Oral S-ketamine effective after deep brain stimulation in severe treatment-resistant depression and extensive comorbidities

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ORIGINAL RESEARCH

Traditional Cardiovascular Risk Factors Strongly Underestimate the 5-Year Occurrence of Cardiovascular Morbidity and Mortality in Spinal Cord Injured Individuals

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Abstract

Objectives: To explore whether traditional models of cardiovascular disease (CVD) risk prediction correctly predict CVD events across a median 5.7-year follow-up period in individuals with spinal cord injury (SCI) and whether adding SCI-related characteristics (ie, lesion level) to the prediction model can improve the prognostic value.

Design: Retrospective analysis of patient records.

Setting: Observation at the start of active rehabilitation of participants in a multicenter cohort study, "Restoration of (Wheelchair) Mobility in SCI Rehabilitation," in the Netherlands.

Participants: Patients with SCI (N=200) The patients were 74% men, aged 40±14 years, and with an American Spinal Injury Association (ASIA) impairment score of A through D. Forty percent had tetraplegia, and 69% were motor complete.

Interventions: Risk profiling/not applicable.

Main Outcome Measures: Survival status and cardiovascular morbidity and mortality qwere obtained from medical records. Five-year Framingham Risk Scores (FRS) and the FRS ability to predict events assessed using receiver operating characteristic (ROC) curves with corresponding areas under the curve (AUC) and 95% confidence intervals (CI). Kaplan-Meier curves and the log-rank test were used to assess the difference in clinical outcome between participants with an FRS score lower or higher than the median FRS score for the cohort. SCI-related factors associated with CVD events, ASIA impairment, motor completeness, level of injury, and sports participation before injury were explored using univariate and multivariate Cox proportional hazard regression.

Results: The median 5-year FRS was 1.36%. Across a median follow-up period of 5.7 years, 39 developed a CVD event, including 10 fatalities. Although the FRS markedly underestimated the true occurrence of CVD events, the Kaplan-Meier curves and the log-rank test showed that the risk ratio for individuals with an FRS score less than the median FRS (eg, low risk) versus a score greater than the median FRS (high risk) was 3.2 (95% CI, 1.6-6.5; $P=.001$). Moreover, ROC with corresponding AUCs suggests acceptable accuracy of the FRS to identify individuals with increased risk for future CVD events (ROC AUC of 0.71; 95% CI, 0.62-0.82). Adding ASIA impairment (0.74; 95% CI, 0.66-0.82), motor

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impairment (0.74; 95% CI, 0.66-0.83), level of injury (0.72; 95% CI, 0.63-0.81), or active engagement in sport before injury (0.72; 95% CI, 0.63-0.88) to the FRS did not improve the level of discrimination.

Conclusions: Our 5.7-year retrospective study reveals that cardiovascular risk factors and risk models markedly underestimate the true risk for CVD events in individuals with SCI. Nonetheless, these markers successfully distinguish between SCI individuals at high versus low risk for future CVD events. Our data may have future clinical implications, both related to (cutoff values of) CVD risk factors, but also for (earlier) prescription of (non)pharmacologic strategies against CVD in SCI individuals.

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Cardiovascular and cerebrovascular diseases (CVD) have become a major concern for individuals with spinal cord injury (SCI). CVD constitutes 26.7% of all-cause mortality[1] and is responsible for the greatest proportion of morbidity and mortality in the SCI population.[2,3] Assessing a person's risk for developing CVD is typically performed using traditional cardiovascular risk factors and, subsequently, risk is predicted using widely available algorithms such as the Framingham Risk Score (FRS). Because these algorithms are based on nondisabled populations, mainly including middle-aged and older white men from Western countries, one may question its generalizability to other populations,[4-6] including SCI.

