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博 士 論 文

Impact of physical frailty on the clinical outcomes of older patients hospitalized for pneumonia

（高齢肺炎入院患者の臨床転帰に身体フレイルが与える影響）

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Impact of physical frailty on the clinical outcomes of older patients hospitalized for pneumonia

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ABSTRACT

Aim: This study aimed to assess the association between physical frailty and clinical outcomes among older patients hospitalized for pneumonia.

Methods: This study examined 852 consecutive patients hospitalized for pneumonia between October 2018 and September 2020. Patients who were < 65 years old, scheduled for admission, did not receive inpatient rehabilitation, or died during admission were excluded. A short physical performance battery (SPPB) test was performed by physical therapists upon discharge. The primary outcome measure was a composite endpoint of readmission or mortality due to any cause within 6 months of discharge.

Results: In total, 521 patients (median age, 80 years; interquartile range, 74–86 years) were included in the analyses, and were divided into the following two groups: robust group with SPPB scores > 9 (n = 150), and physical frailty group with SPPB scores ≤ 9 (n = 371). Of these, 346 (66.4%) patients were men; and the median SPPB score was 6 (interquartile range, 1–10). During the median follow-up period of 53 days (interquartile range, 4–180 days), 92 (17.6%) patients were readmitted and 25 (4.8%) patients died. Patients with physical frailty were at an increased risk for the primary endpoint (hazard ratio, 2.21; 95% confidence interval, 1.44–3.41; $P < 0.001$); the risk remained significant after adjusting for multiple variables (adjusted hazard ratio, 1.70; 95% confidence interval, 1.05–2.74; $P = 0.028$).

Conclusions: Among older patients with pneumonia, physical frailty status at discharge was an independent risk factor for readmission and mortality within 6 months after initial discharge.

Keywords: activities of daily living, elderly frail, mortality, patient readmission, pneumonia

Introduction

Japan's population is aging at an unprecedented rate. Preventing rehospitalization and improving prognosis among older patients with pneumonia are key public health issues for disease burden reduction. Pneumonia is one of the most critical diseases affecting the quality of life and mortality of older adults and has a significant impact on society in general.[1] Pneumonia, including aspiration pneumonia, is the third leading cause of death in Japan. The majority of these mortalities occur in patients aged ≥65 years, and some studies have reported the rehospitalization and mortality rates ranging from 10% to 20% among older adults with pneumonia.[2–5] Previous studies have shown that daily walking habit and early rehabilitation are associated with a decline in mortality rate among patients with pneumonia.[6,7] Identification of prognostic factors is important for future initiatives to reduce the readmission and mortality rates and target the resources for those at highest risk.

Frailty is a common condition arising from an age-associated decline in multiple physiological systems, which results in adverse health outcomes, including disability, hospitalization, reduced quality of life, and mortality.[8–12] Severe frailty has been identified as a predictor of hospital readmission in acute medical units and mortality.[13]

The short physical performance battery (SPPB) is one of the most useful tools for evaluating physical function[14] and it has been used to screen for frailty among community-dwelling older adults.[15] The SPPB is fast and easy to administer, which makes it a valuable tool

for screening physical frailty in clinical setting. We hypothesized that physical frailty among older patients with pneumonia contributes to poor prognosis after hospitalization. Consequently, the present study assessed whether physical frailty at discharge is an independent predictor of readmission and mortality within 6 months of hospitalization among older patients with pneumonia.

Methods

Study design and participants

This study examined 852 consecutive patients who were admitted for pneumonia at the Kobe City Medical Center General Hospital between October 2018 and September 2020. All diagnoses and comorbidities were recorded by the attending physicians. Patients who were ≤64 years of age, were scheduled for admission, did not receive rehabilitation during hospitalization, or died during hospitalization were excluded from this study. The study was approved by the ethics committee of Kobe City Medical Center General Hospital (approval no. zn210516) and was conducted in accordance with the principles of the Declaration of Helsinki regarding investigations on humans. Patients were not required to give informed consent because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. Patients were allowed to opt out of the study if they desired.

