs. < 2), preoperative chemotherapy (y/n), number of laparotomy, degree of hepatectomy (major vs. minor), laparoscopic approach (y/n), operation time (> vs. ≤ 180 min), estimated blood loss (> vs. ≤ 500 mL), and CONUT score.

nutritional status is helpful to know the perioperative risks of patients undergoing abdominal surgery, it could also contribute to better surgical management and improved adherence to recovery protocol in the era of ERAS (32).

With a development of multidisciplinary treatment approach, more and more patients with advanced colorectal cancer including CLM are becoming surgical candidates after intensive chemotherapy. While perioperative chemotherapy and repeated hepatectomy

contributes to better survival outcomes for CLM,⁽¹⁾ the complexity of liver surgery and aggressive chemotherapy still remain the main cause of morbidity and mortality (5,33,34). To ensure perioperative safety, meticulous preoperative workup including assessment of hepatic functional reserve and 3D volumetry has conventionally been performed to mainly avoid the risk of postoperative hepatic insufficiency (18,35,36). However, given the increasing awareness of the importance of nutritional/inflammatory status, preoperative assessment would need to be more comprehensive to adequately assess the surgical risks based on the patients' physical status.

This study aimed to compare the performance of various nutritional/inflammatory scores and to investigate the most efficient evaluation method from the standpoint of reliability and usability. Of course, nutritional scores using continuous variables generally tend to show good performance. However, the noteworthy result of the present study is that nutritional scores using simple categorical variables are not always inferior to those using continuous variables requiring complex calculations. In the field hepatology, ALBI score (26) has gradually been used as an alternate method to evaluate hepatic functional reserve. However, the major issue of this score includes its complex calculation using logarithm and arbitrary cut-off points using 25 percentile and 90 percentiles for grading, though its performance has been validated in various cohorts (37, 38). The CONUT score selected as a potentially effective assessment tool for prediction of short-term surgical outcomes was relatively simple using three variables and it showed acceptable performance in prediction of any morbidity, major morbidity, and postoperative hospital stay (*table 3*). Although the clinical evidence regarding the use of CONUT score in preoperative assessment remains insufficient, (15, 39) it would be practically important that surgical risks of patients undergoing hepatectomy for CLM could be predicted relatively easily through a simple scoring system avoiding complex calculation.

The limitations of the current study include its retrospective design and inherent potential bias in a selected population. However, the current analysis was performed using a prospectively collected database of patients who were treated similarly during the study period. Additionally, it is difficult to evaluate the influence of preoperative chemotherapy on nutritional /inflammatory status and the impact of perioperative nutritional support on surgical outcomes in the present cohort. As presented in *table 3*, advanced under-nutrition grade was correlated with advanced tumor

extension, higher proportion of preoperative therapy, and higher extent of hepatectomy. Although multivariate analysis (*table 4*) demonstrated that the CONUT score was independently correlated with increased incidence of morbidities after hepatectomy for CLM, care should be paid in interpretation of the present results considering the differences in baseline characteristics among the three groups of patients classified according to the CONUT score. Future analysis including prospective study looking at the impact of perioperative nutritional management would be needed to further optimize the ERAS protocol.

CONCLUSION

In conclusion, the current study confirms that short-term surgical outcomes of patients undergoing hepatectomy for CLM is correlated with preoperative nutritional status and the perioperative surgical risk may be predicted relatively easily using the CONUT score.

Disclosure statement

The authors have no conflict of interest to disclose. This study was supported by a grant from Okinaka Memorial Institute for Medical Disease.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for clinical study in Japan under approval of the institutional review board of Toranomon Hospital (No. 1919).

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