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Low body mass index and life prognosis in Parkinson's disease

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ABSTRACT

Introduction: Patients with Parkinson's disease (PD) frequently lose weight, even in the early stages of the disease. Our objective was to clarify the association between low body mass index (BMI) and life prognosis in PD.
Methods: We conducted a retrospective cohort study of 651 PD patients (380 females), with a primary endpoint of survival. Because of sex differences in BMI, male and female data were separated. We compared survival times between underweight (BMI $<$ 18.5) and non-underweight (BMI $\geq$ 18.5) patients and calculated hazard ratios (HRs) adjusted for other relevant factors. To investigate the semi-quantitative relationship between relative risk of death and BMI, we divided patients into lower, middle, and upper thirds of BMI and calculated the HRs of the lower and upper thirds, with reference to the middle third.
Results: Seventy-nine patients (41 females) died over a mean (standard deviation) observation period of 39 (26) months. Underweight patients had poorer life prognosis than non-underweight patients and the difference was larger in males than in females (adjusted HR 3.8 (95% confidence interval 1.9–7.9) in males and 1.8 (0.9–3.5) in females). In males, the relationship between survival and BMI was much poorer in the bottom third and slightly poorer in the top third compared with the middle third. In females, the higher the BMI, the better the survival prognosis; however, the difference was not statistically significant.
Conclusion: Low BMI had a significant impact on the life prognosis of PD patients, especially males.

1. Introduction

Weight loss is one of the common non-motor complications of Parkinson's disease (PD). It often precedes motor symptoms by years [1–3] and continues throughout the course of the disease [4]. Although the causes of weight loss in PD have not been identified, potential contributors may include perturbation of hypothalamic metabolic regulation, alteration of energy expenditure and food intake, and gastrointestinal dysfunction [5–8].

Body mass index (BMI) is a widely used measure of relative body weight and is the gold standard of general nutritional status. Its reduction is directly related to health risks and increased rates of death in populations with and without various diseases. In patients with dementia, a low BMI is associated with reduced survival and is an independent predictor of mortality, regardless of cognitive impairment severity [9]. In patients with amyotrophic lateral sclerosis, a BMI $<$ 18.5 is associated with reduced survival, while a BMI of 30–35 is associated with increased survival [10].

Previous studies in PD demonstrated that nutritional status is associated with disease severity [11] and a reduced BMI may be a clinical marker of rapid worsening of motor symptoms [12]; however, the impact of BMI on survival rates has not been fully clarified. The hypothesis of the current study was that a low BMI could be an important predictor not only for disease progression, but also for poor survival in PD. To investigate the hypothesis, we conducted a retrospective cohort study of 651 patients with PD. In the analysis, the data were separated into females and males because life-span and BMI distributions differ between the sexes [13].

2. Methods

2.1. Study design

To investigate the impact of BMI on life prognosis in patients with PD, we conducted a retrospective cohort study. Survival time was defined as the number of days from the date of study enrollment to the date of death, and patients who were lost to follow-up were regarded as censored. The patients were followed up until the date of death, censored date, or April 30, 2014.

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Table 1
Baseline clinical features between deceased and non-deceased patients (males and females).

