1	TITLE: Differential survival after traumatic spinal cord injury: Evidence from a multi-center
2	longitudinal cohort study in Switzerland
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4	AUTHORS: Chamberlain, JD <sup>1</sup> ; Gmünder, HP <sup>2</sup> ; Hug, K <sup>3</sup> ; Jordan, X <sup>4</sup> ; Moser, A <sup>5,6</sup> ; Schubert,
5	M <sup>7</sup> ; Brinkhof, MWG <sup>1, 8</sup>
6	
7	Affiliations:
8	<sup>1</sup> Swiss Paraplegic Research, Nottwil, Switzerland
9	<sup>2</sup> Swiss Paraplegic Center, Nottwil, Switzerland
10	<sup>3</sup> REHAB Basel, Basel, Switzerland
11	<sup>4</sup> Clinique Romande de Réadaptation, Sion, Switzerland
12	<sup>5</sup> Department of Geriatrics, Bern University Hospital, and Spital Netz Bern Ziegler, and
13	University of Bern, Bern, Switzerland
14	<sup>6</sup> Institute of Social and Preventative Medicine, University of Bern, Switzerland
15	<sup>7</sup> Balgrist University Hospital, Zürich, Switzerland
16	<sup>8</sup> University of Lucerne, Health Sciences and Health Policy, Luzern, Switzerland
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18	FIGURES: 2
19	TABLES: 4
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24	CORRESPONDING AUTHOR:
25	Jonviea Chamberlain, PhD
26	EMAIL: jonviea.chamberlain@paraplegie.ch

#### 27 Abstract

28 **Study design:** Observational cohort study.

29 **Objectives:** To understand differentials in the force of mortality with increasing time since 30 injury according to key spinal cord injury (SCI) characteristics.

31 **Setting:** Specialized rehabilitation centers within Switzerland.

Methods: We used data from the Swiss Spinal Cord Injury (SwiSCI) cohort study to model mortality in relation to age, sex and lesion characteristics. Hazard ratios (HRs) and adjusted survival curves were estimated using flexible parametric survival models of time since discharge from first rehabilitation to death or September 30, 2011, whichever came first.

**Results:** 2 421 persons were included that incurred a new TSCI between 1990 and 2011, contributing a total time at risk of 19 604 person-years and 376 deaths. Controlling for attained age, sex, decade and etiology, there was more than a four-fold higher risk of mortality for complete tetraplegia compared to incomplete paraplegia (HR=4.27; 95% CI 2.72 to 6.69). Survival estimates differed according to SCI characteristics, with differentials steadily increasing with time since injury.

42 **Conclusion:** This study provides evidence of disparities in mortality and survival outcomes 43 according to SCI characteristics that increases with increasing time since injury. These 44 results lend support to the hypothesis of a progressive and disproportionate accumulation of 45 allostatic load according to SCI characteristics. Future research should investigate cause-46 specific mortality for insight into potentially modifiable secondary health conditions 47 contributing to these disparities.

# 48 INTRODUCTION

49 Traumatic spinal cord injuries (TSCIs) are a life-altering condition associated with serious 50 monetary, social and health-related burden that can accumulate over time resulting in 51 reduced health outcomes and life expectancy. Within-population comparisons of all-cause 52 mortality, a measure of disease burden, can support the identification of high-risk groups 53 requiring targeted interventions to improve survival outcomes. Identifying risk factors 54 contributing to associated burdens of TSCI on individual health is crucial for activating 55 resources towards prevention and improvement of health outcomes, increased well-being, 56 reduced socioeconomic inequalities, and in particular reduction in avoidable, or premature, 57 mortality [1].

