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ORIGINAL ARTICLE

Prognostic nutritional index instead of serum Vitamin D levels as a determinant of the presence of osteoporosis in adult male patients with neurological impairment

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Abstract

Background: Complications of non-traumatic fractures and osteoporosis, which reduce mobility and quality of life, should not be ignored in patients with neurological impairment (NI).
Aim: To diagnose osteoporosis in adult patients with NI, a readily available and easily obtained index, instead of serum Vitamin D level or bone mineral density (BMD), was explored.
Methods: This was a single-center retrospective study. The participants were inpatients with NI admitted between August 2020 and June 2022. Patient data regarding (1) patient information, (2) blood data, including the prognostic nutrition index (PNI), which predicts outcomes of various diseases, (3) body composition, (4) T-score by BMD, (5) nutritional measures, and (6) outcome measures were collected. Enrolled patients were divided into two groups, with or without osteoporosis, according to their T-score. The data were analyzed by three methods: (1) comparison of all collected data between the two groups to analyze the factors influencing osteoporosis; (2) multiple logistic regression analysis; and (3) receiving operating characteristic curve analysis.
Results: Patients with osteoporosis had a significantly lower PNI (45 vs. 49, $P = 0.045$), and higher Vitamin D insufficiency (71% vs. 31%, $P = 0.031$). PNI was the strongest influencing factor, and its cutoff value for osteoporosis was 50.
Conclusion: The PNI is the strongest determinant of osteoporosis in patients with NI. Therefore, PNI can potentially be used as a surrogate for BMD instead of serum Vitamin D levels in institutionalized and homebound patients who do not have BMD measurement devices.
Relevance for Patients: Prognostic nutrition index, which is a simple blood test, outperforms serum vitamin D concentration as a good indicator for early detection of osteoporosis.

1. Introduction

Patients with neurological impairments (NI), including cerebral palsy (CP), are often affected by osteoporosis, associated fractures, and bone pain, which often result in reduced mobility. In this context, these complications, which reduce quality of life (QoL), cannot be ignored. Bone pain associated with osteoporosis occurs in 56.4% of patients, followed by deformity and fatigue in 44.2% and 36.9% of patients, respectively [1]. Osteoporosis is a debilitating bone disease characterized by low bone mass and poor bone quality. A major consequence of osteoporosis is the increased risk of fragility and non-traumatic fractures (NTFx). These fractures are a major cause of functional disability, morbidity, impaired QoL, and early mortality. Recent studies reported that the prevalence of osteoporosis in patients with NI showed an odds ratio ranging from 5.76 to 30.5 compared to those without NI [2,3], suggesting that NI is an osteoporosis

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risk factor. Diagnosing osteoporosis with comorbidities is difficult, especially in patients with NI who have spent long periods in nursing homes or other facilities without bone mineral density (BMD) measurement equipment. Overlooking the complications of osteoporosis in patients with NI can lead to the development of fractures and non-traumatic brain injury and reduce their QoL. Therefore, in this study, we developed an easy-to-measure index that could serve as a substitute for BMD measurement and an alternative index that would aid in diagnosing osteoporosis in patients with NI. The study showed that an alternative index to BMD can help detect osteoporosis and its related complications at early stages in patients with NI, allowing early treatment and improving their QoL. Institutionalized patients with NI often present with fragile bones as facilities often do not have the necessary equipment for measuring BMD, for example, in the case of care-related fractures. Therefore, addressing this issue can improve the patient's condition as well as their family, caregivers, and facility staff. However, not all facilities have the equipment to measure BMD to diagnose osteoporosis. A surrogate index can help diagnose osteoporosis in patients living in such institutions without adequate BMD measurements. Consequently, the objective was to develop an easy and reliable index for patients with NI to diagnose osteoporosis when BMD measuring equipment is unavailable.

2. Methods

2.1. Participants

In this single-center and retrospective study, all patients with NI hospitalized at a single medical center between August 2020 and June 2022 were included in the study. Patients diagnosed with NI who stayed at the hospital for more than 3 months during the study period were included. Patients were excluded from the study if they were as follows: (1) female, (2) younger than 18 years, (3) had missing BMD data, (4) had hepatic and renal dysfunction (serum total bilirubin level 1.5 mg/dL or serum creatinine level 1.5 mg/dL, and (5) died during hospitalization.