	Males			Females		
	Non-deceased (n = 233)	Deceased (n = 38)	*p value*	Non-deceased (n = 339)	Deceased (n = 41)	*p* value
Age, mean ± SD	68.8 ± 8.7	74.5 ± 7.5	< **0.001**[b]	70.3 ± 8.8	75.3 ± 6.5	< **0.001**[b]
Duration (years), mean ± SD	6.7 ± 5.7	10.8 ± 6.6	< **0.001**[b]	7.2 ± 5.8	12.3 ± 7.1	< **0.001**[b]
mH–Y, mean ± SD	2.7 ± 0.7	3.5 ± 0.9	< **0.001**[b]	2.8 ± 0.8	3.7 ± 0.9	< **0.001**[b]
mH–Y 4–5, *n* (%)	22 (9.4)	17 (44.7)	< **0.001**[a]	46 (13.6)	21 (51.2)	< **0.001**[a]
Dementia, *n* (%)	46 (19.7)	23 (60.5)	< **0.001**[a]	85 (25.1)	16 (39.0)	0.063[a]
Psychosis, *n* (%)	77 (33)	23 (60.5)	**0.002**[a]	108 (31.9)	24 (58.5)	**0.002**[a]
Dyskinesia, *n* (%)	33 (14.2)	10 (26.3)	0.090[a]	99 (29.2)	17 (41.4)	0.110[a]
Wearing off, *n* (%)	63 (27.0)	11 (28.9)	0.845[a]	137 (40.4)	23 (56.1)	0.066[a]
BMI (kg/m^2), mean ± SD	22.4 ± 3.3	19.4 ± 3.3	< **0.001**[c]	20.8 ± 3.7	19.0 ± 3.4	< **0.001**[b]
BMI < 18.5, *n* (%)	23 (9.9)	17 (44.7)	< **0.001**[a]	89 (26.3)	23 (56.1)	< **0.001**[a]
Levodopa (mg), mean ± SD	270.3 ± 208.2	403.9 ± 191.1	< **0.001**[b]	259.8 ± 218.1	404.3 ± 177.3	< **0.001**[b]
Levodopa/BW (mg), mean ± SD	4.6 ± 3.7	8.1 ± 4.1	< **0.001**[b]	5.9 ± 5.2	10.2 ± 4.5	< **0.001**[b]
Dopamine agonist use, *n* (%)	111 (47.6)	15 (39.5)	0.384[a]	160 (47.2)	19 (46.3)	1.000[a]
Hypertension, *n* (%)	72 (30.9)	6 (15.8)	0.080[a]	109 (32.2)	15 (36.6)	0.599[a]
Hyperlipidemia, *n* (%)	52 (22.3)	8 (21.1)	1.000[a]	125 (36.9)	10 (24.4)	0.124[a]
Diabetes mellitus, *n* (%)	31 (13.3)	3 (7.9)	1.000[a]	26 (7.7)	5 (12.2)	0.359[a]
Gastrostomy, *n* (%)	5 (2.1)	3 (7.9)	0.086[a]	2 (0.6)	4 (9.8)	**0.002**[a]
Deep brain stimulation, *n* (%)	5 (2.1)	1 (2.6)	1.000[a]	10 (2.9)	1 (2.4)	1.000[a]
Untreated patients, *n* (%)	52 (22.3)	3 (7.9)	**0.049**[a]	78 (23.0)	3 (7.3)	**0.024**[a]

SD, standard deviation; mH–Y, modified Hoehn–Yahr scale; BMI, body mass index; LED, levodopa equivalent dose; BW, body weight, PD, Parkinson's disease.
[a] Fisher's exact test.
[b] Mann–Whitney *U* test.
[c] *t*-test.

2.2. Subjects

Consecutive PD patients who were treated at the National Regional Center for Neurological Disorders at Utano National Hospital in Kyoto, Japan, from January 5, 2006 to April 18, 2013, were screened for eligibility. We defined the index date (i.e., the moment when follow up began) as the day that the patient's body weight and height were recorded for the first time. A diagnosis of PD was made according to the United Kingdom Parkinson's Disease Brain Bank Diagnostic Criteria. Patients with dementia with Lewy bodies (DLB) were excluded according to the one-year rule in the third report of the DLB Consortium. All patients underwent 1.5-T brain magnetic resonance imaging (MRI), and patients with MRI findings suggesting multiple system atrophy, progressive supranuclear palsy or vascular parkinsonism were excluded.

2.3. Clinical factors

We collected data for age, BMI (kg/m^2), PD duration (years), and modified Hoehn and Yahr (mH-Y) stages, dementia (defined by the *Diagnostic and Statistical Manual of Mental Disorders*, *fourth edition*), history of psychosis, wearing-off, dyskinesia, and levodopa dose at study enrollment. Underweight status was defined as a BMI of < 18.5 in either sex, according to the World Health Organization (WHO) definition. Vascular risk factors such as hypertension (HT), dyslipidemia (DL), diabetes mellitus (DM), and smoking history were also collected because of their associations with mortality. These vascular risk factors were defined as follows: HT, current or previous antihypertensive medications; DM, current or previous hyper-hemoglobin A1c or hypoglycemic medications; and DL, low-density lipoprotein cholesterol ≥140 mg/dl or hypolipidemic medications. We also determined the date and cause of death in deceased patients from clinical records.