Figure 1 demonstrates our patient selection process. In total, 852 consecutive patients

were eligible for this study, but some patients were later excluded (Fig. 1) because they were <65 years old (n = 147), had a scheduled admission (n = 49), died in the hospital (n = 79), had missing data (n = 33), or did not participate in a rehabilitation program (n = 23). A final cohort of 521 patients was included in this study. Participants were divided into the physical frailty (n = 371) and robust (n = 150) groups according to their SPPB scores.

Outcomes and data collection

The primary outcome was a composite endpoint of readmission and death due to any reason within 6 months of discharge. The secondary outcome was all-cause mortality within 6 months of discharge. Readmission was defined as hospitalization due to any cause, excluding scheduled hospitalizations, within 6 months after discharge. Information on deaths and readmissions after initial hospitalization was collected retrospectively from electronic medical records. Our hospital is a regional core hospital, and it is possible that a patient will be readmitted to our hospital after hospitalization. In addition, patients were encouraged to report if they were admitted into other hospitals for any reason; cooperation with local hospitals ensured ease of gathering information about the patients involved in this study.

Data were retrospectively collected from computerized medical records and included: age; body mass index; sex; severity of pneumonia, defined using the A-DROP score[16]; laboratory values at admission, particularly C-reactive protein, blood urea nitrogen (BUN) and albumin; comorbidity, defined by the Charlson comorbidity index (CCI)[17]; length of stay during

hospitalization; discharge destination; and SPPB score at discharge. Laboratory data and information about the comorbidities at the time of admission were used.

The A-DROP score was utilized to assess the severity of pneumonia based on the following factors: age (men ≥70 years, women ≥75 years), dehydration (BUN ≥21 mg/mL), respiratory failure (pulse oximetry saturation ≤90%), orientation disturbance and low blood pressure (systolic blood pressure ≤90 mmHg). The total ADROP score for each patient ranged from 0 to 5 points, and a higher score indicated more severe pneumonia.

In contrast, the CCI was utilized to assess the prognostic burden of comorbid diseases. The index assigns integer weights to specific diseases, and the total score is calculated by adding the integer weights for all comorbid conditions. Comorbid conditions with a weight of 1 include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, ulcer disease, mild liver disease, and diabetes. Diabetes with end organ damage, any tumor, leukemia and lymphoma are assigned a weight of 2, whereas moderate or severe liver disease is assigned a weight of 3. Metastatic solid tumors and acquired immunodeficiency syndrome are each assigned a weight of 6. CCI is the most widely used comorbidity index, and higher scores indicate poorer medical conditions.

Three discharge outcomes were documented, and patients were discharged to (i) home, (ii) a post-acute hospital, or (iii) nursing home.

Short physical performance battery assessment

SPPB was measured before hospital discharge with stable disease condition. Several studies have utilized the SPPB as a surrogate measure of frailty15because it was developed to evaluate physical function, particularly of the lower extremities.[14] The SPPB consists of three performance tests, which assess standing balance, usual gait speed, and repeated chair stand ability. Each test (balance, gait and chair stand) is scored from 0 to 4, and the total score for all three tests ranges from 0 to 12 points; higher scores indicate better function. The SPPB scores in this study were assessed by a physical therapist during discharge. We defined an SPPB score ≤ 9 as an indicator of physical frailty because a previous study identified low physical performance, defined by an SPPBscore≤9, as a predictor of all-cause mortality.[18]

Statistical analysis

Quantitative variables are expressed as medians (interquartile ranges), whereas qualitative variables are expressed as n (%). The unpaired t-test and chi-squared test were used to compare the patient characteristics and clinical parameters between the two groups.

The composite endpoint of readmission and mortality at 6 months was analyzed using Kaplan–Meier analysis and log-rank test between the two groups. Observations for patients who were lost to follow-up were censored at the date of the last follow-up. The relationship between adverse outcomes at 6 months and physical frailty was assessed using the Cox proportional hazards model. Model 1 included age, sex and physical frailty as confounding variables, whereas Model 2 included the severity of pneumonia, CCI and discharge destination,

in addition to the variables in Model 1, as confounding variables. The independent variables for collinearity were checked using a variance inflation factor.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[19] a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R Commander designed to include statistical functions often used in biostatistics. Differences with $P < 0.05$ were considered statistically significant.

