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Clinical Factors Contributing to Age-Related Gait Dysfunction in Older Adults

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Abstract

Objective: As walking ability and balance deteriorate with age for bipedal humans, ambulating independently becomes cumbersome without using walking aids. However, age-related risk factors for loss of independent walking ability are not well characterized. We aimed to analyze the clinically relevant factors for ambulatory device aid from the perspectives of nutrition, body composition, and postural abnormalities between independent and assisted walkers based on their ambulatory status.
Methods: Among the 3640 patients aged ≥65 years initially enrolled in the study, 1557 patients with a history of fragility fractures were excluded. Patients were categorized into those who could walk independently and those who required assistance. Body composition, including skeletal muscle mass index, whole-spine sagittal alignment, and blood biochemical findings, were compared.
Results: Among the 2083 participants, 1323 and 760 were included in the independent and assisted groups, respectively. The logistic regression analysis identified five significant factors ($P < 0.01$): age, body mass index, red blood cell distribution width, skeletal muscle mass index, and sagittal vertical axis. The receiver operating characteristic analysis determined the threshold for assisted walking to be age 81.0 years, red blood cell distribution width of 14.0%, skeletal muscle mass index of 5.96 kg/m^2, and a sagittal vertical axis of 54.64 mm with areas under the curve of 0.727, 0.677, 0.645, and 0.708, respectively. Combining these four factors as propensity scores revealed an area under the curve of 0.768.
Conclusion: The comparison of independent and assisted walkers among older adults revealed the importance of age, red blood cell distribution width, skeletal muscle mass, and spinal sagittal balance as clinical factors of assisted walkers.

Keywords

gait dysfunction, older adults, postural abnormality, sarcopenia, ambulatory device

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Introduction

Stable gait is essential for performing activities of daily living (ADLs) and maintaining an independent lifestyle, but age-related loss of walking function is a major obstacle for older adults. In Japan, the 2022 Comprehensive Survey of Living Conditions reported that 23.1% of the population had a functional disability affecting their ability to walk, with prevalence increasing with age.[1] Concerning gait disturbance, 8-19% of older adults require some form of assistance[2] and use ambulatory devices, such as canes and walkers. Among those requiring assistance, 6% are in their 60s, while 38% are aged ≥85 years.[3] Contributing factors include cognitive problems, audiovisual disturbances, living environment, cerebrovascular disorders, and functional impairment due to fractures and musculoskeletal diseases[4]; however, issue related mobility, including sarcopenia-related loss of skeletal muscle mass and muscle strength and the resulting walking disorders, are also a problem for older adults.[5] A higher frequency of sarcopenia has been reported in those with dependent ambulatory status,[6] although walking speed remains the current marker for gait status in sarcopenia diagnosis.[7] Currently, there are no reports on the risk of skeletal muscle mass for assisted walking, which directly relates to prevention planning for long-term frailty in older adults. As people age, they often lose their balance and walking ability, making independent ambulation difficult. This functional decline leads many to begin using walking aids, such as canes.[2] When weight-bearing becomes challenging, walkers provide the necessary balance and stability.[8] Furthermore, when older individuals are no longer able to support their weight, standing becomes difficult, leading to wheelchair use for most ADLs. Walking impairment is a major risk factor for falls in older adults, making early detection and assessment of ambulatory status crucial in geriatric care to guide preventive strategies for avoiding falls.

In nursing care prevention, it is important to analyze the factors that contribute to the transition from independent to assisted walking during the loss of mobility in older adults. However, the risk factors for age-related loss of independent ambulation are not well defined. We reported a relationship between anisocytosis, a condition where red blood cells are of different size, and the walking prognosis in patients with osteoporotic vertebral fracture as a clinical indicator associated with aging.[9] Anisocytosis is evaluated as the red blood cell volume distribution width (RDW), which increases with age as it reflects inflammation,[10,11] and we considered the existence of senescence-associated chronic inflammation as a pathological condition that links hematological aging, which has no direct relationship with walking function, to physical function. Although the relationship between anisocytosis and sarcopenia is not known, RDW has also been reported to be associated with falls[12] and lower limb physical function,[13] and we considered it an important factor in the analysis of factors that determine assisted walking in older adults. The center of gravity balance associated with abnormal posture is also important for walking function.[14] Recently, the sagittal vertical axis (SVA), which is the distance from the C7 plumb line from the center of C7 to the posterior edge of the upper sacral endplate, has been used as a parameter for evaluating standing sagittal plane balance in the field of spinal surgery,[15] and its association with the risk of falls in older adults has also been reported.[16] To our knowledge, no studies have analyzed geriatric walking dysfunction, including endogenous aging, skeletal muscles, and postural abnormalities, from a bird's eye view.