Interpretation of traditional CVD risk factors is complicated in the SCI population. For example, elevated arterial blood pressure is recognized as an independent risk factor for CVD in the general population. However, individuals with SCI, particularly those with high thoracic and cervical lesions, exhibit low resting arterial blood pressure that results from autonomic disturbances.[7,8] Furthermore, despite the increased risk for CVD in individuals with SCI, classic cardiovascular risk factors, such as low-density lipoprotein, plasma triglycerides, and fasting glucose, are not different between the SCI and nondisabled populations.[9-15] This raises the question of whether traditional cardiovascular risk factors and risk prediction models that use these risk factors can accurately predict future CVD in individuals with SCI.

The aim of this study was to examine the predictive value of traditional risk factors for future CVD using the FRS in individuals with SCI. For this purpose, we performed an observational cohort study to determine whether the FRS accurately predicts cardiovascular morbidity and mortality across a median of 5.7 years after discharge from inpatient rehabilitation in people with SCI. We also sought to determine whether adding SCI-related characteristics (ie, lesion level) to the FRS can improve the prognostic value of the FRS. Based on the argument we raised earlier, which suggests that SCI may affect interpretation of traditional CVD risk factors, we expect that the FRS underestimates future CVD and that adding SCI characteristics would improve the prognostic value of the FRS in individuals with SCI.

List of abbreviations:

ASIA	**American Spinal Cord Injury Association**
AUC	**area under the curve**
CI	**confidence interval**
CVD	**cardiovascular and cerebrovascular disease**
FRS	**Framingham Risk Score**
HDL	**high-density lipoprotein**
ROC	**receiver operating characteristic**
SCI	**spinal cord injury**

Methods

Participants

The data used in this study were collected as part of the Dutch prospective multicenter cohort study "Restoration of (Wheelchair) Mobility in SCI Rehabilitation"[16] and obtained prospectively. The medical ethics committee of the Stichting Revalidatie Limburg/Institute for Rehabilitation Research in Hoensbroek approved the research protocol in 1999, and the medical ethics committee of the University Hospital of Utrecht approved the follow-up research protocol in 2006. This resulted in a median follow-up period of 5.7 years (interquartile range, 5.2-6.4y). Participants (n=225) were recruited from 8 specialist SCI rehabilitation centers in the Netherlands. Written informed consent was obtained from all participants before the start of this study (fig 1). Inclusion criteria required participants to have traumatic or nontraumatic SCI classified as A, B, C, or D on the American Spinal Cord Injury Association (ASIA) impairment scale,[17] be expected to remain wheelchair-dependent, show no evidence of preexisting cardiovascular diseases, and be aged between 18 and 65 years.

Experimental design

The observation period began at the start of active rehabilitation when the participants could remain seated for a minimum of 3 hours (3 months after injury). Participants were asked to eat only a light meal; to abstain from consuming tobacco, caffeine, and alcohol at least 2 hours before testing; and to void their bladders. All participants continued to take their regular medication. Blood samples were collected and analyzed for serum concentrations of total and high-density lipoprotein (HDL) cholesterol. Resting arterial blood pressure was measured by a physician using a manual sphygmomanometer while participants remained seated in their wheelchair.[18] Participants were considered to have diabetes when the primary care physician reported this or when medical records indicated the participant was taking diabetes medication. Lesion characteristics (level and completeness) were assessed by a specialist physician according to the International Standards for Neurological Classification of Spinal Cord Injury.[19] Survival status and cardiovascular morbidity and mortality were obtained from medical records across the 5.7-year follow-up after discharge from inpatient rehabilitation. The follow-up period of some individuals included in our analysis was longer than 5 years. All of these individuals did, however, develop CVD within 5 years. In some instances, they developed additional cardiovascular complications after the 5 years (fig 2). Cardiovascular complications and causes of death were identified according to the International Classification of Diseases and Related Disorders, 10th revision, volume 2 (codes I00-I99).