2.2. Data collection

Data for catabolic measurements were collected in the same month as the body composition measurements. The following information was collected:

(1) Patient information including age, sex, height, weight, antiepileptic drug (AED) use, and gross motor function classification scale (GMFCS) score (Appendix) evaluated by a single physician.
(2) Blood work data, including serum albumin level (Alb), serum creatinine level, serum total bilirubin level, hemoglobin level, platelet count, total lymphocyte count (TLC), neutrophil count, eosinophil count, basophil count, monocyte count, 25-hydroxyvitamin D (25-(OH) VD), and Onodera's prognostic nutritional index (PNI) calculated by 10 × Alb + 0.005 × TLC [4].
(3) Body composition indices measured using a bioelectrical impedance analysis (BIA) Inbody S10 (Inbody, Tokyo, Japan) device and the following components were measured: body mass index, lean mass, body water content, muscle mass, body fat mass, body fat percentage, extracellular water/total body water ratio, skeletal muscle mass, protein content, bone mineral content, somatic cell mass, basal metabolic rate, appendicular skeletal muscle mass index, and phase angle.
(4) BMD measurements, including the T-score of lumbar vertebrae L1-4 that was measured by dual-energy X-ray absorptiometry (DEX) using PRODIGY (Lunar iDXA; GE Healthcare Japan Co., Tokyo, Japan). T-score was calculated using the following equation: ([measured BMD – young adult average BMD]/[BMD-SD of young adult aged 20 – 44 years of the same sex and ethnicity]) [5]. Patients with a T-score of <−2.5 SD were diagnosed with osteoporosis.
(5) Nutritional measures, including average energy intake (kcal/kg/day) and average protein intake (g/kg/day) for a total of 3 days, including the days before and after the day of body composition measurement. The average Vitamin D intake (μg/day) and average calcium intake (mg/day) were based on the 42-day cycle menu of the research center's diet, and the intake of both Vitamin D and calcium varied daily, and the average salary for a 42-day cycle was used
(6) Outcome measures.

The primary outcome was the presence of osteoporosis (diagnosed using the T-score), and the factors that most influenced this outcome were compared. These data did not suffer from any source bias since the blind collection methodology was adopted.

As hormones strongly influence bone mineral quantification in female participants, they were excluded from this study. All collected data were compared between those with and without osteoporosis to characterize the group with osteoporosis. In addition to BMD, we examined the presence or absence of indicators that can be used to diagnose osteoporosis, particularly using test data that can be more easily collected.

- Method 1: Participants were divided into two groups, and the data collected were compared between the two groups to analyze the factors influencing osteoporosis.
- Method 2: Multiple logistic regression analysis on the factors identified in method 1 was performed to clarify the factors influencing osteoporosis.
- Method 3: Receiving operating characteristic (ROC) curve analysis was used to determine the cutoff values for the most influential factors in osteoporosis.

All procedures conformed to the ethical standards of the institutional and national review boards and the tenets of the 1964 Declaration of Helsinki.

2.3. Statistical analysis

We used a thumb rule for at least 12 people in each group and listed the main cross-tabulations required to ensure that the total number of participants in each table cell would be adequate and decided on the number of subjects.

In method 1, data were presented as medians and 25%, 75%, or percentage points, and differences between the two groups

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were evaluated using the Mann–Whitney *U*-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. In method 2, multiple logistic regression analysis was performed, and in method 3, the area under the curve (AUC) and 95% confidence interval (CI) were determined using ROC curve analysis. The AUC with 95% CI was considered significant when the AUC was 1.0 but not when the AUC was 0.5. The point with the highest sensitivity of (1 - specificity) was defined as the more effective cutoff value. Statistical significance was defined as $P < 0.05$. SPSS version 29 (IBM, Armonk, NY, USA) was used for all the statistical analyses.

3. Results

The study had 68 inpatients, 34 of whom were excluded. Of the 34 males, four with missing BMD data were excluded, and the remaining 30 were included in the analysis (Figure 1). All subjects were bedridden, and their motor function was assessed as equally impaired (level V of complete dependence on mobility) using the gross motor function classification scale (GMFCS) [6], which classifies motor function into five levels, ranging from level I with no limitations (walking, running, and climbing stairs) to level V with complete dependence on mobility support [6]. A single physician performed this assessment. The assessment is highly correlated with mobility, as represented by the World Health Organization "handicap score" [7], and can also be considered an indication of the degree of mobility and dysphagia leading to malnutrition [6].