To reduce the risk of falls in older adults, it is important to prevent dependence on walking aids by maintaining muscle strength,[17] and knowledge of the risk factors can help formulate preventative measures and is valuable in geriatric research on the musculoskeletal system.

In this study, we analyzed the clinically relevant factors for ambulatory device aid from the perspectives of nutrition, body composition, and postural abnormalities between independent older adults and those requiring assisted walking, based on their ambulatory status, to help prevent long-term frailty.

Methods

The study protocol was approved by the institutional review board (approval number: 1688). All participants were informed of the study's objectives, and written informed consent was obtained. This study was conducted in accordance with the tenets of the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Study Population

The study population included 2083 patients (mean age 78.4 ± 6.7 years, 741 men and 1342 women) from the 3640 patients aged ≥65 years enrolled in the Longitudinal Study of Aging in the Locomotor System from April 2022 to December 2023. A total of 1557 patients with a history of fragility fractures, including osteoporotic vertebral fractures and proximal femur fractures, were excluded.

This project was based on clinical data systematically collected by orthopedic specialists (spine and joint surgeons) and biobanking regarding longitudinal

evaluations of older patients with locomotor disorders. The analyses in this study were conducted using cross-sectional data obtained at enrollment. The enrolled patients visited the outpatient orthopedic surgery clinic and provided written consent for the use of their data.

Eligibility criteria included body composition measurement using whole-body dual-energy X-ray absorptiometry (DXA) for bone mineral density evaluation, whole-spine standing X-ray for postural evaluation, blood biochemistry examination, and no orthopedic treatment for ADL impairment due to musculoskeletal disorders, such as osteoarthritis or spondylitis.

All participants were assessed as being able to walk independently (independent group), requiring a cane or walker to ambulate, or being unable to walk and using a wheelchair as a means of transportation. The age-related risk factors for the inability to walk independently were examined by comparing the independent and assisted walker groups.

Exclusion criteria included dementia with decision-making difficulties, history of vertebral fracture or proximal femur fracture with or without osteoporosis, history of cerebrovascular and/or respiratory disease, and history of systemic diseases, such as rheumatoid arthritis, infection, and malignant tumor. In this study, walking speed was not included in the analysis because of the inherent difference between the independent and the assisted groups.

Radiographic Evaluation

Body composition was measured by DXA (Lunar iDXA, GE-Healthcare, Chicago, IL, USA). Bone mineral density was evaluated using the T-score of the lumbar vertebrae (L2-4). Skeletal muscle mass was evaluated using the skeletal muscle mass index (SMI), calculated by dividing the muscle mass of the upper and lower limbs by the square of the height. Body fat was evaluated as the percentage of total body fat divided by body weight. Sagittal spinal alignment on the standing lateral radiograph of the whole spine was assessed using lumbar lordosis (LL), sacral slope (SS), thoracic kyphosis (TK), sagittal vertical axis (SVA), and pelvic tilt (PT). Optimal lumbar kyphosis was evaluated as a spinopelvic mismatch, calculated by subtracting from pelvic incidence (PI), where PI = PT + SS, representing the sacral tilt in the pelvis.

Laboratory Data

Complete blood counts, including red blood cell distribution width (RDW) and platelet distribution width, were performed using automated analysis to assess nutritional status and senescence. Additional measurements included estimated glomerular filtration rate, serum albumin, glycated hemoglobin (HbA1c), creatinine (Cre), and serum 25-hydroxyvitamin D (25-OHD) levels. Serum 25-OHD levels were determined using an electrochemiluminescence immunoassay.

Statistical Analyses

Power analyses were completed using G*Power (version 3.1.9.2, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) with α set at 0.01 for all estimates. We used two-sided testing, odds ratio = 2, Pr (Y = 1| X = 1) H0 = 0.25, α error probability = 0.01, power (1-β error probability) = 0.9, R^2 other X = 0.7, with X following binomial distribution and X parm π = 0.6. The minimum sample size was calculated to be 2043. Proportions and means with standard deviations were calculated for covariates and demographic information, while categorical variables were expressed as frequencies or percentages. Chi-squared or Fisher's exact tests were used to assess differences in categorical variables, and means were compared using an independent *t*-test. A *P*-value <.01 was considered statistically significant.