2.4. Statistical analysis

Clinical features at study enrollment were compared between deceased and non-deceased patients. Categorical data were compared using Fisher's exact test, and scale data were compared using the Mann–Whitney *U*-test or Student's *t*-test according to the distribution of data. Factors that differed with a *p*-value of less than 0.1 between deceased and non-deceased patients were treated as possible predictive factors for survival time analyses; i.e., Kaplan–Meier curves were obtained and compared between the two groups, categorized by possible predictive factors. Statistical differences were examined by a log-rank test and factors that were significantly associated with survival were incorporated into a Cox proportional hazard model. We calculated the adjusted hazard ratios (HRs) of death for low BMI (< 18.5) using a Cox proportional hazard model adjusted for these factors. The hazard proportionality of the model was confirmed using the log-minus-log survival plot.

It is well known that BMI has a J- or U-shaped correlation with mortality, which is lowest in the middle category of BMI, particularly among elderly people and in Asian populations [14,15]. Therefore, we divided patients into three groups, bottom, middle, and top thirds, according to BMI, and investigated the survival rates of the bottom and top thirds using a Cox proportional hazard model adjusted for the other significant predictive factors.

P values of < 0.05 were considered statistically significant. Statistical analyses were performed using the statistical software programs SPSS Statistics version 18.0 (PAWS Statistics, Armonk, NY, USA) and GraphPad Prism version 5.02 (GraphPad Software Inc., CA, USA).

2.5. Ethics

The study was designed and performed according to the principles of the Declaration of Helsinki. The study protocol, which was consistent with ethical guidelines for clinical studies in Japan, was approved by the Ethics Committee of Utano National Hospital (No. 26–37).

3. Results

A total of 889 consecutive PD patients were screened and 238 patients were excluded. Seventy-three patients were excluded because they had no BMI data and 165 patients lacked clinical data on at least one of the following at the entry date: mH-Y stage, dementia, psychosis, wearing off, or dyskinesia (Fig. S1). Finally, 651 patients with PD (271

