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ORIGINAL PAPER

Multicenter prospective study validating the efficacy of a quantitative assessment tool for frailty in patients with urological cancers

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Abstract

We prospectively validate the efficacy of the frailty discriminant score (FDS) in individuals with urological cancers, as there has been growing importance in evaluating frailty in clinical practice. A prospective, multicenter study was conducted from February 2017 to April 2019. We enrolled 258 patients with urological cancers and 301 community-dwelling participants who were assessed for frailty. Frailty was assessed using FDS that includes ten items, such as physical, mental, and blood biochemical tests. The primary outcome was the non-inferiority (margin 5%) of FDS in discriminating patients with urological cancers from controls (Ctrl). The sensitivity, specificity, and area under the receiver operating characteristic (AUROC) curve for each predictive test were calculated. The secondary endpoints included the prediction of overall survival between patients with urological cancer who have high and low FDS. FDS was significantly higher in patients with urological cancers than that in the Ctrl. The AUROC curves for individuals with non-prostate cancers (such as bladder cancer, upper tract urothelial carcinoma, and renal cell carcinoma; 0.942) and those with prostate cancer (0.943) were within the non-inferior margin. The overall survival values were significantly lower in patients with higher FDS score than in those with lower FDS score. The study met its primary and secondary endpoints. The FDS is a reliable and valid tool for assessing frailty and prognosis in patients with urological cancers.

Keywords Frailty · Frailty discriminant score · Urological cancer · Prostate cancer · Renal cell carcinoma · Urothelial carcinoma

Introduction

There has been growing interest in measuring frailty in patients with cancer and facilitating communication between patients and physicians to make more informed decisions [1, 2]. A comprehensive geriatric assessment (CGA) that includes evaluation of physical function, cognition, nutrition, muscle volume, and comorbidities is recommended to detect frailty [3–11]. However, there is no consensus regarding the tools in evaluating frailty. Currently, several models can be used to assess frailty, which include the Fried phenotype (FP) criteria [12], modified frailty index [13], and geriatric 8 (G8) screening score [14]. Although frailty assessment has been widely used in urology [15–23], a full geriatric assessment in all candidates is time-consuming and is not feasible in clinical practice [17, 24].

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We hypothesized that differences in key parameters between healthy individuals and cancer patients might be optimal for quantitative measurement of cancer-related frailty. We developed a quantitative frailty assessment tool (frailty discriminant score: FDS) using the differences between patients with urological cancers and those without, which includes assessment of physical capabilities (hand-grip weakness and slowed walking speed), blood biochemical tests (serum albumin level, renal function, and hemoglobin level), and self-reported exhaustion and depression as a quantitative CGA tool. We have previously reported the significance of the FDS in evaluating the quantitative measurement of cancer-related frailty (training cohort) [25]. FDS showed not only obvious differences between patients with and without cancer, but also poor prognosis in patients with urological cancers. This prospective, multicenter study aimed to validate the efficacy of FDS in assessing for frailty and prognosis in patients with urological cancers in an external validation cohort.

Materials and methods

Ethics statement

This multicenter prospective study was performed according to the ethical standards of the Declaration of Helsinki and was approved by the ethics review board of the Hirosaki University School of Medicine (authorization number: 2014-297), Mutsu General Hospital, Aomori Prefectural Central Hospital, and Oyokyo Kidney Research Institute Hirosaki Hospital. All participants provided a written informed consent. This study was registered as a clinical trial (UMIN000036497).

Study population

This study consisted of training and validation cohorts. The previous study for training cohort evaluated frailty in 605 consecutive patients with urological cancers and 2280 individuals with non-cancer controls (Ctrl) from the Iwaki Health Promotion Project [25–31]. In this validation cohort, we prospectively included 258 patients with urological cancers in Hirosaki University Hospital, Mutsu General Hospital, Aomori Prefectural Central Hospital, and Oyokyo Kidney Research Institute Hirosaki Hospital. We included 301 non-cancer Ctrl from the Iwaki Health Promotion Project between 2017 and 2018 (Fig. 1). The inclusion criteria of cancer patients were as follows: (1) patients with urological cancers, such as prostate cancer (PC), bladder cancer (BC), upper tract urothelial carcinoma (UTUC), or renal cell carcinoma (RCC), who can be evaluated for frailty using the FDS and (2) those who agreed to undergo frailty evaluation. Meanwhile, the exclusion criteria were as follows: (1) patients with cancer except for PC, BC, UTUC, or RCC and (2) those with severe disability and/or dementia who could not be evaluated for frailty. The inclusion criteria of non-cancer Ctrl were age 50 or higher healthy individuals without any history of cancers and severe comorbidities.

