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Clinical Study

The effect of age and injury severity on clinical prediction rules for ambulation among individuals with spinal cord injury

Einat Engel-Haber[a,b,*], Gabi Zeilig[a,b], Simi Haber[c], Lynn Worobey[d], Steven Kirshblum[e,f]

[a] Department of Neurological Rehabilitation, The Chaim Sheba Medical Center, Tel Hashomer, Israel
[b] Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel
[c] Department of Mathematics, Bar-Ilan University, Ramat-Gan, Israel
[d] Department of Physical Medicine & Rehabilitation, University of Pittsburgh, Pittsburgh, PA, USA
[e] Kessler Institute for Rehabilitation, West Orange NJ, USA
[f] Rutgers New Jersey Medical School, Newark, NJ, USA

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ABSTRACT

BACKGROUND CONTEXT: While several models for predicting independent ambulation early after traumatic spinal cord injury (SCI) based upon age and specific motor and sensory level findings have been published and validated, their accuracy, especially in individual American Spinal Injury Association [ASIA] Impairment Scale (AIS) classifications, has been questioned. Further, although age is widely used in prediction rules, its role and possible modifications have not been adequately evaluated until now.

PURPOSE: To evaluate the predictive accuracy of existing clinical prediction rules for independent ambulation among individuals at spinal cord injury model systems (SCIMS) Centers as well as the effect of modifying the age parameter from a cutoff of 65 years to 50 years.

STUDY DESIGN: Retrospective analysis of a longitudinal database.

PATIENT SAMPLE: Adult individuals with traumatic SCI.

OUTCOME MEASURES: The FIM locomotor score was used to assess independent walking ability at the 1-year follow-up.

METHODS: In all, 639 patients were enrolled in the SCIMS database between 2011 and 2015, with complete neurological examination data within 15 days following the injury and a follow-up assessment with functional independence measure (FIM) at 1-year post injury. Two previously validated logistic regression models were evaluated for their ability to predict independent walking at 1-year post injury with participants in the SCIMS database. Area under the receiver operating curve (AUC) was calculated for the individual AIS categories and for different age groups. Prediction accuracy was also calculated for a new modified LR model (with cut-off age of 50).

RESULTS: Overall AUC for each of the previous prediction models was found to be consistent with previous reports (0.919 and 0.904). AUCs for grouped AIS levels (A+D, B+C) were consistent with prior reports, moreover, prediction for individual AIS grades continued to reveal lower values. AUCs by different age categories showed a decline in prognostication accuracy with an increase in age, with statistically significant improvement of AUC when age-cut off was reduced to 50.

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*Corresponding author. Department of Neurological Rehabilitation, The Chaim Sheba Medical Center, Tel Hashomer, Derech Sheba 2, Ramat Gan, Israel. Tel.: +972-35303718.

E-mail address: einat.haber@sheba.health.gov.il (E. Engel-Haber).

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CONCLUSIONS: We confirmed previous results that former prediction models achieve strong prognostic accuracy by combining AIS subgroups, yet prognostication of the separate AIS groups is less accurate. Further, prognostication of persons with AIS B+C, for whom a clinical prediction model has arguably greater clinical utility, is less accurate than those with AIS A+D. Our findings emphasize that age is an important factor in prognosticating ambulation following SCI. Prediction accuracy declines for older individuals compared with younger ones. To improve prediction of independent ambulation, the age of 50 years may be a better cutoff instead of age of 65. © 2020 Elsevier Inc. All rights reserved.

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Introduction

After sustaining a spinal cord injury (SCI), individuals want to know if they will be able to regain the ability to walk. Walking is a priority among persons with SCI across all degrees of severity, chronicity, and age [1]. Particularly in recent years, when more injuries are classified as neurologically incomplete, the potential for such recovery is greatly enhanced.

For many years, determining who will walk after SCI was based on work by Hussey and Stauffer that concluded that functional ambulation requires strength of bilateral hip flexor scores of ≥3/5 and knee extensor ≥3/5 in at least one leg [2]. A limitation of this approach was that it described the motor status of the individual at one year as opposed to being able to predict early after injury future walking function. More recently, clinical prediction rules have been described for estimating the likelihood of independence in walking at one year post injury based upon motor and sensory status early after injury [3,4]. The benefit of these models is that they have few predictors and rely on clinical measures that are already commonly collected. van Middendorp et al. [3] established a prediction rule based on clinical measures obtained within the first 15 days post injury. This was validated on the European Multicenter Study on Human Spinal Cord Injury (EM-SCI) database of 492 persons with SCI with 1-year ambulation outcomes using the Spinal Cord Independent Measure (SCIM)[5] of the ability to walk independently indoors (scores 4−8). The five predictors included age (<65 years versus ≥65 years), L3 and S1 motor and light touch scores (see Table 1a). Area under the receiver-operating-characteristics [ROC] curve (AUC) of this clinical prediction rule was high (AUC=0.956, 95% confidence interval [CI]: 0.936−0.976). Prediction accuracy was comparable (though marginally less) in external validation studies [6,7].

Observation of a strong correlation between the L3 and S1 motor score, as well as L3 and S1 sensory scores, led to development of a more concise clinical prediction rule by Hicks et al. [4], using data from the Rick Hansen Spinal Cord Injury Registry, a Canadian multicenter SCI database. Walking outcomes at one year post injury were estimated based on measures acquired using the international standards for neurologic classification of spinal cord injury [8] within 15 days of admission with acute SCI. For this prediction rule, "independent walking" was defined based on a functional independence measure (FIM) [9] locomotor score of 6 or 7, and a mode of locomotion of either "walk" or "both walk and wheelchair." The three predictors for this rule were age at injury (<65 years versus ≥65 years), L3 motor score and S1 dermatome light touch sensory score (see Table 1b). The discriminative ability was high (AUC=0.866; 95% CI 0.816−0.916).