58 Extant literature has identified key SCI-related factors associated with an increased risk of mortality following a TSCI, particularly high (e.g., C1-C4) and complete lesions [2-4]. 59 60 Recent evidence has found variation in risk of death with the prevalence of self-reported 61 secondary health conditions according to lesion characteristics, as well as an overall higher 62 occurrence of reported health conditions with increasing injury severity [5]. The accumulation 63 of allostatic load associated with health conditions according to lesion characteristics could 64 contribute to the observed discrepancies in mortality estimates [4]. Understanding the within-65 population evolution of discrepancies in mortality and survival estimates could provide 66 evidence for the accumulation of allostatic load and subsequent differentials in survival estimates with increasing time since injury. 67

Comparisons of mortality estimates across settings can serve to highlight competencies 68 or deficiencies of health systems that could potentially inform other health systems towards 69 70 improving long-term outcomes. Although recent large-scale studies in developed countries 71 indicate broadly consistent survival outcomes, previous research has demonstrated 72 discrepancies in the magnitude of risk for mortality following TSCI across settings, highlighting the influence of health systems on mortality and survival outcomes [4]. 73 74 Therefore, country-specific and comparable estimates of mortality and longevity after SCI are 75 needed. Additionally, within-SCI population comparisons of mortality and survival estimates

76 can serve to identify potential modifiable factors associated with increased risk of mortality.
77 The purpose of this study is to thus provide the first, Swiss-specific estimates of mortality and
78 survival outcomes after TSCI using information collected in the Swiss Spinal Cord Injury
79 (SwiSCI) cohort study. Moreover, this study aims to investigate the associated force of
80 mortality within the SCI population with increasing time since injury.

81

#### 82 METHODS

#### 83 Study description

The Swiss Spinal Cord Injury (SwiSCI) study is a longitudinal cohort study that aims to 84 85 understand how to support "functioning, health maintenance, and guality-of-life of persons with SCI", and has been extensively described previously [6-8]. The present study uses data 86 collected from the Medical Record study, encompassed within the broader SwiSCI study, 87 which includes data collected from medical records from before 1970 up until as recently as 88 89 2013 [6,7]. The present study includes persons who incurred a new SCI between 1990 until 90 2011, given a recent vital status update for these individuals. Study eligibility criteria include 91 persons admitted to first rehabilitation in one of the five SCI specialized-rehabilitation centers 92 (operational: REHAB Basel; Balgrist University Hospital; Swiss Paraplegic Centre; Clinique 93 Romande de Réadaption; historic: University Hospital Geneva), with permanent residency in 94 Switzerland at admission to specialized rehabilitation, aged 16 years or older at time of 95 injury, and who did not incur SCI due to a congenital condition (e.g., spina bifida) or 96 neurodegenerative disorder (e.g., multiple sclerosis). Data collected for the SwiSCI study 97 underwent ethical review, and was approved by the ethical committees of Cantons: Lucerne, 98 Basel, Valais, and Zürich (reference numbers: 1008 [Luzern]; 37/11 [Basel]; CCVEM 015/11 [Valais]: 2012–0049 [Zürich]). When investigating AIS grade and injury severity (categorical 99 100 variable combining lesion level and AIS grade) as risk factors for pre-mature mortality, only cases with an incurred TSCI after 2000 were included due to data unavailability and 101 102 incompleteness of data collection pre-2000. Individuals with an AIS grade E were included

- 103 within the analysis given their eligibility for inclusion in the overall SwiSCI study. AIS grades
- 104 E and D were combined due to relatively few cases of AIS grade E (N=23).
- 105

## 106 Data Management

107 All variables were grouped according to ISCOS guidelines to facilitate comparability with

108 other studies [9]. Information on lesion type, level, completeness and AIS score were

109 collected at discharge from first rehabilitation. If data at discharge were missing, when

110 available, data collected at admission to first rehabilitation were used instead (N=10).

111

## 112 Outcome evaluation

113 The outcome of interest for this study was death as of September 30, 2011. In 2011, the first 114 Community Survey (CS 2012) for SwiSCI participants started recruitment based on potential 115 participants identified through the Medical Records study [8]; September 30, 2011 is chosen 116 as the arbitrary start of the CS 2012, when questionnaires were initially sent out. Although 117 the present study only uses information from the Medical Records study, active participation 118 or response to the CS 2012 questionnaire facilitated an update for the vital status of many 119 individuals within the Medical Records study. Missing vital status information for individuals 120 who did not respond to the CS 2012, or who were not included or eligible, was updated in a 121 subsequent tracing effort. This tracing effort updated vital status first through specialized 122 clinics, and if needed through community of last known residence (similar to the study methodology reported for the Swiss Childhood Cancer cohort [10]). Individuals were 123 124 identified as either alive, dead, or lost to follow-up (LTFU) (i.e., no information on vital status) 125 as of September 30, 2011. Given that cauda equina lesions are peripheral lesions with a 126 different prognosis and evolution, cases of cauda equina were excluded from all survival 127 analvsis.