Evaluation of variables

Data about age, sex, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG-PS) score, cardiovascular disease, diabetes mellitus, types of

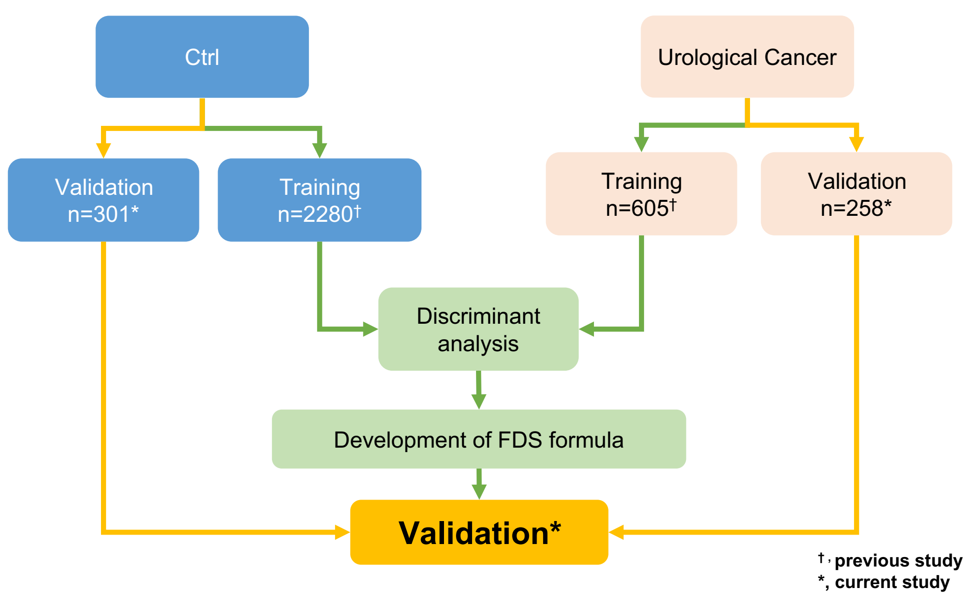

Fig. 1 Study design and patient selection. This is a multicenter, prospective observational study that validated the efficacy of a quantitative frailty assessment tool in patients with urological cancers. This validation cohort included 258 patients with urological cancers and 301 individuals without cancer. The previous training cohort included 605 patients with urological cancers and 2280 individuals without cancer

urological cancers, and clinical stage were obtained from all participants. Routine laboratory investigations were conducted, which include examination of blood count, serum albumin levels, and estimated glomerular filtration rate (eGFR) [32].

Assessment of frailty

FDS included ten items, which were as follows: age, sex, BMI, handgrip strength, gait speed, serum albumin level, renal function, hemoglobin level, exhaustion, and depression [25]. Gait speed was measured using The Timed Get-up-and-Go (TGUG) test [6]. Self-reported exhaustion and depression were assessed in patients with cancer and community-dwelling populations using the fatigue scale of the Center for Epidemiologic Studies Depression (CES-D) scale and vitality questionnaire of the Health-Related Quality of Life, respectively. Answers, such as "all of the time" or "most of the time" were considered positive. The FDS formulas for patients with PC (PC group) and without PC (BC, UTUC, RCC; non-PC group) were as follows: PC group = (5.6418 + age × 0.0110 + BMI × 0.0267 + handgrip × 0.0094 + TGUG × 0.1960 + exhaustion × − 0.0880 + depression × 0.0464 + albumin × − 0.5343 + eGFR × 0.0175 + hemoglobin × − 0.5204) and non-PC group = (6.8698 + age × 0.0053 + sex × 1.4794 + BMI × 0.0105 + handgrip × − 0.0209 + TGUG × 0.1993 + exhaustion × 0.0876 + depression × 0.2005 + albumin × − 0.9037 + eGFR × − 0.0112 + hemoglobin × − 0.2868) [25]. A web-based application for the FDS calculation was posted at https://www.calconic.com/calculator-widgets/frailty-discriminant-score/5cbddc481f2de20026871c94 (Fig. S1). Based on the five FP criteria (weight loss, exhaustion, low physical activity, slowness, and weakness), the participants were divided into three categories: non-frail (score 0), prefrail (score 1–2), and frail (score ≥ 3) [14].