Further, Hicks et al. observed that their study population mostly consisted of persons with American Spinal Injury Association (ASIA) Impairment Scale [AIS] A and D [4], most likely presenting a bias on the models' predictive abilities as long-term outcomes of these individuals are generally predictable. Subsequently, Phan et al. [10] showed that prognostication of individuals with AIS B+C, for whom outcome prediction is most useful, was less accurate than that of AIS A+D. Moreover, existing models also fail to prognosticate ambulatory outcomes for those with AIS A and AIS D separately, a failure that was masked due to the merger of the two populations in previous work [10].

Table 1a
The five-variable clinical prediction rule by van Middendorp et al.

	Range of test scores	Weighted coefficient	Minimum score	Maximum score
Age ≥65	0−1	−10	−10	0
Motor score L3	0−5	2	0	10
Motor score S1	0−5	2	0	10
Light touch score L3	0−2	5	0	10
Light touch score S1	0−2	5	0	10
Total			−10	40

L, lumbar; S, sacral.

Table 1b
The three-variable clinical prediction rule by Hicks et al.

	Range of test scores	Weighted coefficient	Minimum score	Maximum score
Age ≥65	0−1	−10	−10	0
Motor score L3	0−5	2	0	10
Light touch score S1	0−2	5	0	10
Total			−10	20

L, lumbar; S, sacral.

An additional concern with previous prediction models [3,4] relates to the selected cut-off point for age. Other studies have suggested that dichotomizing patients at younger age may improve outcomes [11,12]. We hypothesized that the age of 50 would be a better cut off for prediction as opposed to 65 years; Moreover, we expected a decline in predictive accuracy for older individuals with SCI. This study was set to explore modifications of prediction rules using data from the United States Spinal Cord Injury Model Systems (SCIMS) database to allow for greater prognostication of walking recovery in persons with acute SCI.

Methods

Analysis cohort

Data were obtained from participants enrolled in the SCIMS database and admitted between January 2011 and September 2015. Individuals injured after September 2015 were not included as in October 2016 FIM data collection at the 1-year follow up was discontinued. All participants provided informed consent according to protocols approved by the institutional review boards of the SCIMS at which they enrolled.

Case inclusion criteria for the current investigation included: at least 18 years old at the time of injury, diagnosed with injuries with AIS grades of A through D at admission, had a complete neurological examination within 15 days following the injury, and had a follow-up assessment (with FIM mobility status) at least 1-year post injury.

Prediction model

Baseline assessment of severity and level of injury were completed according to the international standards for neurologic classification of spinal cord injury. To calculate the prediction rule score for our sample data, we first used the five prognostic variables that were outlined by van Middendorp et al. [3] and then calculated the score based on the three-variable rule described by Hicks et al. [4] (See Tables 1a and 1b).

Outcome measures

The primary functional outcome was defined as the ability to walk independently at 1-year post injury. Similar to previous studies [4,10], we used the locomotion component of FIM to predict independent walking ability. Independent ambulation was defined as mode of locomotion="walk" or "both walk and wheelchair" with score of 6 or 7, that is, modified or complete independence, respectively. Only individuals who had a FIM assessment ≥1 year following the injury were included.

Statistical analysis

Using both the van Middendorp and Hicks prediction rules, we calculated the score for each participant and performed a logistic regression (LR) analysis to investigate the effect of each prediction rule on the probability of walking. An ROC curve was plotted to assess the AUC in each model in order to discriminate between patients who can walk independently after one year and those who cannot.

For comparison with the Phan et al. analysis [10], we calculated the classification accuracy, sensitivity, specificity and AUC of the five-variable model, according to the individual AIS categories (A, B, C, and D) as well as AIS A +D and AIS B+C.

Subsequently, we plotted ROC curves of the different age groups and compared the AUC among them. An LR analysis with a new age cutoff was performed to recalibrate the coefficients of the prediction rule and additional ROC curves were plotted. F1-scores were calculated for the existing and the modified prediction models. We also calculated the AUC of a modified model that uses age as a continuous linear parameter.

Relationships between variables were quantified using Spearman correlation coefficients. Associations between categorial variables were tested by chi-square and Fisher's exact tests. A p value of <.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 23), except for comparison of ROC curves, which was performed with MedCalc (version 19.0.5).

Results

Cohort description

Of the 2,634 individuals admitted to a SCIMS center during the study period, a total of 639 patients with SCI fulfilled the inclusion criteria. The clinical characteristics of the individuals included in our cohort and a comparison with the reference models, that is, van Middendorp and Hicks, are described in Table 2. Clinical characteristics of

Table 2
Baseline admission characteristics compared with the reference models

	Analysis cohort (n=639)	van Middendorp et al. (n=492)	Hicks et al. (n=278)
Setting	14 SCIMS centers	19 European SCI centers	31 Canadian SCI centers
Inclusion period	January 2011 to September 2015	July 2001 to June 2008	2004 to 2014
Sex (male)	506 (79%)	381 (77%)	221 (79.5%)
Mean age at injury in years (SD, range)	43 (17, 18−91)	44 (17, 18−92)	44 (18, 18−85)
Age ≥ 65 years at time of injury	60 (9.4%)	77 (15.6%)	38 (13.6%)
Age ≥ 50 years at time of injury	232 (36.3%)		
Mean timing of examination after injury in days (SD, range)	9.8 (3.3, 1−15)	7.7 (4.7, 0−15)*	
Severity of initial neurological deficit			
AIS A	210 (33%)	240 (49%)	113 (41%)
AIS B	74 (12%)	66 (13%)	30 (11%)
AIS C	126 (20%)	76 (15%)	55 (20%)
AIS D	229 (36%)	110 (22%)	74 (27%)
Tetraplegia	378 (59%)	271 (55%)	
Outcome measure	FIM	SCIM	FIM
Independent walker at 1 year	303 (47%)	200 (41%)	123 (44%)