For multivariate analysis, logistic regression analysis was used with $P < .01$ as the explanatory variable for the comparison between the independent and assisted walking groups. The area under the curve (AUC) was calculated using the receiver operating characteristic (ROC) curve to determine the optimal cut-off value for the risk of assisted walking. Outliers were determined and excluded using the Smirnov–Grubbs test.

Statistical analyses were performed using the EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Among the 2083 patients, 1323 and 760 were included in the independent and assisted groups, respectively. The assisted group was significantly older, with a higher proportion of women, and exhibited significant differences in many factors, including anemia, elevated RDW, low albumin level, poor renal function, impaired glucose tolerance, low bone density, low SMI, high SVA, and low PI−LL (Table 1). The logistic regression analysis identified five factors—age, BMI, RDW, SMI, and SVA—as significant in the crude model between independent and assisted walkers ($P < .01$) (Table 2). The same results were obtained in the conditional logistic regression analysis adjusted for age and sex (Table 3). Thus, these results identified old age, physique, senescence, sarcopenia, and abnormal posture as clinical

Table 1. Demographic Data for the Older Patients With Independent and Assisted Walking.

	Independent	Assisted	*P* value	95% CI Upper lower
N	1323	760		
Age	76.48±5.92	81.82±6.65	<.0001	−5.894-4.788
Sex (M:F)	553:770	188:572	<.0001	
BMI (kg/m^2)	23.51±3.38	23.14±4.30	.0278	0.041 0.709
Hb (g/dl)	13.19±1.82	12.42±1.57	<.0001	0.613 0.923
Plt. (10000/μl)	21.80±6.82	21.74±7.43	.8508	−0.568 0.689
RDW (%)	13.41±1.20	13.84±1.43	<.0001	−0.551-0.321
MPV (fl)	10.06±0.95	9.99±0.90	.1754	−0.026 0.141
PDW (%)	11.23±2.00	11.03±1.83	.0210	0.031 0.378
Alb (g/dl)	4.16±0.38	3.93±0.43	<.0001	0.199 0.270
eGFR (mL/min/1.73 m^2)	66.61±16.86	64.12±20.71	.0029	0.854 4.133
Cre. (mg/dl)	0.77±0.23	0.79±0.31	.2978	−0.036 0.011
HbA1C (%)	5.99±0.66	6.12±0.99	.0003	−0.202-0.059
25-OHD (ng/ml)	16.52±6.86	12.95±6.70	.0112	2.887 4.268
L2-4 BMD (g/cm^2)	1.09±0.30	0.99±0.28	<.0001	0.065 0.118
SMI (kg/m^2)	6.30±1.02	5.79±1.08	<.0001	−0.042 0.228
Body fat ratio (%)	32.17±6.86	33.30±7.82	.0258	−2.042-0.131
SVA (degree)	50.46±41.83	87.80±58.51	<.0001	−42.942-31.719
TK (degree)	36.48±11.33	35.64±13.93	.2543	−0.604-2.293
PT (degree)	49.72±10.69	51.57±14.91	.0117	−5.610-3.193
PI-LL	17.90±14.47	25.82±20.80	<.0001	−9.992-6.064

Mean ± S.D.
A *P*-value <.01 was considered statistically significant using two-tailed independent *t* test.
95% CI: 95% coefficient interval.
Abbreviations: BMI, body mass index; Hb, hemoglobin; Plt., platelet; RDW, red-cell distribution width; PDW, platelet distribution width; MPV, mean platelet volume; Alb, albumin; eGFR, estimated glomerular filtration rate; Cre, creatinine; 25OHD, 25-hydroxyvitamin D; BMD, bone mineral density; SMI, skeletal muscle mass index; SVA, sagittal vertical axis; TK, thoracic kyphosis, PT, pelvic tilt; PI, pelvic incidence; LL, lumbar lordosis.

findings that define the need for walking assistance among older adults.