128

129 Statistical Analysis

The study population was described by frequencies (n), percentages (%), person-years 130 (PYRS), mean and standard deviation (SD). Differences between injury cohorts were 131 132 assessed by a chi-squared test or Kruskal-Wallis test. Kaplan-Meier curves were estimated 133 in order to have a nonparametric assessment of survival probabilities, thereby making no 134 assumptions regarding underlying survival distribution. Stratification by secondary variable was used for adjustment of Kaplan-Meier curves for known confounders that could impact 135 136 survival (e.g., age, lesion level and lesion completeness). Log-rank tests were used to test 137 the equality of Kaplan-Meier curves. Kaplan-Meier survival estimates according to years since injury are presented in the supplementary material (Supplementary Table 2). We then 138 139 used flexible parametric proportional hazards models to investigate risk factors for dying to 140 estimate hazard ratios (HR) and survival probabilities with 95% confidence-intervals (CI) [11]. 141 Time at risk started at date of injury, with study entry defined as date of admission to first 142 rehabilitation, and study exit as date of death or September 30, 2011, whichever came first. We reported unadjusted HRs as well as HRs adjusted for sex, age, decade of TSCI, cause of 143 144 TSCI. In a secondary analysis, data were split on follow-up time to account and estimate the 145 effect of follow-up time on mortality and longevity outcomes. These follow-up periods were:

#### 146 1. After admission until discharge from first rehabilitation

- 147 2. One-year post-discharge
- 148 3. More than one-year post-discharge
- 149

Flexible parametric models are intended to model the baseline hazard in a way that 150 151 allows flexibility in the shape of the survival distribution modelled; this flexibility comes from 152 the use of restricted cubic splines [11]. The flexibility of the spline function is dictated by the 153 number of knots, or points at which the baseline hazard is allowed to change. The minimal 154 AIC and BIC values were used to formally select the number of knots included in the model. 155 Violations to the proportional hazards function, implicit to flexible parametric models (as well 156 as other survival models), were assessed using likelihood ratio for time-dependent effects of 157 included covariates. Survival curves were estimated using direct adjustment; with direct

158 adjustment, survival curves - for categorical variables - are estimated at specified time 159 points for a combination of covariate patterns, to provide a final average of these values at 160 each time point. This is importantly different to the mean covariate method which provides 161 survival estimates according to the variable of interest, but while using the mean value of all underlying covariates - an issue for categorical variables [11]. The absolute difference 162 between estimated survival probabilities adjusted for potential confounders was estimated so 163 164 as to demonstrate the impact of lesion characteristics (i.e., completeness and lesion level) on 165 survival probabilities. The figures provided show the difference in survival between selected characteristics of interest (e.g., complete tetraplegic lesions and incomplete paraplegic 166 167 lesions) if they had the same covariate distribution as that of the whole study population (i.e., 168 the same underlying distributions in age, sex, lesion level, cause of TSCI).

169

170 To account for age effects that occur due to biological processes of aging, age was timeupdated using splitting techniques in that, as each individual aged, the individual contributed 171 172 different amounts of time to each risk set. For example, if an individual was injured at the age 173 of 29 and subsequently died at the age of 33, this individual would contribute one year of 174 follow-up time to the age category "16-30 years" and roughly three years to the age group, 175 "31-45 years". Similarly, to account for potential period effects that could result from changes 176 in medical technology and rehabilitation approaches, data were further split on decade of 177 injury: again allowing for an individual to contribute to different risk sets (e.g., 1990-1999 or 178 2000-2011).

179

In a sensitivity to account for persons lost to follow-up, inverse probability weights (IPW) were estimated using logistic regression, including LTFU (yes/no) as the outcome, and decade of SCI, sex, age at injury, lesion level, rehabilitation center, and completeness of lesion as independent variables in the model. For those missing complete information on independent variables, the mean weight for the total population was used.

185

186 We reported p-values from two-sided test statistics. A p-value smaller than 0.05 was

187 considered as significant. All analyses were implemented in STATA software version 14.2

188 [12].