Primary outcome measure

The primary outcome is the discrimination between the urologic cancer patients and non-cancer individuals according to FDS. We compared FDS between patients with non-PC (BC, UTUC, and RCC) and Ctrl, and between patients with PC as well as Ctrl (male).

Secondary outcome measure

The secondary outcome was the effect of FDS on the overall survival (OS) of patients with urological cancers who have FDS-high versus those with FDS-low. FDS-high was defined as > 2.3 in the non-PC group and > 3.3 in the PC group, respectively, in our previous study [25].

Sample size

Sample size for the primary outcome was calculated using the area under the receiver operating characteristic (AUROC) curve in our previous study. The AUROC curve in the non-PC and PC groups was 0.969 (Fig. S2A, 95% confidence interval [CI] 0.957–0.978) and 0.975 (Fig. S2B, 95% CI 0.964–0.985), respectively. For the non-inferiority hypothesis, using 90% power and 2.5% one-sided α, a margin of 5% clinical unimportance, 139 patients and 278 Ctrl (an allocation ratio of 1:2) are required in the non-PC analysis. In the PC analysis, 102 patients and 204 Ctrl are required. The use of 5% as the margin of non-inferiority represents a difference that is considered clinically insignificant in the detection rates. Sample sizes for secondary outcome were calculated using the 2-year OS in patients with FDS-high (73%) and FDS-low (96%) in our previous study (Fig. S2C). Using 90% power and 2.5% two-sided α, 68 participants per arm (an allocation ratio of 1:1) are required to detect the superiority of FDS-high and FDS-low. Accounting for 15% withdrawal/loss to follow-up, 156 (78 vs. 78) participants should be recruited.

Exploratory outcome measure

Exploratory outcomes included the association among the FDS, FP criteria, and G8 screening tool score for the definition of frailty. Optimal cutoff values for frailty were evaluated via AUROC analysis.

Statistical analysis

The statistical analyses of clinical data were performed using the GraphPad Prism 5.03 (GraphPad Software, San Diego, CA), BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), and R 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using Fisher's exact test or the χ^2 test. Quantitative variables were expressed as means ± standard deviations. Differences between groups were compared using Student's t test for normally distributed data or the Mann–Whitney U test for non-normally distributed data. OS was evaluated using the Kaplan–Meier method and log-rank test. Agreement on frailty definition among the three assessment tools was assessed using Cohen's κ coefficient with values < 0, 0–0.2, 0.21–0.4, 0.41–0.6, 0.61–0.8, and ≥ 0.81, indicating poor, slight, fair, moderate, substantial, and almost perfect inter-rater agreement, respectively [33]. A P value < 0.05 was considered statistically significant.

Table 1 Background of participants in the validation study

	Ctrl	Urological cancers
Number of subjects, *n*	301	258
Age, years	72 ± 7.8	73 ± 9.0
Sex (male), *n*	240 (80%)	215 (83%)
ECOG-PS (>1), *n*		16 (6.2%)
Body mass index (Kg/m^2)	24 ± 3.2	23.5 ± 3.4
Hypertension, *n*	102 (34%)	142 (55%)
Diabetes, *n*	30 (10%)	61 (24%)
Cardiovascular disease, *n*	22 (7.3%)	45 (17%)
Handgrip strength (Kg)	33 ± 7.8	27.3 ± 8.6
Timed get-up-and-go test (s)	5.7 ± 1.5	11.8 ± 6.4
Exhaustion (yes), *n*	18 (6.0%)	48 (19%)
Depression (yes), *n*	5 (1.7%)	42 (16%)
Serum albumin (g/dL)	4.3 ± 0.3	3.8 ± 0.6
eGFR (mL/min/1.73 m^2)	70 ± 16	64 ± 21
Hemoglobin (g/dL)	14.5 ± 1.3	12.7 ± 2.0
Bladder cancer (BC), *n*		60 (23%)
Upper tract urothelial carcinoma (UTUC), *n*		47 (18%)
Renal cell carcinoma (RCC), *n*		38 (15%)
Prostate cancer (PC), *n*		113 (44%)
Metastatic disease, *n*		83 (32%)

Results

Outcomes in the training cohort

The outcomes in the training cohort are reported in the previous study [25], and it is summarized in Fig. S2.