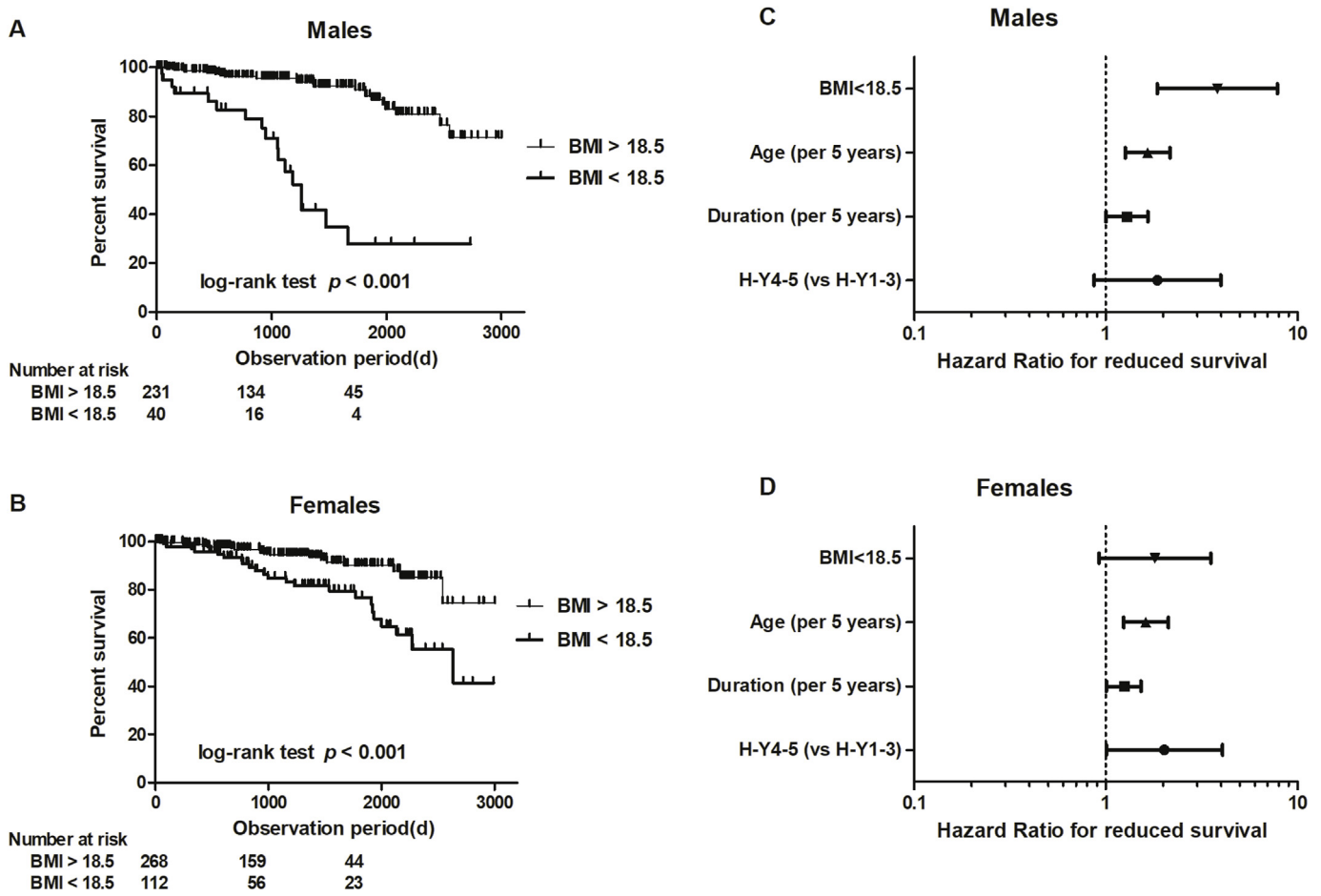

Fig. 1. Survival curves by BMI groups and hazard ratios for death. Kaplan–Meier curves (BMI < 18.5 vs BMI ≥ 18.5) in male (A) and female (B) patients. Adjusted hazard ratios for death in male (C) and female (D) patients. Hazard ratios were calculated adjusting for age, disease duration, and mH–Y stage. BMI, body mass index; mH-Y, modified Hoehn and Yahr scale.

males and 380 females) were enrolled and followed up for a mean (SD) observation period of 39 (26) months. The mean (SD) BMI was 22.0 (3.4) in males and 20.6 (3.7) in females. The female BMI distribution histogram was bell-shaped and left-shifted (downward-shifted) compared with that of males (Fig. S2). Demographic characteristics are shown in Table S1. There were 38 (14.0%) male and 41 (10.8%) female deaths during the observation period. The most common cause of death was pneumonia in both males (n = 20 (52.6%)) and females (n = 11 (26.8%)), mostly due to aspiration (Table S2).

Baseline clinical feature comparisons between deceased and non-deceased patients are shown in Table 1. In male subjects, deceased patients showed statistically significant differences from non-deceased patients in terms of age (deceased patients were older), PD duration (longer durations), severity (higher mH–Y stages), BMI (lower), history of dementia and psychosis, and levodopa and levodopa/body weight (BW; larger). There were similar significant differences between deceased and non-deceased female patients, except for dementia, which was more prevalent in deceased patients but not significantly (p = 0.063). In both sexes, dyskinesias and wearing-off phenomena were more frequent in deceased than non-deceased patients, but the results were not statistically significant. There were no significant differences in the percentages of deceased and non-deceased patients taking dopamine agonists, in either sex. The prevalence of vascular risk factors (HT, HL, and DM) and deep brain stimulation did not differ between deceased and non-deceased patients for either sex. In females, significantly more deceased patients had gastrostomies compared with non-deceased patients. The number of patients who had not been previously treated with any anti-parkinsonian drug was significantly higher in deceased than non-deceased patients in both sexes (Table 1). Smoking history data were available for 72.0% (n = 195) of males and 75.5% (n = 287) of females. We confirmed that the missing smoking data were randomly distributed among the groups; there were no differences in smoking frequency between the two groups in either sex. Because dementia increases the risk of mortality in patients with PD [16,17], we regarded BMI, age, PD duration, mH-Y stage, dementia, psychosis, levodopa, levodopa/BW, wearing-off, and dyskinesia as possible predictive factors. We obtained Kaplan-Meier curves of cumulative survival rates using these factors. The factors significantly related to survival time were BMI (< 18.5 vs ≥ 18.5), mH-Y stage (4–5 vs 1–3), dementia (Y/N), psychosis (Y/N), and levodopa/BW (divided at the median) in both males and females (log-rank tests, p < 0.01; Fig. 1A, B and S3A, B). Similar results were obtained when we excluded gastrostomy patients from both males and females (data not shown). We excluded levodopa/BW because both variables show strong collinearity with disease duration, and excluded dementia and psychosis because of their strong relationship with age. As a result, we regarded the following as predictive factors for survival and incorporated them into the Cox proportional hazard model: age, PD duration, and mH-Y stage.