189

# 190 Results

191 The study population is described in Table 1. Between 1990 and 2011, 2'421 persons 192 incurred a traumatic spinal cord injury and were eligible for inclusion in the present study. Of 193 these individuals, 73.2% were male, 42.2% were paraplegic (excluding cauda equina), and 194 the average age at injury was 44.6 years (SD=19.4; IQR=32). Between the first (1990 to 195 1999) and second decade (2000 to 2011), the average age at injury increased by roughly 196 five years (41.5 years and 46.6 years, respectively). Significant differences were observed between decades according to age at injury, length of stay, etiology of injury, type of SCI and 197 198 completeness. For example, in the latter decade there was a larger proportion of TSCIs with 199 a complete lesion (70.9% compared to 63.0%), fewer transport-related TSCIs (25.9% 200 compared to 34.4%), and a larger proportion of older individuals over the age of 60 years old 201 admitted to specialized rehabilitation (27.4% compared to 19.1%). There was no difference 202 between decades were observed for sex, American Spinal Injury Association (ASIA) 203 Impairment Scale (AIS) score, destination after discharge, and ventilator assistance (Table 204 1). The majority of injuries were due to falls (36.3%) and transport-related incidents (29.2%). 205 The total contributing time-at-risk over the study period was 19 604.0 PYRS (median 7.1 206 years), with 376 recorded deaths of which 67 occurred during the rehabilitation period (see 207 Supplementary Table).

208

## 209 Risk factors for mortality

Attained age, TSCI type, completeness of lesion, and cause of TSCI were associated with an increased risk of mortality (Table 2A). Sex or decade of injury were not associated with risk of mortality. In the analyses stratified according to follow-up time, risk factors for mortality remained relatively stable in terms of the direction of effect, but varied slightly in magnitude.

214 For example, while falls or 'other source of injury' (e.g., surgical) - compared to a transportrelated TSCI – were identified as a significant risk factor for early mortality, estimated hazard 215 216 ratios were attenuated or non-significant during the inpatient period and first-year post-217 discharge (Table 2B). The overall variation in risk was mainly driven by the one-year or more 218 post discharge mortality. A similar pattern of attenuated effect sizes in comparison with the inpatient period was observed for attained age, particularly during the period of less than 219 220 one-year post-discharge (e.g., for individuals aged 76 years and older: Overall HR=38.3, 221 95% CI 20.5 to 71.3 [Table 2A]; one-year post-discharge HR=27.7, 95% CI 7.3 to 104.4 222 [Table 2B]). Contrarily, the risk for mortality increased for complete tetraplegia during the 223 period one-year post-discharge, and then subsequently decreased during the period greater 224 than one-year post-discharge. However, due to the limited number of deaths during the 225 inpatient period (N=67) and the period one-year post-discharge (N=68), the power to capture 226 the true relationship is limited, as demonstrated in the wide confidence intervals. There was 227 evidence for interaction between TSCI type and completeness of lesion ( $p \le 0.01$ ), although 228 not between attained age and sex, or attained age and cause of TSCI. Given the evidence 229 for an interaction, in a secondary analysis based on a categorical variable of a combination 230 of completeness and level of injury, individuals with complete tetraplegic lesions had the 231 highest risk of mortality when compared to subjects with incomplete paraplegic lesions 232 (HR=4.27, 95% CI=2.72-6.69) (Table 2A).

233

#### 234 Survival probabilities

Differences in Kaplan-Meier survival curves were observed according to sex (p<0.001), age (p<0.001), type of TSCI (p<0.001), and injury severity (a combination of lesion level and AIS score) (p<0.001). When controlling for attained age, a difference was additionally observed for completeness (p<0.001), although no longer according to sex (p=0.60). Kaplan-Meier survival curves for completeness and level of lesion are presented in Figure 1; stratified estimates according to years since follow-up are reported in Supplementary Table 2. In comparison with paraplegia, adjusted survival probabilities, estimated using flexible