Data are n (%) unless otherwise stated. AIS, American Spinal Injury Association (ASIA) Impairment Scale; FIM, functional independence measure; SCIM, Spinal Cord Independence Measure; SD, standard deviation

* Assessed in the full cohort before exclusion criteria(n=1,282)

individuals included were mostly similar to those excluded from the study. One-third of the sample included were classified as AIS A, while 36% were AIS D. Within the group of individuals excluded from our cohort, 42% were AIS A compared with 22% with AIS D. Within the 1,995 individuals that were excluded from the study, 10.6% were older than 65, a nonsignificant change from the 9.4% of those included. However, within the exclusion group we noted that an early follow-up (<12 months) was associated with an older age (p<.0001): 15% of the 545 individuals with an early follow-up were ≥ 65 years, while only 8.9% of the remaining 1,450 individuals with late follow-up were older than 65.

Because the effect of age on ambulation was a key question, differences in demographics and clinical presentation based on age are presented (Table 3). Older individuals were more likely to have less severe injuries (AIS D) and sustain a cervical injury regardless of age cutoff. They were also more likely to be independent walkers at the 1-year follow-up. Gender differences were noted between age groups when 65 years was used as a cutoff but not when 50 years was used as a cutoff.

Prediction models

The AUC of the van Middendorp model based on our data was 0.919 (95% CI 0.896−0.941), compared with 0.956 in the original van Middendorp's analysis [3]. High correlations between L3 and S1 motor scores (0.908 correlation) and L3 and S1 light touch sensory score (0.782 correlation) were observed. The AUC of the Hicks three-variable model based on our data was 0.904 (95% CI 0.880−0.929), compared with 0.889 in the original study [4].

A concordance matrix with cutoff 0.5 was used to assess the degree of agreement between the predicted and the true walking status. The overall classification accuracy, sensitivity and specificity generated by each model are summarized in Table 4.

Table 3
Comparison between individuals <65 and ≥65, <50 and ≥50

	Age < 65 (n=579)	Age ≥ 65 (n=60)	p Value	Age < 50 (n=407)	Age ≥ 50 (n=232)	p Value
Sex (male)	467 (81%)	39 (65%)	.012	332 (82%)	174 (75%)	.09
Mean age at injury in years (SD)	39.9 (14)	73.2 (6)		32.3 (10)	61.7 (8)	
Mean timing of examination after injury in days (SD)	9.8 (3.2)	9.7 (3.5)		9.9 (3.2)	9.7 (3.3)	
Severity of initial neurological deficit			<.0001			<.0001
AIS A	203 (35%)	7 (12%)		174 (43%)	36 (15.5%)	
AIS B	73 (13%)	1 (2%)		59 (14%)	15 (6.5%)	
AIS C	117 (20%)	9 (5%)		72 (18%)	54 (23%)	
AIS D	186 (32%)	43 (72%)		102 (25%)	127 (55%)	
Tetraplegia	330 (57%)	48 (80%)	.002	202 (50%)	176 (76%)	<.0001
Independent walker at 1 year	263 (45%)	40 (67%)	.001	174 (43%)	129 (56%)	.002
Mean timing from injury to follow-up (SD)	521 (120)	500 (113)		521 (118)	515 (122)	

Data are n (%) unless otherwise stated. AIS, American Spinal Injury Association (ASIA) Impairment Scale; SD, standard deviation.

Table 4
Concordance matrix for the van Middendorp and Hicks models, cutoff 0.5

Model	Actual outcome (n)	Predicted outcome (n)		OCA(%)	Sensitivity(%)	Specificity(%)
		Not walk	Walk			
van Middendorp	Not walk	288	48	86.1	86.5	85.7
	Walk	41	262			
Hicks	Not walk	285	51	85	85.1	84.8
	Walk	45	258			

OCA, overall classification accuracy.

Prediction errors (van Middendorp model)

In our analysis of the van Middendorp model, there were 89 individuals (13.9%) that were not predicted correctly (Table 4). In reviewing the characteristics of these individuals, we noted that the type of prediction error (false positive or false negative) was associated with age: In the younger age group, which consisted of 45 individuals <50 years, 69% were false negatives, that is, predicted not to be able to walk independently but actually regained this ability. Within the remaining group of 44 individuals ≥50 years, 77% were false positives, that is, predicted to walk but did not.

A chi-square analysis confirmed that individuals <50 years of age were more prone to be erroneously predicted not to walk, while individuals ≥50 were more likely to be erroneously predicted to walk ($p< .0001$).

AIS classification analysis (van Middendorp model)

LR analyses based on the van Middendorp model were performed individually for each of the AIS classifications (A, B, C, and D), as well as for the AIS A+D and B+C subgroups. Analyses of the Hicks model showed strikingly similar results and are therefore not presented.

A concordance matrix with cutoff set at 0.5, the overall classification accuracy, sensitivity and specificity, as well as the AUC, were calculated separately for each subgroup (Table 5). Similar to the analysis from Phan et al. [10], the prediction accuracy for AIS A+D was superior to AIS B+C ($p<.0001$).