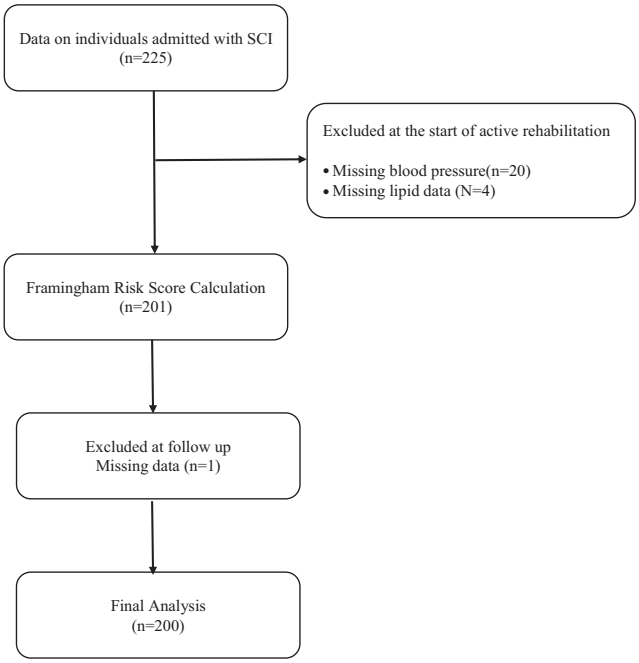

Fig 1 Flow diagram of subject inclusion and retention from the initial measurement period up to follow-up.

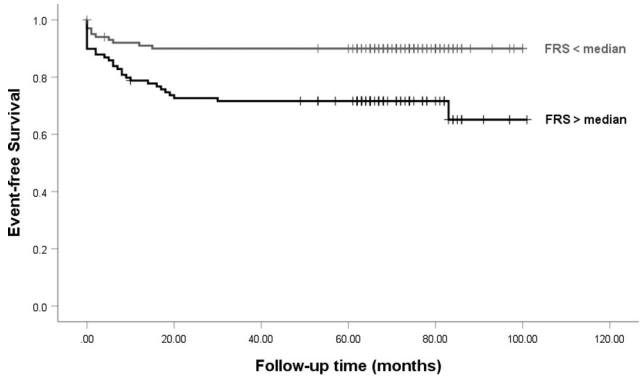

Fig 2 Survival analysis for individuals with SCI (N = 200) across a 5-year follow-up period. Subjects were divided into individuals with an FRS of 1.36 or less (ie, median; gray line, 10 CVD events) and those with an FRS greater than 1.36 (ie, median; black line, 29 CVD events).

FRS

The FRS calculator is a method that uses equations derived from large prospective cohort studies such as the Framingham Heart Study and Framingham Offspring Study[20] to estimate the risk of developing CVD events in the proceeding 5 to 10 years.[21] CVD endpoints using the FRS prediction model can be defined as all coronary events (eg, myocardial infarction, coronary death, coronary insufficiency, and angina), CVD (eg, ischemic stroke, hemorrhagic stroke, and transient ischemic attack), rheumatic disease, heart arrhythmia, valvular disease, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis.[21] Compared with other risk algorithms, the FRS calculator is able to discriminate between those who will and will not develop a CV event[22-26] and has been validated in multiple populations.[27] For every individual, at the start of active rehabilitation, we calculated their 5-year risk score to develop CVD using the FRS calculator from the Centre for Cardiovascular Sciences at the University of Edinburgh.[28] This particular tool is a spreadsheet-based calculator that uses age, sex, systolic blood pressure, total cholesterol, HDL cholesterol, smoking status, and diabetes status to estimate the percentage-based risk of developing CVD over a selected number of years.

Statistical analysis

Participant characteristics were summarized by means and standard deviations for normally distributed continuous variables, medians with interquartile ranges for not normally distributed continuous variables, and percentages for categorical variables. Kaplan–Meier curves and the log-rank test were used to assess the difference in clinical outcome between participants with an FRS greater than 1.36 (median score for the cohort) and an FRS of 1.36 or less. For the context of this study, the group of participants with an FRS of 1.36 or less will be referred to as the "low FRS" group and those with an FRS greater than 1.36 will be referred to as the "high FRS" group. The endpoint was a CV event or CV mortality. Patients who did not reach the endpoint were censored at the end of the observation period. Hazard ratios with 95% confidence intervals (CI) were calculated using Cox proportional hazard regression.