Results

Patient characteristics

The demographic data are shown in Table 1. Age (83 years vs. 76 years; $P < 0.001$), severity of pneumonia (2 points vs. 2 points; $P < 0.001$), BUN (22.3% vs. 17.3%; $P < 0.001$), proportion of dementia (29.2% vs. 3.3%; $P < 0.001$) and proportion of cerebrovascular disease (29.5% vs. 18.0%; $P = 0.008$) were significantly higher in the physical frailty group than the robust group. Body mass index (20.3 kg/m^2 vs. 22.1 kg/m^2; $P = 0.005$), proportion of men (63.6% vs. 73.3%; $P = 0.040$) and proportion of patients discharged to home (43.1% vs. 86.0%; $P < 0.001$) were significantly lower in the physical frailty group than the robust group.

Effect of physical frailty on outcomes

Of the 521 patients enrolled, 92 were readmitted following discharge from initial

hospitalization, and 25 died, within 6 months (Table 2). Pneumonia was the most common reason for readmission (45.7%), followed by respiratory failure (19.6%), heart failure (9.8%), infection (7.6%) and gastrointestinal disease (4.3%). The Kaplan–Meier analysis revealed that the physical frailty group had a significantly higher mortality (P = 0.003; Fig. 2a) and readmission or death rates than the robust group did (log-rank test, $P < 0.001$; Fig. 2b).

The results of the Cox proportional hazards model are presented in Table 3. Upon univariate analysis, age (hazard ratio [HR], 1.02; 95% CI [confidence interval], 1.00–1.05; P = 0.031), severity of pneumonia (HR, 1.35; 95% CI, 1.13–1.61; $P < 0.001$), CCI (HR, 1.09; 95% CI, 1.04–1.15; $P < 0.001$) and physical frailty (HR, 2.21; 95% CI, 1.44–3.41; $P < 0.001$) were significantly associated with the composite endpoint of readmission and death. In contrast, multivariate analysis demonstrated that physical frailty (adjusted HR, 2.07; 95% CI, 1.32–3.25; P = 0.001) remained significant in Model 1. In Model 2, the severity of pneumonia (adjusted HR, 1.35; 95% CI, 1.08–1.68; P = 0.007), CCI (adjusted HR, 1.08; 95% CI, 1.02–1.14; P = 0.005) and physical frailty (adjusted HR, 1.70; 95% CI, 1.05–2.74; P = 0.028) were significant. The proportional hazards assumption was applied for all variables ($P > 0.05$).

Discussion

The present study reported the clinical impact of physical frailty on the prognostication of older adults hospitalized with pneumonia. We found that physical frailty at discharge during

the initial admission predicted readmission or all-cause mortality within6 months. Before this study, the use of SPPB to characterize frailty among patients with pneumonia was limited; however, our study demonstrated that the SPPB could contribute to understand the physical function status in older patients with pneumonia.

Of the patients in this study, 18% were readmitted and 5%died within 6 months of initial discharge. Previous studies reported that rehospitalization and mortality rates ranged from10% to 20% among patients with pneumonia.[2–5] Compared with these studies, the age of the patients and readmission rate in our study were similar; however, the mortality rate in our study was lower, which may be because we discharged some patients to other hospitals. Post-acute care, particularly for severe diseases, functional disability, multimorbidity, and/or older age, may have prevented adverse outcomes in these patients.

Furthermore, Cox proportional hazards model analysis demonstrated that physical frailty was significantly associated with readmission and mortality within 6 months of initial hospitalization. Some studies have reported a similar association between frailty and unplanned hospital readmission or death among geriatric patients.[8,13,20] Frailty is caused by age-associated decline in multiple physiological systems and is characterized by the impaired functioning of homeostatic systems.[9] Therefore, individuals with frailty are more vulnerable to the negative effects of acutestressors.[21] Hospital inpatinets with frailty are likely to have poor general health conditions, and frailty may be the strongest prognostic factor for readmission and mortality

among patients with pneumonia. Among older patients hospitalized for pneumonia, frailty has been shown to be associated with functional decline or an increased risk for mortality within 30 days of hospitalization.[22] Other studies have also investigated the impact of physical frailty on clinical outcomes, including readmission and mortality following acute illness. The contribution of this study to the literature is that it supports the feasibility and importance of measuring frailty in acute care settings among patients with pneumonia, for subsequent prognostication.