Among these five factors, multicollinearity was considered for BMI due to the high variance inflation factor; thus, ROC analysis was performed for the remaining four factors: age, RDW, SMI, and SVA. The ROC analysis revealed the following thresholds for assisted walking: age, 81.0 years; RDW, 14.0%; SMI,

Table 2. Logistic Regression Analysis for the Risk of Assisted Walking in Older Adults. (Crude Model).

	Regression coefficient	Standard error	*P* value	OR	95% CI lower	95% CI upper	VIF
Age	0.0984	0.0161	<.0001	1.100	0.000	0.003	1.170
Sex (female)	0.1943	0.2942	.5088	1.210	0.682	2.160	2.437
BMI	0.2573	0.0638	<.0001	1.290	1.140	1.170	7.832
Hb	−0.1090	0.0637	.0870	0.897	0.791	1.020	1.339
RDW	0.2266	0.0590	.0001	1.250	1.120	1.410	1.145
Alb	−0.2234	0.2446	.3610	0.800	0.495	1.290	1.112
eGFR	−0.0038	0.0052	.4693	0.996	0.986	1.010	1.129
HbA1C	0.1529	0.1147	.1826	1.170	0.931	1.460	1.118
L2-4 BMD	−0.6645	0.3821	.0820	0.515	0.243	1.090	1.687
SMI (kg/m^2)	−0.7048	0.1951	.0003	0.494	0.337	0.724	5.088
SVA	0.0160	0.0019	<.0001	1.020	1.010	1.020	1.130
PI-LL	0.0133	0.0091	.1464	1.010	0.995	1.030	1.229

Logistic regression analysis was used with $P < 0.01$ as the explanatory variable for the comparison between the independent and assisted walking groups.
Abbreviations: BMI, body mass index; Hb, hemoglobin; RDW, red-cell distribution width; MPV, mean platelet volume; Alb, albumin; eGFR, estimated glomerular filtration rate; Cre, creatinine; BMD, bone mineral density; SMI, skeletal muscle mass index; SVA, sagittal vertical axis; PI, pelvic incidence; LL, lumbar lordosis.

Table 3. Logistic Regression Analysis for the Risk of Assisted Walking in Older Adults. (Conditional Model).

			95% CI	
Model 1	*P* value	OR	Lower	Upper
Age	-	-	-	-
Sex (female)	.3518	0.750	0.410	1.370
BMI	.0002	1.300	1.130	1.500
Hb	.1641	0.913	0.803	1.040
RDW	.0004	1.250	1.100	1.410
Alb	.4005	0.810	0.495	1.320
eGFR	.6209	0.997	0.987	1.010
HbA1C	.2387	1.150	0.913	1.440
L2-4 BMD	.0817	0.502	0.231	1.090
SMI (kg/m2)	.0006	0.464	0.298	0.721
SVA	<.0001	1.010	1.010	1.020
PI-LL	.1199	1.010	0.996	1.030
			95% CI	
Model 2	*P* value	OR	Lower	Upper
Age	<.0001	1.100	1.070	1.140
Sex (female)	-	-	-	-
BMI	<.0001	1.290	1.140	1.460
Hb	.0824	0.895	0.790	1.010
RDW	.0001	1.260	1.120	1.420
Alb	.3740	0.805	0.499	1.300
eGFR	.4627	0.996	0.986	1.010
HbA1C	.1800	1.170	0.932	1.460
L2-4 BMD	.0664	0.488	0.227	1.050
SMI (kg/m2)	.0005	0.503	0.343	0.738
SVA	<.0001	1.020	1.010	1.020
PI-LL	.1742	1.010	0.994	1.030

Model 1: Age matched Logistic regression analysis.
Model 2: Sex matched Logistic regression analysis.
Abbreviations: BMI, body mass index; Hb, hemoglobin; RDW, red-cell distribution width; MPV, mean platelet volume; Alb, albumin; eGFR, estimated glomerular filtration rate; Cre, creatinine; BMD, bone mineral density; SMI, skeletal muscle mass index; SVA, sagittal vertical axis; PI, pelvic incidence; LL, lumbar lordosis.

5.96 kg/m^2; and SVA, 54.64 mm. The AUCs were 0.727, 0.677, 0.645, and 0.708, respectively (Figure 1). None of these factors were found to be significantly associated with the deterioration of walking function, which was thought to be a multifactorial event. ROC analysis using these four factors as propensity scores revealed an AUC of 0.768 (0.796 for men and 0.708 for women) (Figure 2).