Subject population of the validation cohort

A total of 559 participants were included in this validation study. The characteristic of the Ctrl and patients with urological cancers are summarized in Table 1. BC, UTUC, RCC, and PC were observed in 60 (23%), 47 (18%), 38 (15%), and 113 (44%) patients, respectively.

Primary outcome in the validation cohort

The median values of FDS in the Ctrl (n = 301) and non-PC (n = 145) groups were 0.166 and 2.66, respectively, in this validation study (Fig. 2a: P < 0.001). The predictive accuracy of FDS in discriminating the healthy Ctrl group from the non-PC groups was significant (Fig. 2b: AUROC curve: 0.942; 95% CI 0.918–0.966, P < 0.001). The median values of FDS in the Ctrl (male, n = 240) and PC (n = 113) groups were − 0.451 and 1.563, respectively

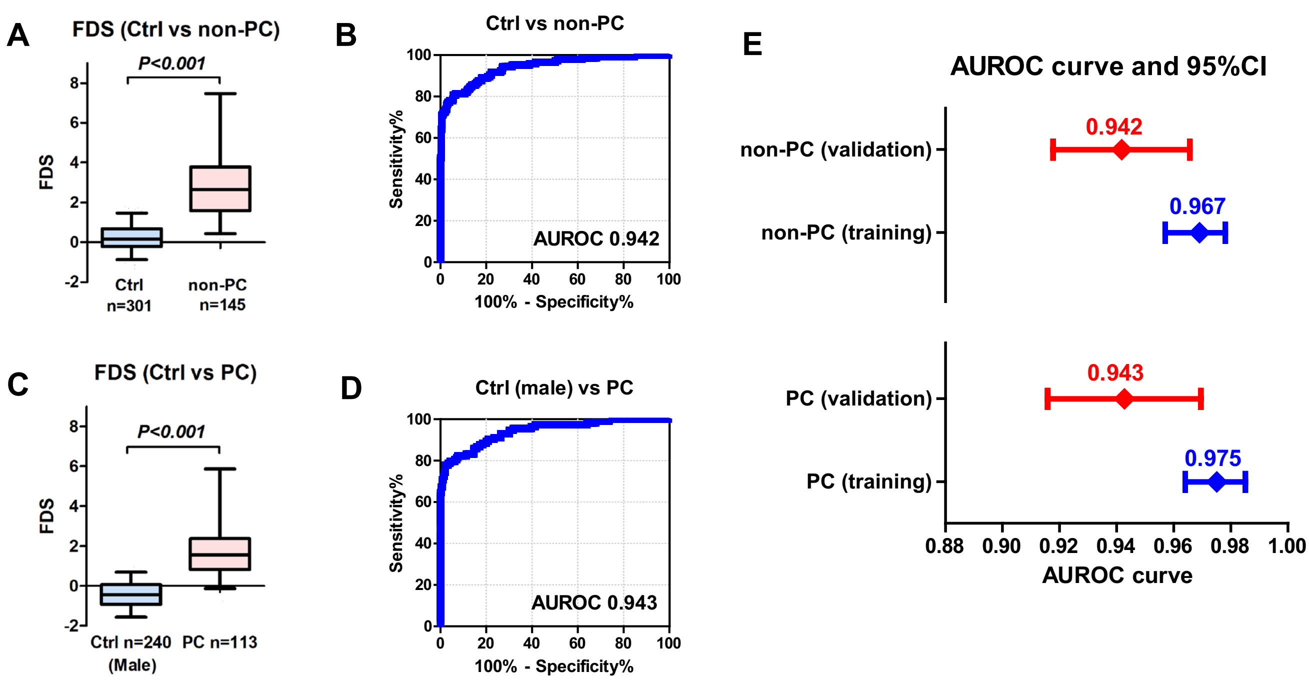

Fig. 2 Primary outcome measure. The median values of frailty discriminant score (FDS) in the control (Ctrl) and non-prostate cancer (non-PC) groups were compared (**a**). The predictive accuracy of FDS in discriminating the Ctrl and non-PC groups was investigated by area under the receiver operating characteristic (AUROC) curve (**b**). The median values of the FDS in the Ctrl and PC groups were compared (**c**). The predictive accuracy of FDS in discriminating the Ctrl and PC groups was investigated by AUROC curve (**d**). In the validation cohort, the AUROC was within the inferior margin (< 5%) in both the non-PC and PC groups (**e**)