3.1. An association of osteoporosis with lower PNI and vitamin insufficiency

Table 1 shows the results of the comparison between patients with NI with and without osteoporosis (T-score $-2.5 \leq$ vs. < -2.5). As a result, Alb and PNI were significantly lower in the osteoporosis group (3.6 g/dL vs. 3.9 g/dL, $P = 0.002$; 45 vs. 49, $P = 0.045$). Furthermore, the number of patients with 25-OH VD levels of <30 ng/mL was significantly higher in the osteoporosis group (71% vs. 31%, $P = 0.031$). These results indicate that, compared with patients without osteoporosis, patients diagnosed with osteoporosis by their T-score had (1) significantly lower Alb and PNI and (2) serum 25-OH VD <30 ng/mL and the number of patients with Vitamin D insufficiency was significantly higher in the osteoporosis group.

3.2. Lower PNI and Vitamin D insufficiency influence osteoporosis in patients with NI

Multiple logistic regression analysis revealed that PNI and 25-(OH) VD levels <30 mg/dL remained significant factors that influence osteoporosis or low BMD, with odds ratios of 1.233 ($P = 0.037$) and 0.132 ($P = 0.033$), respectively (Table 2). From the analysis of the factors influencing osteoporosis using method 2, the PNI was considered the strongest influencing factor.

3.3. ROC curve analysis results of factors that influence osteoporosis the most

The cutoff value for osteoporosis was calculated using ROC curve analysis. The cutoff value for the PNI without osteoporosis was 50 for severely disabled male subjects. The sensitivity and specificity were 0.500 and 0.857, respectively, and AUC was 0.714 ($P = 0.046$) (Figure 2).

4. Discussion

4.1. PNI can help predict health outcomes of various diseases, including cancer and non-cancer diagnoses

Onodera *et al.* reported that the PNI can help predict postoperative complications in patients with colorectal cancer [4]. Since then,

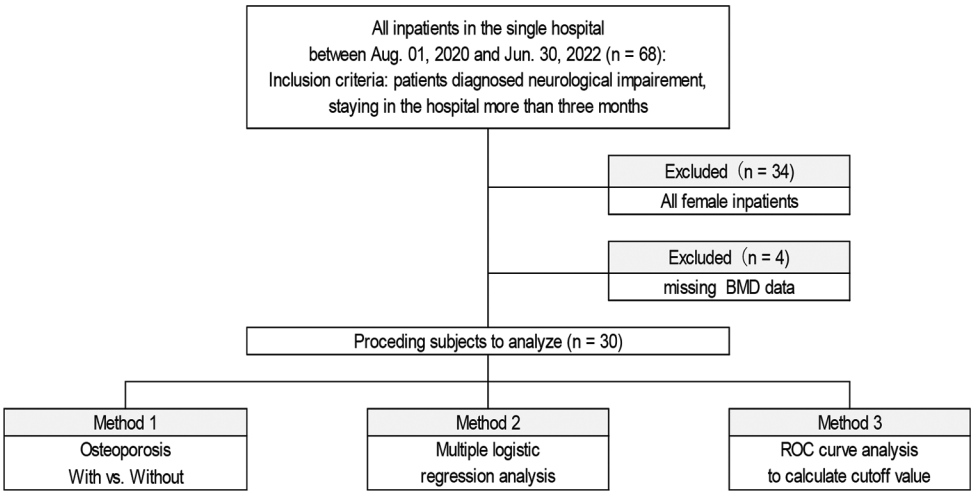

Figure 1. Flowchart of the study. A total of 68 adult patients with NI were enrolled in this study. Inclusion criteria were patients who had stayed at the study hospital for more than 3 months during the study period and were diagnosed with NI. To eliminate the confounding effect of gender, all female patients were excluded. In addition, four male patients were also excluded due to lack of BMD data. The remaining 30 male patients with NI were then further evaluated using the three methods shown in this flowchart.
Abbreviations, Aug: August; BMD: Bone mineral density; Jun: June; NI: Neurological impairment; ROC: Receiver operating characteristic.