Discussion

The results of this cross-sectional study revealed clinical factors associated with the decline in gait function, particularly the differences between independent and assisted walking in older adults without fractures or cerebrovascular disorders. While walking ability declines with age,[2] no detailed study data have ascertained the age at which a person begins to require assistance in walking. With advanced age, gait often becomes a slowed-down version of the gait of younger adults, suggesting that gait changes in older adults are characterized by a cautious attitude toward walking. This cautious gait is essentially an exaggeration of the normal age-related gait changes.[18] Therefore, to prevent falls, reducing step length and increasing step width makes it easier to maintain balance while walking.

Gait speed decline accelerates after the age of 63 years in individuals without orthopedic, cardiorespiratory, neurological, or cognitive dysfunctions,[19] with slower cadence most apparent after the age of 75 or 80 years.[18] Furthermore, in Japan's Comprehensive Survey of Living Conditions, 56.3% of those aged ≥70 years and 34.9% of those aged ≥80 years reported functional limitations in ADLs.[2] These findings align with the present study's age threshold of 81 years for requiring walking assistance, supporting clinical observations.

Senescence is associated with advanced aging in older adults. Senescent cells with irreversible proliferative arrest can develop a senescence-associated secretory phenotype (SASP) consisting of proinflammatory cytokines and extracellular matrix-degrading proteins, leading to deleterious paracrine and systemic mild inflammation.[20] This age-related inflammation ("inflammaging") is considered a pervasive feature of aging tissues and age-related diseases.[21] The RDW represents the variations in the size of the red blood cells and has been evaluated as a potential screening marker for cancer[22] and a prognostic marker for heart failure and coronary heart diseases.[23] Recent studies have reported that RDW is associated with inflammation,[10,11] establishing its usefulness as a biomarker for rheumatoid arthritis,[24] metabolic syndrome,[25] mortality after femoral neck fracture,[26] and artificial joint replacement surgery.[27] A previous study reported the usefulness of RDW as a prognostic predictor of walking ability after osteoporotic vertebral fractures.[9] Although the exact mechanisms remain unknown, RDW is increasingly being recognized as a global marker of chronic inflammation[10,11] and oxidative stress,[28,29] reflecting changes in red blood cell production and their half-life in circulation. Oxidative damage is an inducer of irreversible cellular senescence mediated by DNA damage, leading to cell survival reduction.[30]

As humans age, cells undergo irreversible arrest of cell proliferation and enter a state of SASP, in which they secrete inflammatory cytokines and proteases involved in the remodeling of the extracellular matrix. This activates