In the Cox proportional hazard model, a BMI of < 18.5 was significantly associated with reduced survival in males (HR 3.8 (1.9–7.9), p < 0.001; Fig. 1C), but was not significantly associated in females (HR 1.8 (0.9–3.5), p = 0.084; Fig. 1D). Similar results were obtained in Cox proportional hazard models that used psychosis and dementia as adjusting factors (data not shown).

Dividing patients into three groups according to BMI (lower

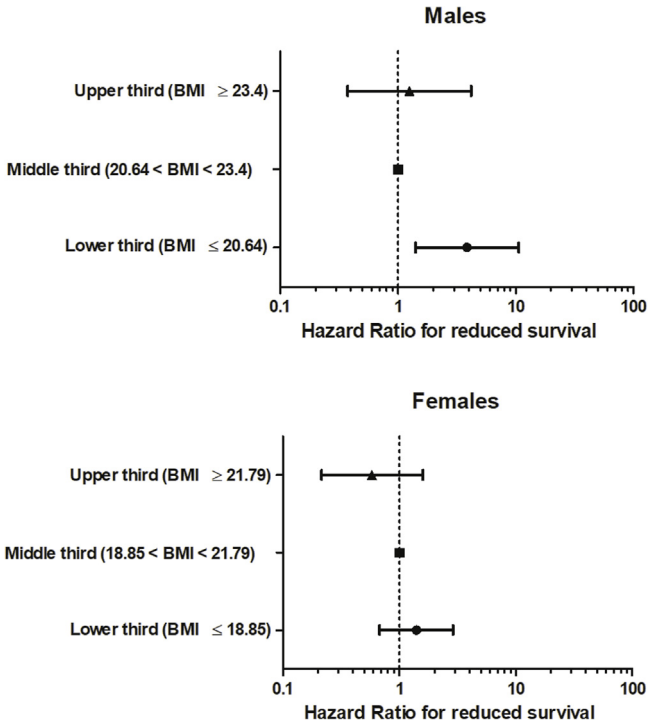

Fig. 2. Hazard ratio for death in patients with a BMI in the lower and upper thirds, relative to patients in the middle third. Males: lower third ≤20.64, 20.64 < middle third < 24.0, 24.0 ≤ upper third. Females: lower third ≤18.85, 18.85 < middle third < 21.79, 21.79 ≤ upper third). Hazard ratios were calculated adjusting for age, disease duration, and modified Hoehn and Yahr stage. BMI, body mass index.

third ≤ 20.64, 20.64 < middle third < 23.4, 23.4 ≤ upper third) showed that survival was significantly reduced in male PD patients within the lower third compared with the middle third. In males, the HRs of the lower third and upper third were 3.9 (1.4–10.6; $p = 0.009$) and 1.3 (0.38–4.2; $p = 0.717$), respectively, adjusted for age, PD duration, and mH-Y (Fig. 2).

In contrast to males, the impact of low BMI on survival was not statistically significant in females (Fig. 2), even though the distribution of BMI in females exhibited a left-shift (lower-shift) compared with that in males (Fig. S2). The log-minus-log survival plot confirmed proportionality in the models.