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Table 1. Comparison of male CP patients with a T-score<2.5 SD (with osteoporosis) and a group above (without osteoporosis)

Parameters	Total	Osteoporosis (T-score≤−2.5)			BMD decrease (Z-score≤−2.0)		
		Present	Absent	*P*-value	With	Without	*P*-value
Characteristics							
Subject number	30	14	16		16	14	
Age, years	55 (48, 66)	60 (51, 67)	50 (34, 62)	0.092	56 (49, 67)	51 (44, 63)	0.519
BMI, kg/m^2	16.8 (15.0, 19.8)	17.5 (14.9, 20.1)	16.4 (15.0, 18.8)	0.506	17.1 (14.9, 19.9)	16.5 (15.1, 19.3)	0.901
Weight, kg	41.3 (36.0, 46.7)	41.5 (35.2, 45.8)	40.2 (35.5, 47.6)	0.868	41.5 (32.8, 44.5)	40.2 (36.0, 48.7)	0.934
Blood sampling parameters							
Alb, g/dL	3.8 (3.5, 4.0)	3.6 (3.2, 3.8)	3.9 (3.7, 4.2)	0.002	3.6 (3.2, 3.9)	3.9 (3.7, 4.2)	0.024
Hb, g/dL	13.7 (12.5, 14.6)	12.9 (11.6, 14.2)	14.5 (12.9, 14.9)	0.067	13.3 (11.9, 14.4)	14.1 (12.8, 14.8)	0.279
Plt, ×10^4/μL	20.8 (17.7, 25.8)	19.6 (17.1, 22.9)	22.4 (17.9, 27.5)	0.262	20.8 (17.4, 23.8)	20.5 (17.7, 27.8)	0.575
WBC, counts/μL	5315 (4770, 6540)	5240 (4698, 5933)	5485 (4805, 6580)	0.394	5240 (4725, 6498)	5485 (4780, 6540)	0.693
TLC, counts/μL	1748 (1290, 2254)	1915 (1399, 2254)	1694 (1177, 2427)	0.603	1915 (1355, 2325)	1694 (1242, 2308)	0.603
Onodera-PNI	46 (43, 51)	45 (41, 48)	49 (43, 53)	0.045	45 (41, 50)	48 (43, 54)	0.208
25(OH) vitamin D, ng/mL	31.4 (22.5, 37.4)	24.7 (20.5, 35.6)	34.3 (24.6, 38.1)	0.146	24.7 (20.7, 33.9)	35.1 (30.7, 38.3)]	0.081
25(OH) vitamin D<30 ng/mL, n (%)	15 (50)	10 (71)	5 (31)	0.031	12 (75)	3 (21)	0.004
Body composition measures							
Fat mass, %	29 (20, 43)	35 (20, 45)	25 (21, 36)	0.467	28 (19, 45)	29 (21, 38)	0.950
Fat-free mass, %	35 (29, 41)	31.5 (27.5, 40.2)	38 (32, 41)	0.244	34 (28, 42)	36 (30, 41)	0.708
ASMI, kg/m^2	4.40 (3.48, 5.43)	4.1 (3.3, 5.5)	4.6 (4.2, 5.2)	0.190	4.2 (3.3, 5.5)	4.6 (4.0, 5.1)	0.417
BMD measures							
T-score	−2.35 (−2.93, −1.43)	−2.95 (−3.53, −2.60)	−1.55 (−2.00, −0.83)	<0.001	−2.85 (−3.45, −2.53)	−1.35 (−1.93, −0.80)	<0.001
Z-score	−2.10 (−2.40, −1.18)	−2.50 (−3.43, −2.20)	−1.35 (−1.78, −0.55)	<0.001	−2.30 (−3.35, −2.20)	−1.15 (−1.63, −0.45)	<0.001
Medication							
AED, n (%)	18 (60)	9 (64)	9 (56)	0.659	10 (63)	8 (57)	0.769

Compared with male CP patients with a T-score<2.5 SD (with osteoporosis) and a group above (without osteoporosis), male CP patients with osteoporosis had a lower Onodera PNI score and a higher prevalence of serum Vitamin D concentration<30 ng/mL than those without osteoporosis.
Notes: (i) Continuous variables were tested using Mann–Whitney *U* test; (ii) categorical variables were tested using Chi-square test or Fisher's exact test.
Abbreviations: Alb: Serum albumin concentration; ALI: Advanced lung cancer inflammation index; BMD: Bone mineral density; BMI: Body mass index; ECW: Extra-cellular water; Hb: Hemoglobin; PNI: Prognostic nutritional index; TBW: Total body water; SII: Systemic immune-inflammation index; TLC: Total lymphocyte count; WBC: White blood cell; AED: Antiepileptic drugs.