A systematic review reported that SPPB scores <10 predicted all-cause mortality in older people.[18] The SPPB is a standardized and reproducible group of measures that predicts global physical function. It has been validated among frail and older persons and is easy to use in clinical practice. While this instrument provides non-specific data, it is a highly sensitive indicator for vulnerability[23] and reflects several underlying physiological impairments.[24] Moreover, physical performance measurements have been suggested as a vital sign among older patients.[25] Among patients with acute pneumonia, the SPPB, as a physical performance measurement tool, may predict the risk of adverse outcomes. Future studies are required to identify interventions that can effectively prevent hospital readmissions or death among patients with physical frailty who were admitted for pneumonia.

Our study has some limitations. First, this retrospective study was performed at a single hospital. Therefore, there was a risk of sampling bias; owing to the small sample size of our

study, the data cannot be generalized to external populations. Second, it was not possible to assess the SPPB scores directly upon admission in this population because these patients often presented with dyspnea and fatigue that required oxygen therapy or mechanical sup-port, such as through ventilators and high-flow nasal cannulas. As such, the impact of physical functioning on the SPPB score before hospitalization and during treatment is unknown. Third, additional factors, such as muscle mass and swallowing function, were challenging to investigate using a retrospective study design. Fourth, we did not adjust for whether invasive procedures were performed during the index hospitalization, which may affect frailty before discharge. Finally, some patients were lost to follow-up, and we may not have observed other events such as readmission to other hospitals.

In conclusion, our study demonstrated that physical frailty among older patients with pneumonia was an independent risk factor for readmission and mortality within 6 months of initial dis-charge. Moreover, our data suggested that the SPPB could predict the prognosis of older patients hospitalized for pneumonia. Further studies are needed to identify effective interventions that can prevent hospital readmission and death among frail patients with pneumonia.

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Table 1. Clinical characteristics of participants

	Physical frailty group (n = 371)	**Robust group (n = 150)**	***P* value**
Age (years)	83 (76–88)	76 (70–80)	<0.001
Men, n (%)	236 (63.6)	110 (73.3)	0.040
BMI (kg/m^2)	20.3 (17.9–23.8)	22.1 (19.8–23.9)	0.005
Severity of pneumonia (points)	2 (2–3)	2 (1–2)	<0.001
Clinical parameters			
Albumin (g/dL)	3.1 (2.6–3.5)	3.2 (2.7–3.6)	0.165
BUN (mg/dL)	22.3 (15.88–32.02)	17.3 (13.5–24.5)	<0.001
CRP (mg/dL)	7.75 (2.12–15.75)	8.85 (3.35–16.06)	0.137
CCI (points)	4 (2–6)	3 (2–5)	0.242
Comorbidity, n (%)			
Chronic respiratory disease	174 (47.2)	83 (55.3)	0.100
Heart failure	106 (28.6)	40 (26.7)	0.668
Diabetes	137 (37)	56 (37.3)	0.999
Malignant tumor	131 (35.4)	59 (39.3)	0.422
Chronic kidney disease	64 (17.3)	24 (16.0)	0.797
Dementia	108 (29.2)	5 (3.3)	<0.001
Cerebrovascular disease	109 (29.5)	27 (18)	0.008
LOS (days)	14 (8–23)	12 (8–20)	0.065
Discharge destination, n (%)			<0.001
Home	160 (43.1)	129 (86)	

Hospital	182 (49.1)	19 (12.7)
Nursing home	29 (7.8)	2 (1.3)

Data are presented as medians (interquartile ranges) or numbers (percentages).