4. Discussion

The mean BMI of patients with PD in the current study was lower than that of healthy controls in Japan, particularly in females (the mean BMI is 23.6 in men and 23.2 in women aged 70–74, according to the National Health and Nutrition Survey in Japan, 2013). As shown in Table S1, levodopa dosage by body weight was significantly higher in females than in males, and dyskinesias were much more prevalent in females than males, consistent with a previous report [18]. In this context, a lower BMI in female PD patients may be associated with larger doses of levodopa per body weight [19], which induces more frequent dyskinesias and leads to weight loss [20,21]. However, we found that low BMI was associated with poor life prognosis, even after adjustment for dyskinesia and after exclusion of patients with dyskinesia, suggesting that the relationship was independent of dyskinesia.

Generally, a low BMI or weight loss is closely related to malnutrition [22]. Malnutrition is an imbalance between nutritional intake and nutritional needs that results in altered metabolism of carbohydrates, proteins and lipids, and impaired energy homeostasis. As malnutrition progresses, fat-free mass loss and decreased protein synthesis are thought to lead to infection-prone conditions via bacterial translocation from the gastrointestinal tract to the mesenteric lymph nodes, and insufficient immune responses [22,23]. In conditions involving serious infections, pro-inflammatory cytokines are released that elicit systemic inflammatory responses, which require energy and can exhaust nutritional reserves in elderly people with malnutrition [23]. Thus, a vicious cycle of malnutrition development and progression can leave patients increasingly vulnerable to infections [22,24]. The most common cause of death in both sexes in our study was aspiration pneumonia, consistent with a previous report stating that an estimated 45% of patients with PD succumb to pneumonia [25]. Poor immune responses might also affect the clinical course of PD after aspiration pneumonia or other infectious diseases that progress to an advanced stage.

In the present study, low BMI was significantly associated with reduced survival time in PD. The association was statistically significant in males but not in females, even though low BMI was more prominent in females with PD compared with the general population. Dividing patients into three groups according to BMI showed the relationship between BMI and survival, and those with the lowest BMI had the lowest survival rates. These data demonstrate a sex difference in the impact of BMI on survival. Although the reason for the sex difference is unknown, males usually have less body fat and more muscle than females of the same age and BMI, and males also need to burn more calories. As skeletal muscle has a high mitochondrial density and oxygen flux, it is potentially exposed to higher amounts of oxidative stress. Therefore, males potentially require a greater metabolic flux of oxygen and electrons. In fact, age-related loss of muscle mass is more common in males than females [26]. In the elderly, the more lean muscle mass that is retained, the longer the life expectancy [27,28], and a loss of muscle mass increases mortality [29]. A low fat-free mass index predicts mortality in older males but not in older females [30]. Taken together, severe weight loss may lead to the loss of lean muscle mass and increase mortality in male patients, whereas in females it may not lead to muscle loss but rather to loss of fatty tissue. Further research should therefore focus on sex differences to better understand the influence of body composition on mortality in patients with PD.

There are several limitations to the current study. This was a retrospective cohort study and PD diagnosis was based on diagnostic criteria. All clinical information was derived from clinical records, although we rigorously applied our predetermined definitions of various clinical factors. The number of subjects and the observation period were also limited. Prospective and large cohort studies are needed to resolve questions that remain regarding the mechanisms of weight loss in patients with PD.

In conclusion, a low BMI (< 18.5) was related to reduced survival in male patients with PD and there was a sex-based difference in the impact of BMI on survival. Regular monitoring of BMI is thus important for patients with PD, particularly male patients.

Authors' roles

Kwiyoung Park: the conception and design of the study, acquisition of data, analysis, manuscript writing, and editing.

Tomoko Oeda: the conception and design of the study, and critical revision for important intellectual content.

Masayuki Kohsaka, Satoshi Tomita, Atsushi Umemura: the conception and design of the study, and interpretation of the data.

Hideyuki Sawada: the conception and design of the study, critical revision for important intellectual content, and final approval of the version to be submitted.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2018.05.011.

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