242 parametric survival models, for tetraplegia were diminished, with the divergence increasing 243 over time (Table 3). For example, a 4.2% difference between survival probabilities for 244 paraplegia (93.4%; 95% CI 91.6 to 95.2%) compared to tetraplegia (89.2%; 95% CI 86.7 to 245 91.8%) was observed at one-year post admission, while for 20-year survival estimates the 246 difference grew to nearly 10% (Table 3). The increasing trend results in an overall augmentation in the discrepancy between survival probabilities for paraplegia compared to 247 248 tetraplegia of 5.6% overall (Figure 2). The discrepancy was even more pronounced for 249 estimates according to level and completeness of lesion, whereas there was a 11.6% 250 increase in the gap between complete tetraplegia and incomplete paraplegia at one-year 251 survival (12.7% difference) and 20-year survival (24.3% difference) (Table 3). The absolute 252 difference in survival probabilities for complete tetraplegia compared to incomplete 253 paraplegia, standardized for underlying population characteristics, are presented in Figure 2. 254 Accounting for attained age, as a proxy for biological aging, the survival of complete 255 tetraplegia was 4.8% (95% CI 1.8 to 7.9%) below that of incomplete paraplegia in absolute, 256 standardized terms at 10 years (Figure 2.C). This implies that at 10 years roughly 5% of the 257 difference in survival probabilities is attributable to the difference in level and completeness 258 of lesion. This discrepancy was slightly larger when adjusting for age at injury, rather than 259 attained age (Supplementary figures).

260

## 261 Discussion

Older age, tetraplegia, completeness of lesion, and TSCIs due to falls or 'other causes' are associated with an increased risk of mortality following TSCI in Switzerland. Disparities in mortality and survival estimates according to SCI-specific characteristics were found to augment with increasing time since injury. Additionally, stratified results based on follow-up time post-injury suggest the potential modification in the magnitude of mortality risk according to sociodemographic and SCI-specific characteristics.

270 As individuals age with spinal cord injuries, there is an increasing gap in survival outcomes 271 according to SCI-specific characteristics. It should be noted, however, that due to the limited 272 follow-up time (i.e., 21 years) it is not known whether this trend towards a widening gap 273 would continue, and whether it would continue at a similar rate. However, although 274 comparison with previous literature is limited due to few studies providing stratified estimates, or only presenting evidence in figures of unadjusted Kaplan-Meier curves, of those studies 275 276 that have provided stratified estimates for long-term follow-up have found similar results 277 [2,3,13]. For example, a 50-year longitudinal study by Middleton et al estimated a five-year 278 survival for individuals with paraplegia and tetraplegia of 98% and 94%, respectively; after 279 fifteen years, the twenty-year survival dropped to 88% and 78%. This represents an 280 augmentation in the gap between survival estimates of 6% (4% between 5-year estimates to 281 10% between 20-year estimates); the present study estimated an increase of 3.7%, including those who survived the first year, whereas Middleton et al excluded those that perished 282 283 during the first year [2]. Discrepancies in survival estimates according to SCI-specific 284 characteristics with increasing follow-up time could be due to the disproportionate 285 accumulation of secondary health conditions. It should also be noted that due to the limited 286 follow-up time (i.e., 21 years), it is not known whether this trend towards a widening gap 287 would continue, and whether it would continue at a similar rate; additional long-term studies 288 investigating this guestion are needed to confirm whether or not this pattern continues. 289 Furthermore, in order to investigate the influence of secondary health conditions (HCs) 290 accumulation, or allostatic load, on mortality differentials, according to SCI-specific 291 characteristics, follow-up studies including time-updated information on secondary health 292 conditions are required.

Biological plausibility studies have suggested an increased immunological strain on the SCI-affected individual, and premature onset of immune frailty [14,15], with animal experiments suggesting a dependency on lesion level [16]. Evidencing this, epidemiological studies have shown that individuals aging with SCI report a higher frequency of health conditions [17]. Additionally, in the recent SwiSCI 2012 Community Survey, lesion type and

298 completeness have been shown to play a role as individuals with higher, more severe lesions 299 reported HCs more often, and reported different health conditions [5]. For example, 300 community members with a complete SCI reported a higher frequency of pressure ulcers, 301 and members with tetraplegia reported more respiratory problems [5]. Secondary health 302 conditions - such as pressure injuries, depression, and infections - have been shown to be 303 associated with an increased risk of mortality [18,19], likely due to sepsis [20]. However, as 304 evidenced in the recent nomenclature change from pressure ulcer to pressure injury, 305 pressure injuries are preventable [21]. Identifying secondary health conditions associated 306 with cause-specific mortality can highlight potential areas to target interventions of modifiable 307 risk factors for mortality, towards reducing the disparity in survival outcomes within the SCI 308 population. Prospective studies are thus needed that simultaneously measure health 309 conditions and mortality.