Table 2. Osteoporosis variables and their odds ratios, 95% confidence intervals, and *P* values

Variable	OR	(95% CI)	*P*-value
PNI	1.233	(1.013, 1.501)	0.037
25(OH) Vit.D<30	0.132	(0.021, 0.849)	0.033

The multiple logistic regression analysis performed on the factors to clarify the factors influencing osteoporosis, both PNI and serum 25-(OH) Vitamin D concentration<30 ng/mL. According to these results, lower PNI and serum Vitamin D levels below 30 ng/mL indicate that patients with NI have a higher prevalence of osteoporosis.
Abbreviations: CI: Confidence interval; OR: Odds ratio; PNI: Prognostic nutritional index; Vit.D: Vitamin D.

more than 3,000 studies have been published for similar clinical purposes for various diseases, mainly in patients with cancer and less frequently in patients with other ailments [8-11]. As PNI is a comprehensive index of anti-inflammatory response and immune competence [8], it suggests that our subjects may be relatively acceptable in terms of the stabilization of inflammatory cytokines and oxidative stress markers, which play important roles in regulating albumin [11]. In this context, it can be interpreted that patients with NI with osteoporosis have a lower PNI, greater inflammation, and lower levels of Alb, which have an anti-inflammatory effect, than patients without osteoporosis [12-14].

4.2. PNI as a surrogate to identify osteoporosis in male patients with NI

It was recently reported to be 8.0%, 10.3%, 14.5%, and 25.9% in adults aged 18–30, 31–40, 41–50, and >50 years, respectively [15]. These observations suggest that the prevalence of osteoporosis in patients with CP increases at a rate of 1.5-fold per decade from 30 to >50 years. The present study suggested that PNI is the strongest factor influencing the coexistence of osteoporosis in patients with NI. Therefore, the PNI can potentially be a surrogate for BMD, especially in institutionalized and homebound patients who lack BMD measurement instruments. According to a report that examined the prevalence of osteoporosis in patients with CP by different age group with 10-year difference, female patients in their 30s to over 70 years of age accounted for up to 33.1% of the total prevalence, showing a linearly increasing trend with age. In contrast, male patients showed a peak of 12.4% in their 60s and a decrease to 10% in their 70s, indicating a clear sex difference in the prevalence [15]. However, detecting osteoporosis in patients with NI at home or in facilities without BMD measurement equipment is challenging. As factors such as sex and AED usage correlate with decreased BMD, we restricted the subjects in this study to

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males and included AED usage as a factor for our study. When the osteoporosis group was classified according to BMD measurements using a T-score of 2.5 SD or less as the criterion for osteoporosis, 14 patients (47%) in the osteoporosis group had significantly lower PNI values than those without osteoporosis. Therefore, a male patient with NI can be diagnosed with osteoporosis using the PNI. A previous study showed that NTFx was associated with an increased risk of 12-month mortality in adults with CP compared to those without CP, and NTFx is considered a major contributor to functional disability [13]. Therefore, special attention should be paid to adverse events occurring during the 12 months following NTFx. Based on these results, the PNI appears to be a surrogate for identifying the coexistence of osteoporosis in adult male patients with NI. Taken together, PNI is an indicator of adverse events such as aspiration, pneumonia, fractures, NTFx, and death.