The FRS ability to predict events in patients with SCI was assessed using receiver operating characteristic (ROC) curves with corresponding areas under the curve (AUC) and 95% CIs. SCI-related factors associated with CVD events were explored using univariate Cox proportional hazard regression. Severity of injury, as indicated by ASIA impairment, motor completeness, and level of injury, was included as a factor in the regression analysis owing to its direct association with impaired CV function.[7,8] Considering the beneficial effects of physical activity on CV health in able bodied individuals, we also decided to include sports participation before injury as a factor and explore its influence on predicting CVD after injury. These factors were separately added to the FRS and $X^{*}\beta$ values were calculated using multivariate Cox proportional hazard regression. Using the $X*\beta$ values, ROC curves with corresponding AUCs and 95% CIs were determined. All statistical analyses were performed in SPSS 20.0.[a] A P value less than .05 was considered statistically significant.

Results

Survival analysis

Table 1 summarizes the baseline characteristics and table 2 indicates the cardiovascular events for the 200 individuals included in the analysis. In the 5.7 years after discharge from inpatient rehabilitation, a total of 39 participants (19.5%) developed a CVD event, 10 of which were fatal events. Deep venous thrombosis was the most commonly observed CVD event with 5% of the study participants having an incidence of deep venous thrombosis.

Figure 2 shows the survival analysis for the groups with a low FRS (≤1.36 [median]) and a high FRS (>1.36). One individual was excluded from the survival analysis owing to missing follow-up data. We found a significant difference in CVD events between both groups (hazard ratio for high FRS vs low FRS, 3.2; 95% CI, 1.6-6.5; $P = .001$). A total of 10 and 29 CVD events were recorded in the low and high FRS groups, respectively.

Table 1 Baseline characteristics of participants at start of the observation period

Characteristic	Value
Age, y	40 (14)
Sex, male	149 (74)
Smoking status, yes	46 (23)
Systolic blood pressure, mmHg	118 (16)
Cholesterol, mmol/L	
HDL	1.02
Total	4.70
Diabetes	3 (2)
BMI, kg/m^2	22.8 (3.8)
ASIA impairment scale (n = 197)	
A	91 (46)
B	47 (24)
C	42 (21)
D	17 (9)
Motor impairment, complete	139 (69)
Lesion level, tetraplegia	80 (40)
Performed sports before injury, yes	127 (63)
FRS, 5-year probability, %	1.36 (0.14-4.49)

NOTE. Data are presented as mean ± SD, median (Q25-Q75), or n (%).
Abbreviation: BMI, body mass index.

FRS prediction model using SCI characteristics

Table 3 illustrates the calculated hazard ratios with 95% CIs, regression coefficients, and statistical significance for various SCI characteristic individual predictors for CVD events. Each factor was assessed through separate univariate Cox regressions. Older age at the time of SCI (1.05; 95% CI, 1.02-1.07; $P<.001$), a higher 5-year FRS (1.10; 95% CI, 1.05-1.16; $P<.001$), and no participation in sport activities before the SCI injury (1.25; 95% CI, 0.65-2.41; $P=.013$) were identified as significant independent predictors for CVD events across the mean 5.7-year follow-up period. When the predictive value of the FRS alone was assessed by ROC curves (fig 3), the AUC was 0.71 (95% CI, 0.62-0.82). For the new models, which included the FRS combined with SCI characteristics, we found no significant improvement in ROC curves. More specifically, the predictive power of the FRS was not improved when adding ASIA impairment (0.74; 95% CI, 0.66-0.82), motor impairment (0.74; 95% CI, 0.66-0.83), level of injury (0.72; 95% CI, 0.63-0.81), or active engagement in sport before injury (0.72; 95% CI, 0.63-0.88).