Age classification analysis

The individuals in our cohort were classified according to the different age groups (by decade starting at age 18), similar to work performed elsewhere [13]. AUCs were calculated separately for each subgroup (Table 6).

Prediction accuracy of independent ambulation in both models was highest for the three younger age groups. In an analysis of the van Middendorp model on our SCIMS data,

Table 6
AUC of the van Middendorp and Hicks model for the different age categories

Age	N (%)	van Middendorp AUC (95% CI)	Hicks AUC (95% CI)
18−29	206 (32%)	0.948 (0.913−0.984)	0.945 (0.904−0.972)
30−39	93 (15%)	0.947 (0.902−0.991)	0.949 (0.882−0.984)
40−49	108 (17%)	0.942 (0.900−0.983)	0.929 (0.863−0.969)
≥50	232 (36%)	0.855 (0.802−0.908)	0.815 (0.757−0.872)

AUC, area under the receiver operating characteristics curve; CI, confidence interval.

Table 5
Concordance matrices (cutoff 0.5) and predictive accuracy for AIS A, B, C, and D individually, and AIS A+D and B+C cohorts, based on the van Middendorp logistic regression model

AIS grade	Actual outcome	Predicted		OCA (%)	Sensitivity (%)	Specificity (%)	AUC (95% CI)
		Cannot walk	Walk				
A (n=210)	Cannot walk	195	3	96.2	58.3	98.5	0.899 (0.775−1.0)
	Walk	5	7				
B (n=74)	Cannot walk	48	5	81.1	57.1	90.6	0.809 (0.685−0.932)
	Walk	9	12				
C (n=126)	Cannot walk	35	23	66.7	72.1	60.3	0.702 (0.609−0.795)
	Walk	19	49				
D (n=229)	Cannot walk	1	26	88.2	99.5	3.7	0.657 (0.528−0.786)
	Walk	1	201				
A+D (n=439)	Cannot walk	200	25	92	95.3	88.9	0.950 (0.927−0.973)
	Walk	10	204				
B+C (n=200)	Cannot walk	87	24	72.0	64.0	78.4	0.779 (0.714−0.843)
	Walk	32	57				

AIS, American Spinal Injury Association (ASIA) Impairment Scale; AUC, area under the receiver operating characteristics curve; CI, confidence interval; OCA, overall classification accuracy.

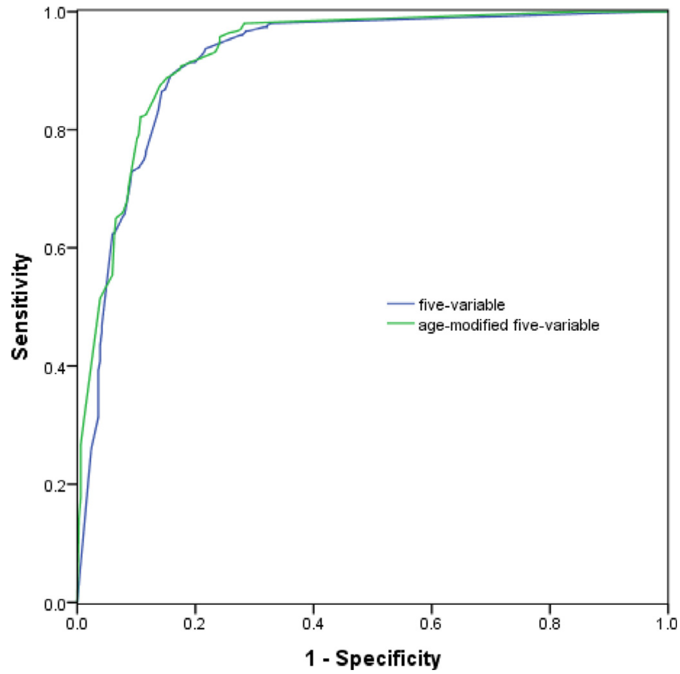

Fig. 1. Area under the operating curve for the five-variable model (blue line) and the age-modified five-variable model (green line).

the differences in AUC between each of the three younger age groups (18−29, 30−39 and 40−49), and the ≥50 age group were all statistically significant, with p=.003, p=.008, p=.010, respectively. We obtained similar results using the Hicks model on our data, with p=.0001, p=.0003 and p=.002, respectively.

Modification of the age parameter

For the van Middendorp five-variable model, using a cutoff age of 50 instead of 65 improved the AUC to 0.929 (95% CI 0.910−0.949), a statistically significant increase from 0.919 (p=.005). A comparison of the ROC curves of the original five-variable model and the age-modified five-variable model is presented in Fig. 1.

Based on an LR analysis of the new age-modified five-variable prediction rule, the estimated probability of being able to walk independently one year following the injury was:

$$\frac{e^{-2.44+0.16\ \times score}}{1+e^{-2.44+0.16\ \times score}}$$

A concordance matrix for the modified prediction rule is presented in Table 7.

A comparison of the five-variable age-modified rule with the original five-variable rule indicated that AUC of AIS A increased from 0.899 to 0.914 (p=.055), AIS B from 0.809 to 0.856 (p=.005), AIC C changed from 0.702 to 0.719 although this change was not statistically significant (p=.44), and AIS D increased from 0.657 to 0.732, with a trend towards significance (p=.06). The combined A+D group did not show a significant difference between the original model and the modified age model, nor did B+C.