(Fig. 2c: $P < 0.001$). The predictive accuracy of FDS in discriminating the Ctrl group from the PC group was significant (Fig. 2d: AUROC curve: 0.943; 95% CI 0.916–0.970, $P < 0.001$). In the validation cohort, AUROC value was within the inferior margin in both the non-PC (AUROC curve > 0.919) and PC (AUROC curve > 0.926) groups (Fig. 2e).

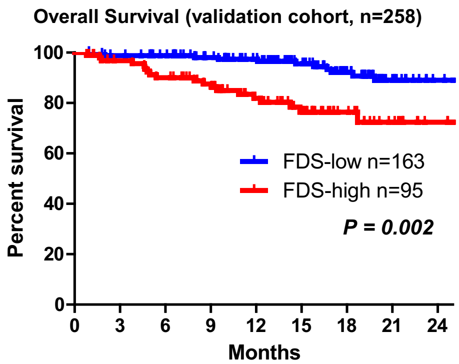

Fig. 3 Secondary outcome measure. The median follow-up of 15.7 months. The overall survival (OS) was significantly shorter in the frailty discriminant score (FDS)-high group than in the FDS-low group ($P = 0.002$). The 2-year OS values of the FDS-high and FDS-low groups were 72% and 89%, respectively

Secondary outcome in the validation cohort

Of the 258 patients with urological cancer, 30 (12%) died within the median follow-up of 15.7 months, which included 11/163 (6.7%) in the FDS-low group and 19/95 (20%) in the FDS-high group. The OS was significantly lower in the FDS-high group than in the FDS-low group (Fig. 3: P = 0.002). The 2-year OS values of the FDS-high and FDS-low groups were 72% and 89%, respectively.

Exploratory outcomes in the validation cohort

We investigated the association between frailty as well as the FDS, FP criteria, and G8 screening tool score. A significant association was observed between the FDS and FP criteria (Fig. 4a: $P < 0.001$, AUROC curve: 0.845), between the FP criteria and G8 screening tool score (Fig. 4b: $P < 0.001$, AUROC curve: 0.780), and between the FDS and G8 screening tool score (Fig. 4c: $P < 0.001$, AUROC curve: 0.726). The optimal cutoff values for FP ≥ 3 in the FDS, FP ≥ 3 in the G8 screening tool score, and FDS-high (> 2.30 in the non-PC group and > 3.30 in the PC group) for G8 screening tool score were 2.93, 12.5, and 12.5, respectively. The identical values of FDS on prefrail and frail for the FP criteria and G8 screening tool score are summarized in Table 2. The sensitivity and specificity of FDS for FP ≥ 3 and G8 screening tool score for FDS-high were 61% and 75%, and 59% and