Table 2 Cardiovascular disease events developed by participants during the observation period (n = 39)

Cardiovascular Event	No.
Deceased	
Pulmonary embolism	3
Other cardiovascular death	7
Cardiovascular morbidity	
Chronic venous insufficiency	2
Deep venous thrombosis	10
Transient ischemic attack	1
Atrial flutter/fibrillation	4
Peripheral vascular disease	2
Aortic diseases (Aneurysms, valve diseases, dissection)	3
Myocardial infarction	5
Angina	2
Total	39

Discussion

The purpose of this study was to investigate whether traditional cardiovascular risk factors, through the calculation of the commonly used FRS, can predict the occurrence of CVD events over a 5.7-year follow-up period in individuals with SCI. To our knowledge, this is the first study to test the accuracy of the FRS to predict future CVD events in individuals with SCI. First, we found that the FRS markedly underestimates the occurrence of CVD mortality and morbidity in individuals with SCI. Second, despite this marked underestimation of the true CVD event rate, the FRS was able to successfully identify individuals with SCI at increased risk for future CVD. These novel observations have an important clinical impact, because our findings suggest that aggressive (pharmaceutical) interventions may be required in individuals with SCI to lower risk for future CVD events, even when traditional CVD risk factors suggest a low-to-moderate risk.

An FRS of less than 10% in nondisabled individuals is classified to be "low" risk of 10-year CVD. Although it is difficult to translate this number to a 5-year CVD risk calculation, we expected to see very few events in our relatively young population (age, 40±14y) of SCI individuals across the 5.7-year period. In marked contrast, we found 39 CVD events, 10 of which were fatalities, which represents an unexpectedly high rate of CVD events. Although previous work suggested that the FRS may underestimate the actual CVD risk in the SCI population,[15,29,30] our study represents the first retrospective study to support this hypothesis. The CVD events were quite varied and featured typical CVD incidents, but approximately 25% originated from venous thromboembolism, which might be overrepresented in this sample. Observations of events began within 3 months after injury, which might have caused the capture of acute cardiovascular changes secondary to SCI in addition to chronic events. Despite the marked underestimation, the FRS was successful in distinguishing individuals who were at an increased risk for a CVD event. When comparing the "high" versus "low" risk group, our survival analysis indicated that the group of SCI individuals with an FRS greater than the median had a 3.2-fold greater risk for developing a CVD event than those with an FRS less than the median. Interestingly, data from the ROC curve indicates that the ability of the FRS to predict CVD events in individuals with SCI (ie, 0.71) is comparable to that typically observed in nondisabled populations (0.68-0.75).[31-33] Taken together, this indicates that the FRS successfully identifies individuals with SCI who have an increased risk for CVD, but markedly underestimates the true risk.

One potential implication of our observations is that different cutoff values for factors such as blood pressure and cholesterol should be adopted to calculate the correct CVD risk in individuals with SCI.[10] Indeed, in our study sample, cholesterol levels were within healthy ranges specified for nondisabled individuals and, therefore, a low FRS was calculated, despite being at an apparently higher risk for CVD. This finding supports previous work indicating the presence of low-to-normal levels of triglycerides, total cholesterol, and low-density lipoprotein cholesterol for individuals with SCI.[9,12,15,34] In addition, systolic blood pressure in the subset of individuals who developed a CVD event was also within the normal

Table 3 Cox regression analysis of individual predictors for cardiovascular disease events

Predictors	Hazard Ratio (95% CI)	Beta Coefficients	*P* Value
Age, years	1.05 (1.02-1.07)	0.044	<.001
Diabetes, yes	3.53 (0.85-14.7)	1.26	.08
Smoking, yes	0.727 (0.32-1.65)	−0.319	.44
Total cholesterol, mmol/L	1.28 (0.97-1.69)	0.248	.08
HDL cholesterol, mmol/L	0.96 (0.32-2.91)	−0.040	.94
BMI, kg/m^2	1.04 (0.96-1.13)	0.042	.30
5-year FRS, %	1.10 (1.05-1.16)	0.099	<.001
ASIA impairment scale			
B	1.84 (0.89-3.81)	0.610	.10
C	0.86 (0.33-3.79)	−0.151	.75
D	1.10 (0.32-3.79)	0.093	.88
Motor impairment, complete	1.21 (0.59-2.48)	0.187	.61
Level of injury, paraplegia	1.25 (0.65-2.41)	0.226	.50
Performed sports before injury, yes	0.45 (0.24-0.85)	−0.798	.01