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; CCI, Charlson comorbidity index; LOS, length of stay during hospitalization

Table 2. Number of events within six months

	All (n = 521)	**Physical frailty group (n = 371)**	**Robust group (n = 150)**
Composite endpoint	117 (22.4)	90 (17.2)	27 (5.1)
Readmission	92 (17.6)	66 (12.6)	26 (5)
Death	25 (4.8)	24 (4.6)	1 (0.2)

Data are presented as numbers (percentages).

Table 3. Cox proportional hazards regression model for the factors associated with events within six months

	Univariate analysis			**Multivariate analysis**					
				Model 1			*Model 2*		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Physical frailty	2.21	1.44–3.41	<0.001	2.07	1.32–3.25	0.001	1.70	1.05–2.74	0.028
Age (years)	1.02	1.00–1.05	0.031	1.01	0.98–1.03	0.328	1.00	0.97–1.00	0.949
Male sex	0.88	0.60–1.30	0.533	0.93	0.63–1.37	0.719	0.63	0.40–1.002	0.051
A-DROP (points)	1.35	1.13–1.61	<0.001				1.35	1.08–1.68	0.007
CCI (points)	1.09	1.04–1.15	<0.001				1.08	1.02–1.14	0.005
Discharge destination									
Home	1.00	Reference					1.00	Reference	
Hospital	0.55	0.25–1.21	0.140				0.63	0.28–1.44	0.266
Nursing home	0.76	0.34–1.69	0.504				0.63	0.28–1.44	0.279
				Likelihood ratio test, p =0.001; Wald test, p =0.003;			Likelihood ratio test, p <0.001; Wald test, p <0.001;		

Abbreviations: HR, hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index

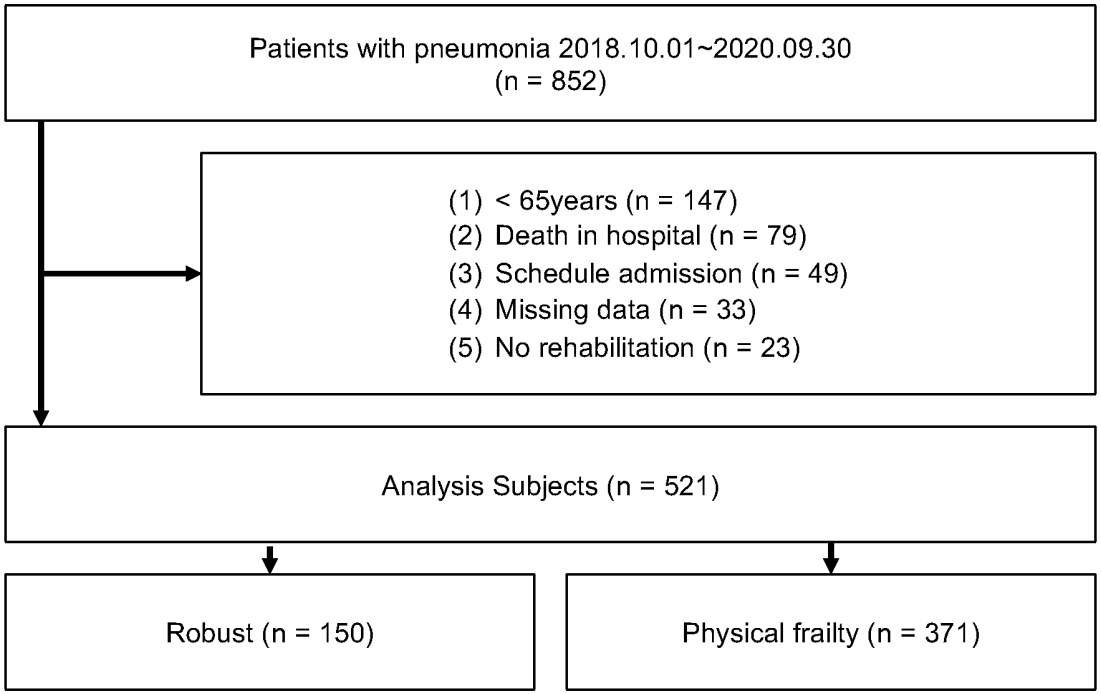

Figure 1 Flowchart for patient selection.