310

#### 311 Comparisons within SCI literature

312 Differences in the results of the current study in comparison with previous studies, as well as 313 differences between previous studies could be influenced by contextual factors, for example, 314 access to care, particularly when considering lower-income countries [4]. In order to exploit 315 these discrepancies to improve mortality and survival outcomes and identify modifiable 316 contextual factors associated with non-modifiable risk factors of mortality (e.g., TSCI lesion 317 level, completeness, severity, age or sex), comparative estimates are essential. Presently, 318 there are a number of aspects hampering comparability of estimates in SCI literature; 319 namely, denotation of time-at-risk, definitions for acute mortality, differences in reference 320 groups, and statistical approaches to analysis. For example, a study by Middleton et al starts 321 risk with date of SCI, uses a period of one-year post-injury for acute mortality, and estimates 322 long-term survival after excluding those who did not survive one-year post-injury [2]. The 323 aforementioned study by Cao et al similarly excludes those who perished within the first year 324 post-injury [22]. Another study by Hagen et al defines acute mortality as 30 days post-injury, 325 and commences time-at-risk with admission to first rehabilitation [3]. Other studies stratify time-at-risk by two-years and more than two-years post-injury [23] or one-year post-injury[24].

328 Approaches to statistical analyses in SCI literature vary considerably, as evidenced in 329 a recent systematic review and meta-analysis [4], with some studies reporting hazard ratios, 330 others odds ratios or relative risks. Moving forward, a standard approach should be adopted that uses advanced, up-to-date statistical techniques which adequately take into account 331 332 time-dependent exposures and long-term follow-up to ensure accurate estimates of survival 333 and mortality outcomes, as well as cohesion across SCI literature for ensuring comparable 334 estimates. The flexible parametric survival model methodology employed within this paper is 335 a modern and highly relevant approach often preferable to Cox regression due to the 336 associated issues, for example, regarding predictions of life expectancy, and non-337 proportional hazards [11]. Additionally, implementation of an individual-based meta-analysis 338 - using data from multiple studies and sources - would ensure standardized stratification, 339 inclusion and exclusion criteria, and mortality definitions [25].

340

#### 341 Strengths & Limitations

342 This study reports results of a longitudinal cohort study with a clearly defined source 343 population, and includes more than 2 400 included cases of TSCI and 376 deaths. However, 344 given that information on AIS scores was only available post-2000, there were a limited 345 number of cases and deaths to include in the analyses. The reduced number of cases, and 346 thereby resulting limited power, may have contributed to the higher risk of mortality estimated 347 for persons with a C5-C8 AIS A, B, or C lesion compared to those with a C1-C4 AIS A, B, or 348 C lesion. This is contrary to estimates from many - albeit not all [2,26] - previous studies [4]. 349 However, given the wide confidence intervals, no concrete conclusions regarding this pattern 350 can be made for this study. Another issue related to data availability in the present study, is 351 the potential bias related to loss to follow-up (N=171; 7.1%) (e.g., selection bias due to 352 younger individuals being less likely to stay in contact with the rehabilitation clinic and 353 thereby having a higher likelihood of becoming LTFU due to undocumented address

changes that would have impacted tracing methodology). To overcome this potential issue, sensitivity analyses including inverse-probability weights were employed (Supplementary table). No significant differences in estimates were observed. However, use of IPWs does not account for informative censoring where, for example, persons LTFU may have a differential risk of mortality not related to collected covariates. To correctly adjust estimates, a pattern-mixture approach, for instance, could be used to inform mortality risk of those censored [27].