Table 7
Concordance matrix for the modified five and three variable models, cutoff 0.5

Model	Actual outcome (n)	Predicted outcome (n)	
		Not walk	Walk
Modified five-variable	Not walk	292	44
	Walk	44	259
Modified three-variable	Not walk	292	44
	Walk	47	256

For the Hicks et al. model, using 50 years of age as the cutoff resulted in an AUC of 0.899; This was not a significant change from the AUC of 0.904 we obtained for the original Hicks model with age 65 as the cutoff (p=.56). We then sought to modify the prediction rule, as the weighted coefficients that were previously used for the three-variable rule (−10 for age, 2 for motor score, 5 for light touch score) were obtained from LR of the five-variable rule and were optimized for it.

Following an LR analysis of the coefficients, we concluded that the best representation of a simplified three-variable prediction rule in our cohort was:

$$score = L3\ motor\ score + S1\ light\ touch\ score + \begin{cases} -2 & age \geq 50 \\ 0 & otherwise \end{cases}$$

The probability of walking based on LR analysis the newly modified three-variable rule was:

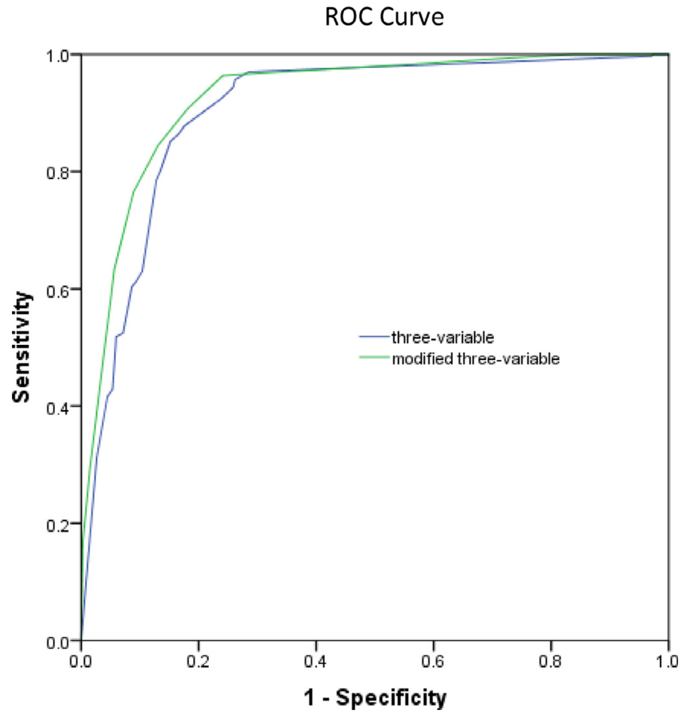

Fig. 2. Area under the operating curve for the three-variable model (blue line) and the modified three-variable model with new coefficients (green line).

$$\frac{e^{-2.22+0.88\ \times score}}{1+e^{-2.22+0.88\ \times score}}$$

This prediction rule showed excellent discrimination between patients who were able to walk independently and those who were not (AUC 0.927, 95% CI 0.907 −0.947). A statistically significant change from the original AUC of 0.904 (p=.001). Fig. 2 shows a comparison of ROC curves of the original three-variable Hicks model and our modified three-variable model. The concordance matrix of the modified three-variable LR model is shown in Table 7.

F1-scores were calculated for the original and modified models and the obtained scores were very similar. The F1-scores were 0.855 and 0.849 in the original and modified five-variable models, respectively, and 0.843 and 0.849 in the original and modified three-variable models, respectively.

As age is continuous by its nature, we attempted to replace the dichotomized parameter with a continuous linear variable. The equation for the new variable was:

$$age_{score} = 4-0.2\ \times age$$

Using the new score, a 20 years old would score 0 and a 70 years old would score −10, fitting the values in the original prediction models. The AUC of the five-variable and three-variable rules using age as a linear parameter were 0.923 and 0.909, respectively. These improvements were not statistically significant.

Discussion

In this study, we investigated the effects of age and injury severity on the performance of the van Middendorp and Hicks multivariate LR prediction models utilizing data from the SCIMS database. In the sections describing classification according to the different AIS groups and the analysis of the prediction errors, merely the original van Middendorp model was described since the Hicks model showed remarkably similar results.

When individuals with different injury severities were grouped together, both models achieved a high predictive accuracy for discrimination between those who will be able to walk at one year following the injury and those who will not. However, similar to the results obtained by Phan et al. [10], when we applied the five-variable prediction model to the individual AIS classifications (A, B, C and D), each classification had a lower predictive accuracy than the combined cohort. We also found (similarly to Phan et al.), that the failure to effectively prognosticate AIS A and AIS D separately was masked by amalgamating the two patient populations. In the analysis of the five-variable model in the SCIMS database, prognostication for AIS A was impaired (AUC 0.899) with low sensitivity (58.3%), and prognostication for AIS D was markedly impaired (AUC 0.657) with extremely low specificity (3.7%). When combined into a single cohort of AIS A+D, prognostication strikingly improved (AUC 0.950), effectively masking the actual poor prognostication of the model for the separate AIS classifications.

Furthermore, the five-variable model demonstrated a lower predictive accuracy for AIS B+C (AUC 0.779) compared with AIS A+D (AUC 0.950). This effect is expected as prognosis of AIS B and AIS C is more variable while outcomes are usually more certain in AIS A and AIS D. However, due to the high proportion of A+D patients in our cohort (68.7%), the model that consists of all AIS grades has a misleadingly high prediction accuracy.