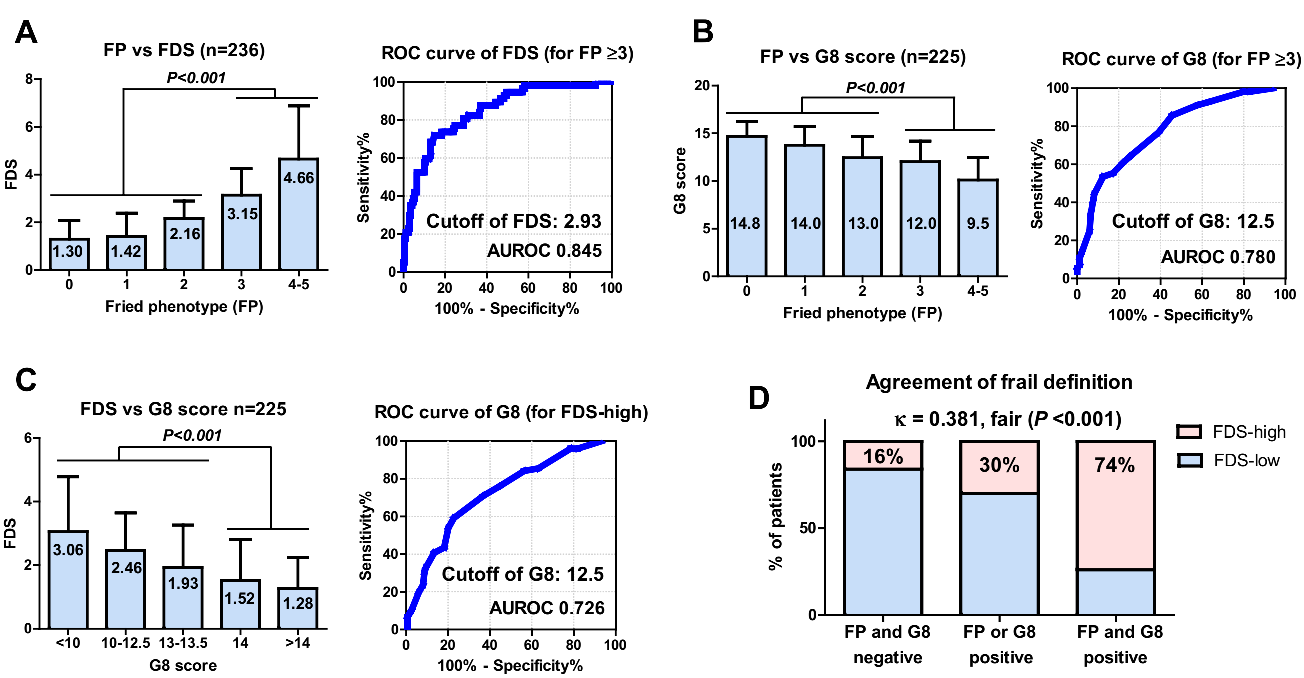

Fig. 4 Exploratory outcome measures. A significant association was observed between the frailty discriminant score (FDS) and Fried phenotype (FP) criteria (**a**), between the FP criteria and geriatric 8 (G8) screening tool score (**b**), and between the FDS and G8 screening tool score (**c**). The agreement for the definition of frail (G8 screening tool score < 14 and FP criteria score ≥ 3) versus FDS-high was investigated using Cohen's κ coefficient (**d**)

Table 2 The identical values of FDS on prefrail and frail for the FP criteria and G8 score

Assessment tool	FDS cutoff	AUROC	Sensitivity (%)	Specificity (%)
FP criteria				
1 or 2	> 1.59	0.69	67	63
≥ 3	> 2.93	0.75	61	75
G8 score				
< 14	> 1.58	0.72	60	78
< 12.5	FDS-high[a]	0.73	59	77

[a] > 2.30 and > 3.30 for non-PC and PC groups, respectively

77%, respectively (Table 2). The agreement for the definition of frailty (G8 screening tool score < 14 and FP criteria ≥ 3) versus FDS-high was fair (Fig. 4d: $\kappa = 0.381$, $P < 0.001$). A linear association was observed in the three frailty assessment tools in the three-dimensional Scatter plot (Fig. S3).

Discussion

We previously developed the FDS, a quantitative CGA tool that includes the assessment of ten items, which include physical, mental, and biochemical parameters comparing patients with urological cancer and non-cancer individuals. As most parameters in the FDS formula consisted of basic clinical data, FDS requires only four additional measurements (handgrip strength, TGUG test, and a few questionnaires) in the evaluation of quantitative frailty. The strength of our model was the inclusion of key physical and biochemical parameters, such as gait speed, serum albumin level, renal function, and hemoglobin level, which were significantly associated with frailty and mortality [6, 34–38]. Our previous study suggested that frailty was different between the patients with prostate cancer and those with other urologic cancers. For example, renal function was significantly lower in non-PC patients than that in non-cancer individuals. However, renal function was significantly higher in PC patients than that in non-cancer individuals. Based on these findings, we separately developed frailty discriminant formulas for non-PC and PC patients to distinguish between cancer patients and that in non-cancer individuals [25]. In our training cohort, the accuracy of FDS in discriminating patients with urological cancers and healthy individuals was high, with an AUROC value of 0.969 in the non-PC group (Fig. S2A) and 0.975 in the PC group (Fig. S2B) [25]. Additionally, the association between FDS and prognosis was significant in patients with FDS-high (Fig. S2C) [25]. Based on these results, we conducted a multicenter, external validation study of FDS in patients with urological cancers.