361 In a previous study assessing the coverage of the SwiSCI Medical Records study with respect to TSCI, it was shown that SwiSCI likely underrepresents less severe cases as well 362 363 as the elderly population; this potentially affects the generalizability of the study, and 364 subsequent external validity [28,29]. In particular, caution should be taken when interpreting 365 overall estimates of survival as they could be under- or over-estimated depending on the added risk from underrepresented groups. However, this study covers the population 366 367 receiving specialized rehabilitation, as SwiSCI includes all recognized centers. Presented 368 estimates can thus be said to be internally valid and generalizable to the Swiss TSCI 369 population admitted to specialized first rehabilitation. Another limitation of the present study 370 is the absence of information on known contributing risk factors for mortality. Identification of 371 major mediating factors down-stream from SCI-specific characteristics (e.g., completeness of 372 lesion) is important for identifying critical, modifiable factors contributing to potentially 373 preventable mortality [30]; for example, secondary health conditions are known to contribute to risk of mortality [19,31]. In the next steps, cause of death information is needed for cause-374 375 specific mortality analyses, as to further evaluate the role of secondary health conditions in 376 risk of mortality.

377

#### 378 Conclusion

This study provides evidence of disparities in mortality and survival outcomes between SCIspecific characteristics. Estimates of mortality and survival provided within this study provide an initial evidence base for informing resource allocation and future research directions,

whereas future research is needed that focuses on the identification of modifiable contextual 382 factors contributing to risk differentials between SCI characteristics. Analysis of cause-383 384 specific mortality is the next step needed towards identifying modifiable risk factors 385 contributing to this disparity. Additionally, in medical record studies - or other studies based 386 on routinely collected data, for which information of secondary health conditions is not available - analysis of cause-specific mortality may offer insight regarding the influential 387 388 secondary health conditions contributing to the aforementioned disparities within the SCI 389 population.

390

## 391 Conflicts of interest

392 The authors have no conflict of interest to declare.

393

## 394 Authors' contributions

JDC and MWGB were responsible for conceptual framing of the present study. MWGB further provided statistical support as well as critical feedback on manuscript content. HPG, KH, XJ, and SM provided clinical support and feedback of the present manuscript, as well as support in data collection at their respective clinics. AM provided statistical support for analyses, as well as critical evaluation of statistical methods implemented. Finally, JDC was responsible for all analyses, drafting, and finalization of the present manuscript.

# 401 Supplementary information

402

# Figure S1. Differences in absolute survival probabilities according to lesion level and completeness, using age at injury in flexible parametric model

405 This figure is similar to Figure 2 presented in the manuscript, but instead uses age at injury as opposed to attained age when estimating differences in survival probabilities. The grey 406 407 area on either side of the line represents the 95% confidence interval. Figure 2.A compares 408 the reference group with complete paraplegia; 2.B compares the reference group with 409 incomplete tetraplegia; 2.C compares the reference group with complete tetraplegia. 410 Interpretation: The absolute difference can be interpreted as a percent, for example, 0.04 411 equates to a 4% difference. The positive increase of the absolute difference, for example in 412 Figure 2.C, is indicative of an absolute survival advantage for incomplete paraplegic lesions 413 as compared to complete tetraplegic lesions. The continued upwards trend implies a lack of 414 stabilization (i.e., a continued augmentation in the absolute difference between survival 415 probabilities).

416

# Table S1. Time-at-risk and number of deaths for demographic and TSCI-specific characteristics by injury cohort

This table provides information on follow-up time for participants and the number of deaths
stratified by key sociodemographic and SCI-specific characteristics.

421

422 **Table S2. Non-parametric Kaplan-Meier survival estimates according to time since** 423 **injury** 

This table provides Kaplan-Meier estimates for survival probabilities according to specifiedtime points following date of SCI.

426

Table S3A. Univariable and multivariable results from flexible parametric survival
 model using inverse probability weights

- 429 This table is the same as Table 2A presented in the manuscript, but uses inverse probability
- 430 weights (IPWs) to account for cases lost to follow-up (LTFU).
- 431
- 432 Table S3B. Risk factors according to follow-up period: Multivariable results from

# 433 flexible parametric survival model using inverse probability weights

- This table is the same as Table 2B presented in the manuscript, but uses IPWs to accountfor LTFU.
- 436

# 437Table S4. Marginally estimated survival probabilities using inverse probability weights

- 438 This table is the same as Table 3 presented in the manuscript, but uses IPWs to account for
- 439 LTFU.
- 440
- 441

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# Titles and legends to figures

# Figure 1. Kaplan-Meier curves of the survival function stratified by SCI characteristics

*Legend:* Figure 2.A represents the Kaplan-Meier estimates for lesion completeness. Figure 2.B represents the Kaplan-Meier estimates for lesion level.