These findings reflect some of the main issues with the complex problem of prognostication of ambulation following SCI. Although the majority of individuals with AIS A have unfavorable ambulation outcomes, there are some for whom AIS grades will improve and a small group, specifically those with paraplegia, may even achieve independent ambulation [14,15]. It is reported that 5.8% to 13.9% of individuals initially diagnosed with cervical AIS A tetraplegia within the first 30 days convert to motor incomplete status at one year, although only a smaller percent may regain ambulation [16−18].

The opposite is seen with AIS D, as ambulation is expected, yet not all individuals achieve independent ambulation, especially those older than 50 [11,19]. As mentioned earlier, individuals with AIS B or AIS C have a more variable outcome, adding to the difficulty of correctly predicting ambulation [15].

The ineffectiveness of the models to predict independent ambulation when evaluating within a single AIS classification level, suggests that future prediction rules may benefit from the addition of variables that would represent the different AIS grades. Using more advanced analytical methods from the data sciences fields, as described further in this paper, may also improve prediction accuracy for the individual AIS grades.

In the second part of this study, we examined the effect of age on prediction rules. At first, we investigated the different types of prediction errors in our cohort. We noted that individuals older than 50 were more likely to be erroneously predicted to walk, while individuals <50 had a higher chance of being erroneously predicted not to walk.

In the van Middendorp and Hicks models, as well as in several subsequent studies [12,20], the age of 65 was a dichotomized variable. This age division is common and is used to denote the “elderly” population [21−23]. The age of 50 as a cutoff for predicting SCI outcomes has also been widely used before [11,24−26]. Lowering the cutoff age in the prediction algorithm has been previously suggested [12].

We observed a decline in prediction accuracy as age increases, emphasizing the fact that age is important in prediction of independent ambulation. Similar to other medical conditions, older individuals with a SCI tend to have worse functional outcomes compared with younger individuals [21,27,28]. Therefore, the recovery course of the older SCI patient is more variable, and it is more difficult to predict who will or will not walk. Another factor that probably contributed to the decline in accuracy is the dichotomization of the age parameter at 65. In the case of two theoretical patients, aged 64 and 66, with the same L3 and S1 motor and sensory scores, the slightly younger person will be predicted to have a significantly higher chance of independent ambulation compared with the older person (even 70% vs. 20% in our simulations).

In the five-variable prediction model, prediction accuracy significantly improved when the dichotomized age parameter was reduced to 50 instead of 65. With the new age cutoff at 50, a significant increase in AUC was also seen in the subgroup of individuals with AIS B grade injury, and to a lesser extent in AIS A and AIS D. As previously noted [4], we also observed high collinearity between predictors in the five-variable model. Since multicollinearity is known to adversely affect prediction [29,30], no further modifications of the five-variable model were performed.

The original three-variable prediction model did not show a significant change in AUC when age was dichotomized at 50. Subsequently, we conducted a new multivariate LR analysis to obtain the new coefficients for the three variables. Using the new coefficients, we derived a very simple prediction rule for the three variables, described in the results section. This rule showed excellent prediction capabilities, with an AUC of 0.927.

In an external validation study of the van Middendorp model that was performed by Malla [6], an LR analysis of the five-variable rule yielded coefficients that were quite different from the original coefficients. Nevertheless, AUC calculated using the re-estimated coefficients was still adequate and was comparable with the original AUC. Clearly, there are additional modifications that can be made to optimize the prediction, however, limitations of LR, such as collinearity and the complex interactions between predictors, will probably interfere with further major optimizations of prediction rules [31−33].

In a recent study, DeVries et al. suggested that F1-scores may be superior to the commonly used AUCs in prediction of ambulation following SCI, especially when the data are imbalanced [20]. Nevertheless, in our study, in which the data is rather balanced (with a similar number of positive and negative instances) F1-scores remain unchanged for both the original and modified models. Indeed, work by Saito et al. demonstrated that F1-scores are more accurate when predicting performance of imbalanced data, but when datasets are balanced, it is comparable to AUC studies [34]. Furthermore, DeVries et al. showed that an increase in false negative predictions is not well detected in AUC, while the F1-score measure is more sensitive in this scenario [20]. By lowering the cut-off age in the modified prediction models, we are in fact increasing the number of false negatives, but this increment was minimal and insignificant.

Age is a continuous parameter. In an additional attempt to improve prediction accuracy, we chose an implementation of a linear continuous variable for age. A linear parameter was chosen to maintain model simplicity, as it was one of the main goals of the van Middendorp and Hicks prediction models. Prognostication did not significantly improve using linear score instead of a dichotomized parameter for age. This is evidence for the nonlinear effect of age. While out of the scope of this study, additional implementations of the age parameter, for example as a sigmoid variable, should be explored.

In addition to the regression models described above, other methodologies have been described for prediction of outcomes following SCI. Wilson et al. used both logistic and linear regression, and a combination of clinical and imaging data to predict FIM motor scores at 1-year post injury [35]. Tanadini et al. developed a novel technique, unbiased recursive partitioning regression with conditional inference trees, to predict upper extremity motor recovery among individuals with SCI [33]. Facchinello et al. also utilized regression tree analysis for predicting functional outcomes following SCI [36]. Belliveau et al. and Rowland et al. used artificial neural networks to predict ambulation and functional outcomes [12,37]. Regression trees and neural networks are supervised machine learning algorithms. Very recently, DeVries et al. developed an unsupervised machine learning algorithm for prognostication of walking ability in SCI patients [20].

Both machine-learning based algorithms by Belliveau et al. [12] and DeVries et al. [20] use the dichotomized age variable with a cutoff of 65. This highlights the importance of the age variable in the prediction models, and our findings suggest that lowering the age cutoff to 50 may further improve their prediction accuracy.