This validation study met its endpoints and confirmed the reliability of FDS as a quantitative CGA tool for patients with urological cancers. We found the non-inferior predictive accuracy of FDS between the healthy Ctrl and patients with urological cancers. Additionally, we successfully validated the effect of FDS on the prediction of prognosis between patients with urological cancer who have FDS-high and FDS-low. All our results indicated that the difference in physical, mental, and biochemical parameters between participants with and without cancer can predict frailty and prognosis. We also confirmed the feasibility of FDS compared with other frailty assessment tools, such as the FP criteria and G8 screening tool. In the FP criteria, the definition of prefrail (1–2) and frail (≥ 3) was similar to that of FDS > 1.59 and > 2.93, respectively. Similarly, the definition of frailty in the G8 screening tool score (< 14) was similar to that of FDS score > 1.58. Additionally, FDS-high and the FP criteria score ≥ 3 were similar to that of the G8 screening tool score < 12.5. These results indicated that G8 screening tool scores < 14 and < 12.5 might be associated with prefrail and frail, respectively. A G8 screening tool cutoff score < 12.5 for frailty was recommended by a previous study that has conducted an evaluation using the G8 screening tool and the Groningen Frailty Indicator in older patients with cancers [39].

The agreement between different frailty assessment tools is controversial. The optimal CGA tools for frailty remain inconclusive, as each tool evaluated different aspects of frailty. The FP criterion is a commonly used method in geriatric studies evaluating five phenotypes. The G8 screening tool is a questionnaire-based screening tool consisting of eight items. FDS was developed to identify frailty as the accumulation of ten deficits across various domains between individuals with or without cancer. Although we observed a significant association among the three tools, FDS could not detect 26% of frail patients who were positive in both the FP criteria (score ≥ 3) and G8 screening toll (score < 14). However, FDS could detect 16% of frail patients who were negative in the FP criteria (score of 0–2) and G8 screening tool (score ≥ 14) (Fig. 4d). A similar finding was observed in a systematic review that has investigated the sensitivity and specificity of the assessment tools for predicting frailty in elderly patients with cancer [14]. They reported that the G8 screening tool has a high sensitivity for frailty (87%) but poor specificity (61%). Conversely, the FP criteria had a high specificity for frailty (91%) but poor sensitivity (31%). In conclusion, the use of a single frailty screening tool is not sufficient in identifying patients with frailty [14]. As we found that the optimal cutoff values are not similar between the non-PC and PC groups, optimal frailty tools and cutoffs may change depending on diseases [13]. Further studies need to be conducted to identify a suitable combination of frailty tools and diseases.

This study had several limitations, which include the small sample size, selection bias according to the type of cancer and clinical stage, and other unmeasurable confounding factors. Urological cancers included both metastatic and non-metastatic disease in this study could not allow to disentangle the impact of frailty on clinical decision-making in each urological cancer. For example, the assessment of frailty in patients with small renal masses who are eligible for active surveillance versus surgical treatment might be different from that in patients with muscle-invasive bladder cancer who are candidates for bladder-sparing treatment versus radical cystectomy. Therefore, our ongoing study need to address the impact of frailty on treatment selection and outcomes in specific diseases. In addition, our results may not be generalized to other countries due to racial and regional differences. Furthermore, our study could not address how to improve frailty-related adverse outcomes, which is the definitive endpoint of frailty assessment. Despite these limitations, we successfully validated the clinical implication of FDS on frailty in patients with urological cancers. Our findings indicated that the accumulation of frailty difference between an individual with or without cancer may be useful in predicting frailty and poor prognosis in patients with urological cancers.

Conclusions

The FDS was an effective and valid tool for measuring frailty in patients with urological cancers. Further efforts need to be directed in determining the optimal components and methods used to improve frailty.

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Compliance with ethical standards

Conflicts of interest All authors have declared no conflicts of interests.

Ethical approval This multicenter prospective study was performed according to the ethical standards of the Declaration of Helsinki and was approved by the ethics review board of the Hirosaki University School of Medicine (authorization number: 2014-297), Mutsu General Hospital, Aomori Prefectural Central Hospital, and Oyokyo Kidney Research Institute Hirosaki Hospital. All participants provided a written informed consent.

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