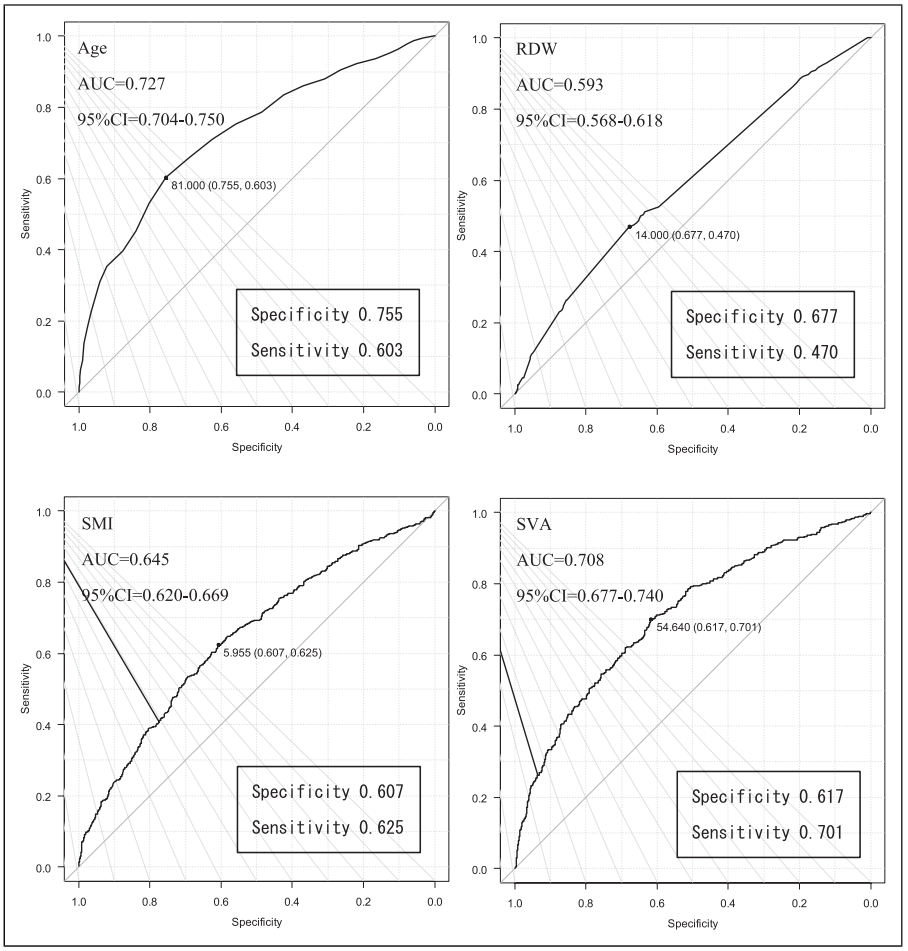

Figure 1. ROC Analysis of Each Factor for Assisted Walking Risk according to the ROC Analysis, the AUCs for Age, RDW, SMI, and SVA were 0.727, 0.593, 0.645, and 0.708, Respectively. The Cut-off Values for Age, RDW, SMI, and SVA Threshold for the Risk of Assisted Walking were 81.0 Years, 14.0%, 5.955 kg/m^2, and 54.64 mm, Respectively. No Factor had an Outstandingly High AUC, and it was Considered Unlikely that the Regulation of Assisted Walking in Older Adults was due to a Single Factor. AUC, Area Under the Curve; RDW, Red Cell Distribution width; ROC, Receiver Operating Curve; SMI, Skeletal Muscle Mass index; SVA, Sagittal Vertical Axis.

inflammatory signaling in the tissues and induces an underlying low-level inflammatory state.[20] Therefore, SASP contributes to sarcopenia, an age-related muscle mass reduction.[31] The inclusion of SMI, an indicator of skeletal muscle mass, and RDW, an indicator of chronic inflammation, in our multivariate analysis of factors indicates their relevance to limitations of independent walking in older adults. Research into the pathophysiology and role of RDW in senescent mechanisms has been progressing of late, and it is expected that the establishment of a unique threshold specific to mobility in older adults will lead to the integration of identified thresholds into digital health tools for monitoring mobility risks. As gait in older adults is characterized by a decrease in stride length and an increase in step length, the pathological basis for this is considered to be a decrease in lower limb muscle strength[32] and balance function.[33] Given the association of balance function decline with proprioception loss and the impact of skeletal muscle mass reduction on lower limb sensory function in older adults,[34] the relationship between SMI and gait status in the present study indicates the clinical importance of skeletal muscle condition in managing age-related gait disorders.

Regarding spinal alignment, as postural control impairment is a major risk factor for falls in older adults,[14] a close relationship between gait and standing postural balance has been observed, and SVA, which increases with age, is suitable as an assessment of physical performance decline in older adults.[35] In older patients with reduced lower limb skeletal muscle mass, anterior trunk inclination is induced along with posterior pelvic tilt,[36] suggesting that sarcopenic muscle mass loss is associated with increased SVA. Increased SVA and a forward shift in trunk balance cause a forward shift in the center of gravity, which in turn induces a