NOTE. ASIA A, motor incomplete, and tetraplegia are reference categories.

range. Future studies adopting a prospective design should explore whether adjustment of cutoff values is required for the traditional CVD risk factors. One aspect to consider here is that it is not known how many participants might have been taking medications for hypertension, dyslipidemia, or dysglycemia, either before or after their injury, which could have affected these key CVD risk factors and morbidity and mortality outcomes. Similarly, the study in which data were collected for the current retrospective study was first approved in 1999. In the approximately 20 proceeding years, assessment methods for CVD risk factors and level of SCI and impairment and risk determination could have changed and possibly modified the study's current findings.

In addition to adjusting the cutoff values of traditional risk factors, one should also consider alternative risk factors in this population. First, although blood pressure is recognized as a strong predictor for CVD in the nondisabled population, frequent exposure to blood pressure variability may pose an additional risk. Individuals with SCI often experience episodes of autonomic dysreflexia, which represents an important CVD risk factor, independent of basal mean arterial blood pressure.[35,36] Second, current models of CVD risk prediction do not include a measure of physical activity. This is of special importance because recent work has revealed that physical inactivity has overtaken smoking as the leading cause of noncommunicable diseases,[37] and individuals with SCI are exposed to marked physical inactivity.[38] Their life-long exposure to an extreme form of sedentary behavior may accelerate the atherosclerotic processes. A final alternative explanation relates to the detrimental impact of SCI on vascular health.[38,39] This is of special importance, because impaired vascular function and structure may increase CVD risk independent from known risk factors.[40-43]

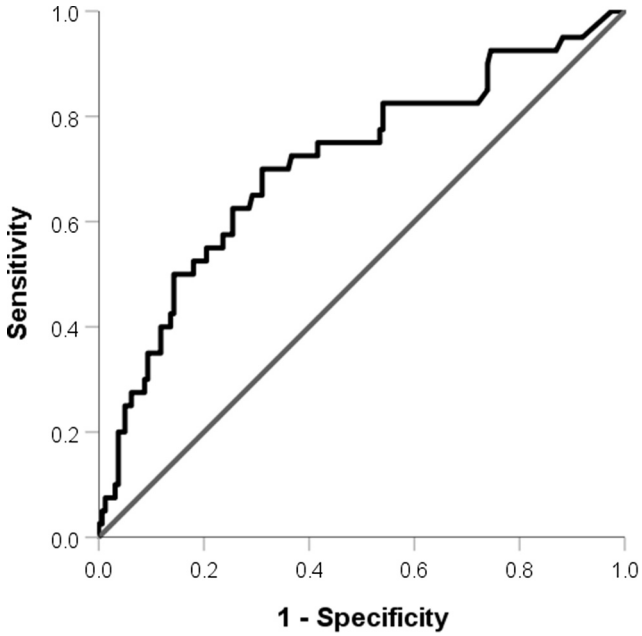

Fig 3 ROC curve for the FRS for the prediction of 5-year occurrence of an CVD event in individuals with SCI (N = 200) across a 5-year follow-up period.