We also anticipate that prediction models may be able to achieve a higher accuracy by using data science methodologies, including but not limited to support vector machines, classification trees and deep neural networks if dataset size permits.

Strengths of our study include the coverage of SCIMS, a large multicenter database that represents about 6% of new SCI cases in the United States each year. Furthermore, although previous studies referred to the impact of age on functional outcomes, this is the first paper that provides an extensive analysis of the age parameter within prediction models.

This study has several limitations. Although the cohort in our study is larger compared to the previous prediction studies, the size of the cohort is still limited. In addition, reducing the cutoff age to 50 does not solve the dichotomization problem, that is, in prognostication of individuals around the age of 50 we will still observe large variations in prediction accuracy. Further, only 9.4% of individuals in our study were older than 65 compared with 14% to 17% in the previously mentioned prediction papers [3,4,6,7]. The low proportion observed in our cohort may be explained by the fact that only individuals whose timing of FIM assessment was more than one year following the injury were included. We observed a statistically significant relationship between older age and earlier examination, and since we only included patients who had a FIM assessment one year and later, this probably explains the higher proportion of younger individuals in our cohort. Furthermore, in at least one of the other prediction studies there was a substantial higher proportion of persons with tetraplegia, which tend to be older [6].

Conclusions

Age is an important factor in prognosticating of independent ambulation following SCI. We have shown that using the age of 50 instead of 65 is more accurate for prediction of independent ambulation. Since earlier prediction studies have mostly used the age 65 as a dichotomized variable, this is a significant consideration for future studies. In addition, we have validated previous results and demonstrated that prediction rules are less effective at prognosticating patients when evaluating within a single AIS classification level. Further, results demonstrate prognostication of persons with AIS B+C, for whom a clinical prediction model has arguably greater clinical utility, is less accurate than those with AIS A+D

As further major improvements in prediction of ambulation and functional outcomes may be limited in traditional statistical analysis, including logistic regression studies, to further improve prediction rules, advanced methodologies using machine learning should be explored. In particular, these methodologies would enable further investigation of the age parameter.

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References

[1] Ditunno PL, Patrick M, Stineman M, Ditunno JF. Who wants to walk? Preferences for recovery after SCI: a longitudinal and cross-sectional study. Spinal Cord 2008;46(7):500–6. https://doi.org/10.1038/sj.sc.3102172.

[2] Hussey RW, Stauffer ES. Spinal cord injury: requirements for ambulation. Arch Phys Med Rehabil 1973;54(12):544–7. https://www.ncbi.nlm.nih.gov/pubmed/4759444.

[3] Van Middendorp JJ, Hosman AJ, Donders ART, et al. A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: a longitudinal cohort study. Lancet 2011;377(9770):1004–10. https://doi.org/10.1016/S0140-6736(10)62276-3.

[4] Hicks KE, Zhao Y, Fallah N, et al. A simplified clinical prediction rule for prognosticating independent walking after spinal cord injury: a prospective study from a Canadian multicenter spinal cord injury registry. Spine J 2017;17(10):1383–92. https://doi.org/10.1016/j.spinee.2017.05.031.

[5] Catz A, Itzkovich M, Tesio L, et al. A multicenter international study on the Spinal Cord Independence Measure, version III: Rasch psychometric validation. Spinal Cord 2007;45(4):275–91. https://doi.org/10.1038/sj.sc.3101960.

[6] Malla R. External validation study of a clinical prediction rule for ambulation outcomes after traumatic spinal cord injury. [Thesis].