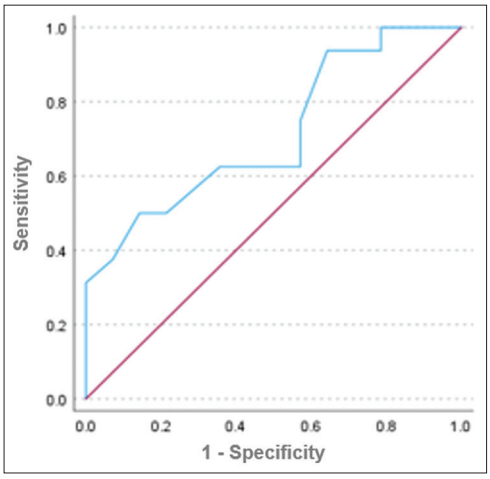

Figure 2. ROC curve analysis for determining cutoff value of PNI. Based on this curve, the cutoff value of PNI in adult NI patients to detect the association of osteoporosis was below the cutoff value of 50 of PNI. The sensitivity and specificity were 0.500 and 0.857, respectively, and the area under the curve AUC was 0.714 ($P = 0.046$).
Abbreviations: AUC: Area under curve; NI: Neurological impairment; PNI: Prognostic nutritional index; ROC: Receiver operating characteristic.

4.3. PNI cutoff values analyzed from the latest 1000 PNI-related articles

We reviewed 1000 articles on PNI studies published recently, except meta-analyses or reviews, to determine the cutoff value for PNI in patients with NI. Among these papers, 201 indicated clear cutoff values for both patients with cancer (125 papers) and patients with other ailments (76 papers) (Figure 3). This reflects that the first report of the PNI involved a study of patients with colorectal cancer. The latest PNI-related research, published in 2023, also used systematic reviews and meta-analyses to show that PNI is a helpful indicator for predicting outcomes in patients with cancer [16,17]. However, among patients with other ailments, there have been no studies on the PNI in patients with osteoporosis undergoing NI. To the best of our knowledge, this is the first report of PNI in a patient with NI and osteoporosis. From the comparison results of the two box plots showing the PNI cutoff values for patients with cancer and less frequently reported non-cancer diseases, at least two factors were found. First, the PNI of patients with cancer was closely scattered around 46 compared to those without cancer, and second, the PNI cutoff for patients without cancer was significantly lower than that for patients with cancer. Furthermore, in nearly 3000 PNI-related articles in addition to the 1000 papers, we analyzed, no study has examined NI and PNI in patients with osteoporosis. Therefore, we used PNI to assess patients with NI who also had osteoporosis. This study provides valuable results that can be used as indicators for osteoporosis risk assessment. Moreover, when 75 PNI articles in the non-cancer disease group

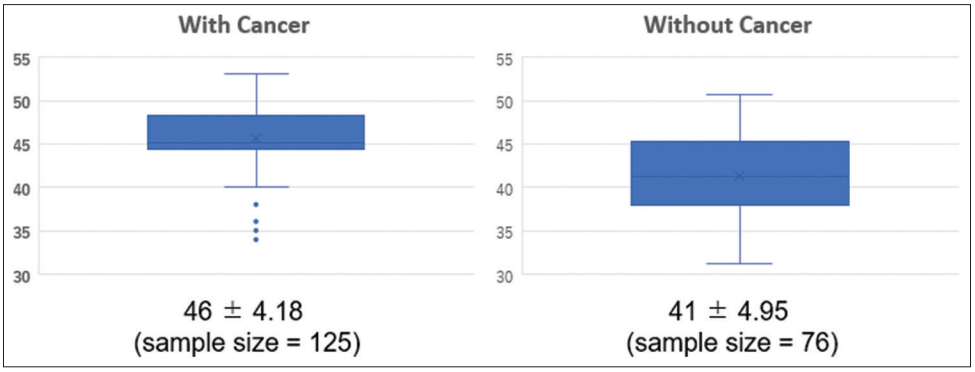

Figure 3. Comparison of the cutoff value of PNI in patients with and without cancer. Left: PNI cutoff value in patients with cancer was 46 ± 4 (sample size = 125). Right: PNI cutoff value in patients without cancer was 41 ± 5 (sample size = 76). The PNI cutoff for non-cancer patients was significantly lower than that for cancer patients. Furthermore, comparing this result with the PNI cutoff value of 50.0 in NI patients with osteoporosis in this study, PNI is a comprehensive index of nutritional status and immune competence. In addition, among the latest 1000 PNI articles, specifically, there were 201 arcs with cutoff values for PNI, of which 125 were PNI from patients with different types of cancer. This may reflect the fact that the first report of PNI was a study of patients with colorectal cancer. On the other hand, among non-cancer patients, there were no studies of PNI in patients with osteoporosis and NI, and this study appears to be the first report on PNI in patients with NI and osteoporosis.
Abbreviations: NI: Neurological impairment; PNI: Prognostic nutritional index.