We tested individual predictors for CVD events using separate univariate Cox regressions to establish whether adding SCI characteristics to the Framingham model can improve the accuracy and prognostic value of the FRS. Unlike ASIA impairment and level of the injury, older age at time of injury, no sports participation before injury, and a higher FRS were all significant predictors for CVD events. When comparing the models' accuracy and ability to identify individuals who will develop a CVD event, adding these individual predictors did not improve the FRS model. This is somewhat surprising considering that CVD risk increases relative to serum HDL levels[44] and direct associations have been reported between lipid concentrations (eg, low HDL) and neurologic deficit or severity of the spinal injury.[34] Possibly, the link between lipids and lesion level may be caused by the strong physical inactivity experienced by individuals with a higher level SCI rather than the lesion characteristics per se. The lack of the ability of the no sports participation before injury question to identify individuals who will develop a CVD event in this current sample may have been influenced by the method of assessment (eg, recall), and it may not be relevant to those patients who develop a CVD event several years after their injury. Although SCI lesion characteristics did not improve the accuracy of the FRS, older age at time of injury was a significant independent predictor. These results corroborate with others who report that older age at time of injury accelerates the aging

process and is an independent predictor of mortality in the first 5 years after injury.[45] In addition, advancing age is associated with a higher prevalence of risk factors such as metabolic syndrome,[46] and possibly further accelerates the development of CVD in older individuals after SCI. Similarly, some of the older individuals may have been asymptomatic or had subclinical CVD at the time of their injury or CVD events after study enrollment may reflect a carryover from preinjury states of hypercholesterolemia, low HDL, or hypertension. Furthermore, the prevalence of diabetes was low for the general population and especially for the SCI population.[47] Taken together, our data do not support adding SCI-specific factors to the FRS to improve the prediction of future CVD events in individuals with SCI.

Study limitations

There are some limitations of this study that require recognition. Observations of CVD events began within 3 months after injury, which might have caused the capture of acute cardiovascular changes secondary to SCI. Similarly, approximately 25% of the CVD events originated from venous thromboembolism, which might be overrepresented in this sample. It was not known if some individuals may have been asymptomatic or had subclinical CVD before or at the time of injury, as well as how many participants were possibly taking medications before or after injury. Finally, the assessment methods for the level and extent of SCI, the CVD risk factors, and risk determination could have changed in the approximately 20 years since the study in which data were collected for the current retrospective study occurred. Moreover, the no sports participation before injury question was via recall and may not be relevant to those patients who developed a CVD event several years after injury.

Conclusions

Accurate CVD estimation is essential to balancing the risks and benefits of prescribing preventive therapies and interventions. The findings in the current study may have important clinical consequences as they suggest that individuals with SCI, even in the presence of risk factors that are within the low range of nondisabled individuals, may benefit from (pharmaceutical) interventions to prevent CVD. Some evidence also shows that using interventions that lower the risk of CVD in individuals with risk factors within the "normal" range can have beneficial effects on overall CVD risk development in the nondisabled population.[48,49] Although future work is required to better understand this area, adjustment of current risk-prediction models and exploring their clinical implication for individuals with SCI seems warranted. In this light, one should also consider adding novel risk factors (eg, physical inactivity) or alternative screening methods. For the latter, carotid intima-media thickness is a known surrogate marker for CVD in the general population.[50-52] In individuals with SCI, no correlation was found between lipid profile and carotid intima-media thickness, despite signs of subclinical atherosclerosis.[53] Possibly, vascular imaging techniques may be an appropriate CVD screening tool that, independent of current risk factors, provide independent predictive capacity. In conclusion, our findings suggest that, although a higher FRS corresponds with an increased rate of CVD, the FRS and traditional cardiovascular risk factors significantly underestimate the 5-year risk of CVD morbidity and mortality in individuals with SCI. Furthermore, the increased risk and greater prevalence of a CVD event was independent of SCI lesion characteristics. Therefore, these data suggest that CVD risk estimation using the FRS or traditional cardiovascular risk factors should be interpreted with caution in this vulnerable population of SCI individuals. Given the high risk of CVD in this population, prospective follow-up studies are required to better understand CVD risk estimation in individuals with SCI, but also how this could adjust current medical care in individuals with SCI to prevent future CVD.

Supplier

a. SPSS, version 20.0; SPSS Inc.

Keywords

Spinal cord injury; Cardiovascular disease risk prediction

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