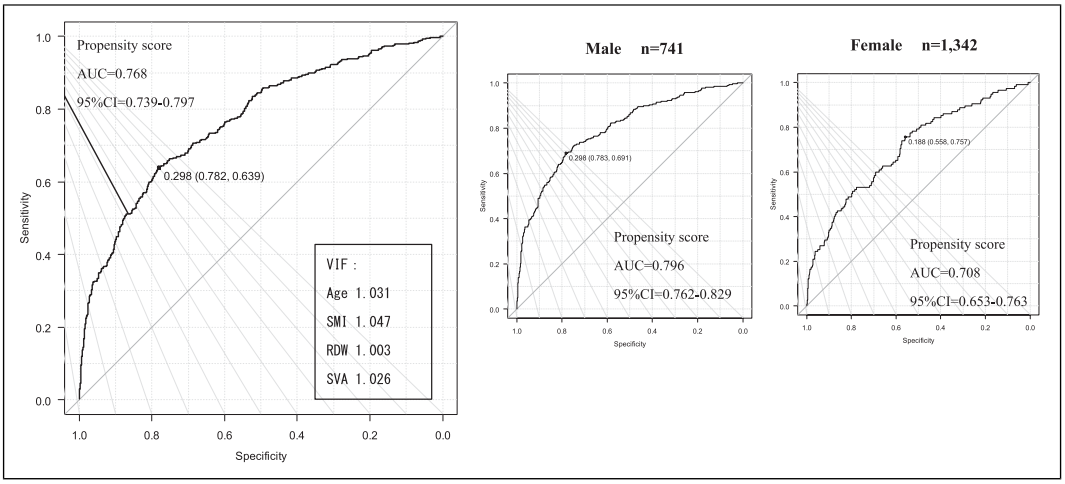

Figure 2. ROC Analysis for Assisted Walking Risk Using Propensity Scores for Age, RDW, SMI, and SVA. According to the ROC Analysis, the AUC for the Propensity Scores for Age, RDW, SMI, and SVA was 0.768 (Male, 0.796; Female, 0.708). The Fact that a High AUC was Calculated by Using the Four Factors that Showed a Significant Difference in Multivariate Analysis as the Propensity Score Suggested that Assisted Walking in Older Adults is Determined by Multiple Factors. AUC, Area Under the Curve; RDW, Red-Cell Distribution width; ROC, Receiver Operating Curve; SMI, Skeletal Muscle Mass index; SVA, Sagittal Vertical Axis

fall risk.[14] However, the index for spinal sagittal balance that leads to gait disturbances in older adults and the limiting value of the SVA in the transition from independent to assisted walking remain unknown. In this study, the critical SVA value between assisted and independent walking was calculated to be 54 mm. It is necessary to consider that multiple factors cause gait disturbance and is strongly influenced not only by trunk balance but also by the condition of the lower limb skeletal muscles.

The results of the multivariate analysis in this study showed that the four factors affecting assisted walking (age, RDW, SMI, and SVA) had a relatively good AUC of 0.768 in the ROC analysis using the propensity score. This suggests that these factors can be used to estimate the risk of assisted walking in older adults. Therefore, it is possible to assess the risk of assisted walking in older adults using these factors. The findings of this research are expected to help set targets in geriatric rehabilitation medicine, including maintenance of physical functions so that older people do not have to rely on walking aids, selection of candidates for medical intervention, and future formulation of a protocol for preventing frailty according to the results of international research that has become increasingly important in recent years,[37] thereby increasing the applicability of the research results.

A limitation of this study is that it was a cross-sectional study and not a longitudinal evaluation of the transition from independent to assisted walking. Therefore, the results are not definitive for causality. Clinical evaluation becomes more important when independent walkers begin to require walking assistance. In addition, because spinal alignment was assessed in a standing still position and not during actual walking, a more accurate assessment requires measurements during walking. Furthermore, the study did not include variables that affects walking ability, such as the living environment. These limitations of cross-sectional studies should be addressed in future, and the validity of our results should be evaluated in longitudinal studies evaluating the dependence of older people on walking aids.

Conclusion

In comparing independent and assisted walkers among adults aged ≥65, this study revealed the importance of age, RDW, skeletal muscle mass, and spinal sagittal balance as clinical factors characteristic of assisted walkers. In the future, we hope to set clinical criteria for the inability to maintain physical functions that do not rely on walking aids in the field of geriatric medicine and determine treatment interventions from the perspective of locomotor disorders in order to maintain walking function in older adults.

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Ethical Statement

Ethical Approval

The study was approved by the Institutional Ethics Committee of the National Center for Geriatrics and Gerontology (approval number: 1688) and was conducted according to the ethical standards of the Helsinki Declaration (1964) and its subsequent amendment.

Consent to Participate

The consent for the study was obtained from all participants.

Consent for Publication

Patients provided written consent for the use of their data.

Author Contributions

YS, AK, and KW conceived the idea for the work, designed the study, interpreted the data, and wrote the final version of the article. YS was involved in data analysis and data management. TW, NW, HM, NO, YA, and YT collected the data, prepared all tables and figures, and revised the manuscript. All authors provided input for the editing of the manuscript for publication. The corresponding author has full access to all data in the study data and the final responsibility for publication.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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