Texas Medical Center Dissertations: The University of Texas School of Public Health; 2013.
[7] Silfhout L Van, Peters AEJ, Graco M, Schembri R, Nunn AK, Berlowitz DJ. Validation of the Dutch clinical prediction rule for ambulation outcomes in an inpatient setting following traumatic spinal cord injury. Spinal Cord 2016;54(8):614–8. https://doi.org/10.1038/sc.2015.201.
[8] International standards for neurological classification of spinal cord injury. Atlanta, GA: American spinal injury association; 2015. Revised.
[9] Keith RA, Granger C V, Hamilton BB, Sherwin FS. The functional independence measure: a new tool for rehabilitation. Adv Clin Rehabil 1987;1:6–18.
[10] Phan P, Budhram B, Zhang Q, et al. Highlighting discrepancies in walking prediction accuracy for patients with traumatic spinal cord injury: an evaluation of validated prediction models using a Canadian Multicenter Spinal Cord Injury Registry. Spine J 2019;19(4):703–10. https://doi.org/10.1016/j.spinee.2018.08.016.
[11] Penrod LE, Hegde SK, Ditunno JF. Age effect on prognosis for functional recovery in acute, traumatic central cord syndrome. Arch Phys Med Rehabil 1990;71(12):963–8.
[12] Belliveau T, Jette AM, Seetharama S, et al. Developing artificial neural network models to predict functioning one year after traumatic spinal cord injury. Arch Phys Med Rehabil 2016;97(10):1663–8. https://doi.org/10.1016/j.apmr.2016.04.014.
[13] Couris CM, Guilcher SJT, Munce SEP, et al. Characteristics of adults with incident traumatic spinal cord injury in Ontario, Canada. Spinal Cord 2010;48(1):39–44. https://doi.org/10.1038/sc.2009.77.
[14] Wilson JR, Cadotte DW, Fehlings MG. Clinical predictors of neurological outcome, functional status, and survival after traumatic spinal cord injury: a systematic review. J Neurosurg Spine 2012;17(Suppl1):11–26. https://doi.org/10.3171/2012.4.AOSPINE1245.
[15] Scivoletto G, Tamburella F, Laurenza L, Torre M, Molinari M. Who is going to walk? A review of the factors influencing walking recovery after spinal cord injury. Front Hum Neurosci 2014;8:141. https://doi.org/10.3389/fnhum.2014.00141.
[16] Marino RJ, Burns S, Graves DE, Leiby BE, Kirshblum S, Lammertse DP. Upper- and lower-extremity motor recovery after traumatic cervical spinal cord injury: an update from the national spinal cord injury database. Arch Phys Med Rehabil 2011;92(3):369–75. https://doi.org/10.1016/j.apmr.2010.09.027.
[17] Spiess MR, Müller RM, Rupp R, Schuld C, Van Hedel HJA. Conversion in ASIA impairment scale during the first year after traumatic spinal cord injury. J Neurotrauma 2009;26(11):2027–36. https://doi.org/10.1089/neu.2008.0760.
[18] Kirshblum SC, Botticello AL, Dyson-Hudson TA, Byrne R, Marino RJ, Lammertse DP. Patterns of sacral sparing components on neurologic recovery in newly injured persons with traumatic spinal cord injury. Arch Phys Med Rehabil 2016;97(10):1647–55. https://doi.org/10.1016/j.apmr.2016.02.012.
[19] Aito S, D'Andrea M, Werhagen L, et al. Neurological and functional outcome in traumatic central cord syndrome. Spinal Cord 2007;45:292–7. https://doi.org/10.1038/sj.sc.3101944.
[20] DeVries Z, Hoda M, Rivers CS, et al. Development of an unsupervised machine learning algorithm for the prognostication of walking ability in spinal cord injury patients. Spine J 2020;20(2):213–24. https://doi.org/10.1016/j.spinee.2019.09.007.
[21] Furlan JC, Fehlings MG. The impact of age on mortality, impairment, and disability among adults with acute traumatic spinal cord injury. J Neurotrauma 2009;26(10):1707–17. https://doi.org/10.1089/neu.2009-0888.
[22] Jackson AP, Haak MH, Khan N, Meyer PR. Cervical spine injuries in the elderly: acute postoperative mortality. Spine (Phila Pa 1976) 2005;30(13):1524–7. https://doi.org/10.1097/01.brs.0000167822.75063.8c.
[23] Irwin ZN, Arthur M, Mullins RJ, Hart RA. Variations in injury patterns, treatment, and outcome for spinal fracture and paralysis in adult versus geriatric patients. Spine (Phila Pa 1976) 2004;29(7):796–802. https://doi.org/10.1097/01.BRS.0000119400.92204.B5.
[24] Whiteneck G, Tate D, Charlifue S. Predicting community reintegration after spinal cord injury from demographic and injury characteristics. Arch Phys Med Rehabil 1999;80(11):1485–91.
[25] McDonald JW, Sadowsky C. Spinal-cord injury. Lancet 2002;359(9304):417–25. https://doi.org/10.1016/S0140-6736(02)07603-1.
[26] Oleson CV, Marino RJ, Leiby BE, Ditunno JF. Influence of age alone, and age combined with pinprick, on recovery of walking function in motor complete, sensory incomplete spinal cord injury. Arch Phys Med Rehabil 2016;97(10):1635–41. https://doi.org/10.1016/j.apmr.2016.01.024.
[27] Devivo MJ. Epidemiology of traumatic spinal cord injury : trends and future implications. Spinal Cord 2012;50(5):365–72. https://doi.org/10.1038/sc.2011.178.
[28] Scivoletto G, Morganti B, Ditunno P, Ditunno JF, Molinari M. Effects on age on spinal cord lesion patients' rehabilitation. Spinal Cord 2003;41:457–64. https://doi.org/10.1038/sj.sc.3101489.
[29] Midi H, Sarkar SK, Rana S. Collinearity diagnostics of binary logistic regression model. J Interdiscip Math 2010;13(3):253–67. https://doi.org/10.1080/09720502.2010.10700699.
[30] Allison P. Multiple regression: a primer. Pine Forge Press; 1999.
[31] Cross SS, Harrison RF, Kennedy RL. Introduction to neural networks. Lancet 1995;346(8982):1075–9. doi:10.5555/URI:PII:S0140673695917462.
[32] Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: logistic regression. Perspect Clin Res 2017;8:148–51. https://doi.org/10.4103/picr.PICR_87_17.
[33] Tanadini LG, Steeves JD, Hothorn T, et al. Identifying homogeneous subgroups in neurological disorders: unbiased recursive partitioning in cervical complete spinal cord injury. Neurorehabil Neural Repair 2014;28(6):507–15. https://doi.org/10.1177/1545968313520413.
[34] Saito T, Rehmsmeier M. The precision-recall plot is more informative than the ROC plot when evaluating binary classifiers on imbalanced datasets. PLoS One 2015;10(3). https://doi.org/10.1371/journal.pone.0118432.
[35] Wilson JR, Grossman RG, Frankowski RF, et al. A clinical prediction model for long-term functional outcome after traumatic spinal cord injury based on acute clinical and imaging factors. J Neurotrauma 2012;29(13):2263–71. https://doi.org/10.1089/neu.2012.2417.
[36] Facchinello Y, Beauséjour M, Richard-Denis A, Thompson C, Mac-Thiong J-M. The use of regression tree analysis for predicting the functional outcome following traumatic spinal cord injury. J Neurotrauma 2017. https://doi.org/10.1089/neu.2017.5321. [Epub].
[37] Rowland T, Ohno-Machadomd L, Ohrn A. Comparison of multiple prediction models for ambulation following spinal cord injury. Proceedings AMIA Symp 1998:528–32.