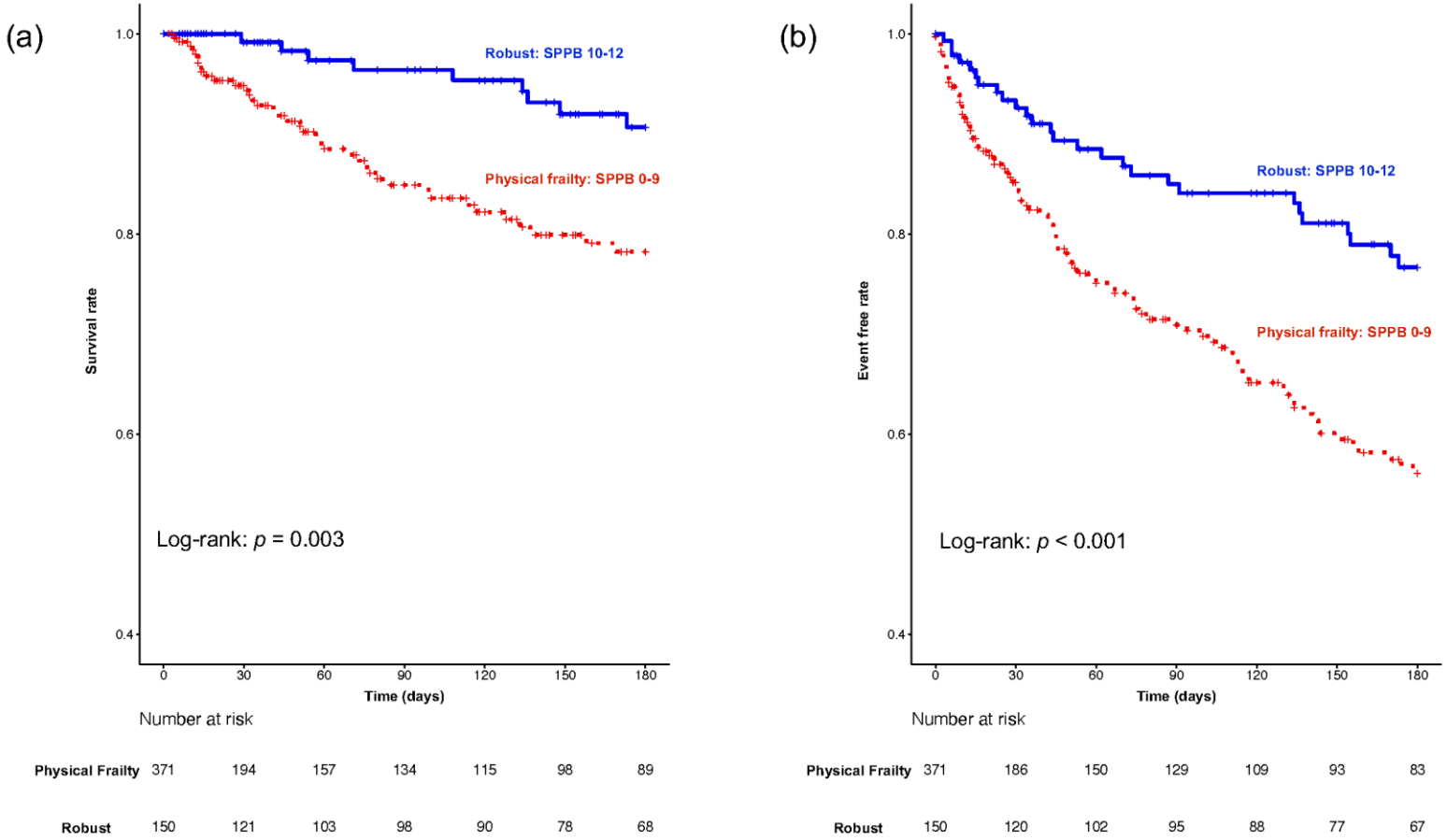

Figure 2 Kaplan–Meier analysis plot for (a) mortality within 6 months of discharge stratified based on physical frailty status, and (b) a composite endpoint of readmission and mortality within 6 months of discharge stratified by physical frailty status. SPPB, short physical performance battery.