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were arranged in descending order of PNI value, the PNI cutoff value of 50 for patients with NI shown in this study was next to the cutoff value for non-ST segment elevation myocardial infarction, which was 50.7 [18]. The PNI cutoff in this study was the second highest. The cutoff value to identify osteoporosis in patients with NI was 50, which is the second highest among non-cancer diseases. It has been suggested that this may be largely due to the loss of mobility. However, there is insufficient evidence to conclude that the magnitude of the PNI cutoff indicates the magnitude of inflammation underlying the target disease. Therefore, it is necessary to investigate whether diseases with the same PNI cutoff can be considered equivalent in terms of the incidence of inflammation and inflammation-related adverse events based on other aspects, such as cytokine storm parameters.

4.4. Strengths and limitations

To the best of our knowledge, this is the first study to report that PNI can be used to diagnose osteoporosis in patients with NI. We added the PNI cutoff value for patients with NI who are bedridden in hospitals. If these patients have osteoporosis with a PNI lower than the cutoff value, they may have a high probability of developing osteoporosis and experiencing adverse events. This information can notify caregivers to pay care-related attention to them to avoid adverse events such as aspiration pneumonia or choking during eating or drinking. In addition, for patients living at home or in facilities without BMD measurement equipment, PNI can be a feasible substitute if it can be measured through blood testing instead of a bone density scan. In subsequent care, this may help screen for osteoporosis and prevent complications, such as aspiration or pneumonia.

This study has several limitations. In the first study, the PNI was shown to be effective in predicting adverse events in patients with cancer [4,16,17]. Since the publication of the first article, there have been at least 76 reports on the efficacy of PNI to establish it as a predictor of noncancerous AEs (Figure 2). The present study demonstrated that PNI can help detect coexisting osteoporosis in bedridden male patients with NI. Therefore, the relationship between PNI and osteoporosis and between PNI and death was clarified. However, the relationship between PNI and death was not clarified. Second, during body composition analysis, we did not observe an association between Vitamin D deficiency and osteoporosis, skeletal sarcopenia, or sarcopenia. Recently, it has been proposed that sarcopenia and osteoporosis simultaneously affect muscles and bones, which are the target organs for Vitamin D hormones. The coexistence of these pathologies, termed "osteosarcopenia" [19], could not be demonstrated in the subjects of this study. In addition to the small number of subjects, it is unclear whether the essential existence of this pathology is problematic. Third, the number of studies included for assessment was too small to draw definitive conclusions. A larger number of participants must be included to gain more statistical power to detect all relevant associations and obtain a strong conclusion. In addition, a larger number of subjects may provide an additional and more accurate parameter for predicting osteoporosis comorbidity than the PNI.

5. Conclusion

The PNI was found to be the strongest determinant of osteoporosis in patients with NI. The PNI instead of serum Vitamin D levels can potentially be used as a surrogate for BMD in institutionalized and homebound patients who do not have BMD measurement devices.

Acknowledgments

We are grateful to Professor Eiji Yamato from the Department of Food Science and Nutrition, Mukogawa Women's University, Japan, for his collaboration on all parts of this study.

Funding

None to declare.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate

Informed consent was obtained using the opt-out method and the study was approved by the Research Center's Ethics Committee (R04-001).

Consent for Publication

The authors obtained the written informed consent from the subjects for publishing their data.

Availability of Data

Datasets generated during and/or analyzed during the present study, as well as the list of 1000 PNI-related articles and the extracted PNI cutoff values from 76 articles, are available from the corresponding author on reasonable request.

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Appendix

GMFCS scoring system

- Level I: No limitations (walks, runs, climbs stairs, etc.); impaired coordination.
- Level II: Limitations walking on uneven surfaces or long distances; needs support climbing stairs; difficulties running and jumping.
- Level III: Walks with a cane or crutches; needs a wheelchair to travel long distances.
- Level IV: Uses a walker at home; used in a wheelchair in other situations.
- Level V: Complete dependence for mobility.

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