# Figure 2. Differences in absolute survival probabilities according to lesion level and completeness

*Legend:* All figures include incomplete paraplegia as the group of reference. The grey area on either side of the line represents the 95% confidence interval. Figure 2.A compares the reference group with complete paraplegia; 2.B compares the reference group with incomplete tetraplegia; 2.C compares the reference group with complete tetraplegia. Interpretation: The absolute difference can be interpreted as a percent, for example, 0.04 equates to a 4% difference. The positive increase of the absolute difference, for example in Figure 2.C, is indicative of an absolute survival advantage for incomplete paraplegic lesions as compared to complete tetraplegic lesions. The continued upwards trend implies a lack of stabilization (i.e., a continued augmentation in the absolute difference between survival probabilities).

$\begin{array}{c c} \mbox{Characteristics} & 1990-1999 & 2000-2011 \\ (n=950) & (n=1 \ 471) & P-value \\ \end{array}$
$\begin{array}{c c} \mbox{Age at injury, years: mean; S.D. (IQR)} \\ \mbox{Length of stay, months: mean; S.D.} \\ (IQR) \\ \mbox{Sex [1]} \\ \mbox{Male} \\ \mbox{Female} \\ \mbox{Age at injury [0]} \\ \mbox{Age at injury [0]} \\ \mbox{16-30} \\ \mbox{31-45} \\ \mbox{46-60} \\ \end{array} \begin{array}{c} \mbox{41.5; 18.5 (29)} \\ \mbox{46.6; 19.6 (33)} \\ \mbox{40.001} \\ \mbox{6.2; 9.9 (4.7)} \\ \mbox{5.2; 4.4 (4.3)} \\ \mbox{60.001} \\ \mbox{6.2; 9.9 (4.7)} \\ \mbox{5.2; 4.4 (4.3)} \\ \mbox{60.001} \\ \mbox{6.2; 9.9 (4.7)} \\ \mbox{5.2; 4.4 (4.3)} \\ \mbox{60.001} \\ \mbox{6.2; 9.9 (4.7)} \\ \mbox{5.2; 4.4 (4.3)} \\ \mbox{6.2; 9.9 (4.7)} \\ \mbox{6.2; 9.9 (4.7)} \\ \mbox{5.2; 4.4 (4.3)} \\ \mbox{6.2; 9.9 (4.7)} \\ 6.2; 9.9$
$\begin{array}{c c} \mbox{Length of stay, months: mean; S.D.} & 6.2; 9.9 (4.7) & 5.2; 4.4 (4.3) & <0.001 \\ (IQR) & & & 0.24 \\ \mbox{Sex [1]} & & & 0.24 \\ \mbox{Male} & 708 (74.5) & 1 064 (72.4) \\ \mbox{Female} & 242 (25.5) & 406 (27.6) \\ \mbox{Age at injury [0]} & & <0.001 \\ \mbox{16-30} & 351 (36.9) & 385 (26.2) \\ \mbox{31-45} & 227 (23.9) & 372 (25.3) \\ \mbox{46-60} & 191 (20.1) & 310 (21.1) \end{array}$
Sex [1]       0.24         Male       708 (74.5)       1 064 (72.4)         Female       242 (25.5)       406 (27.6)         Age at injury [0]       <0.001
Male       708 (74.5)       1 064 (72.4)         Female       242 (25.5)       406 (27.6)         Age at injury [0]       <0.001
Female       242 (25.5)       406 (27.6)         Age at injury [0]       <0.001
Age at injury [0]       <0.001
16-30351 (36.9)385 (26.2)31-45227 (23.9)372 (25.3)46-60191 (20.1)310 (21.1)
31-45227 (23.9)372 (25.3)46-60191 (20.1)310 (21.1)
46-60 191 (20.1) 310 (21.1)
61-75 125 (13.2) 261 (17.7)
76+ 56 (5.9) 143 (9.7)
Etiology [2] <0.001
Sports and leisure 186 (19.6) 359 (24.4)
Transport 326 (34.4) 381 (25.9)
Falls 324 (34.2) 555 (37.7)
Other cause 112 (11.8) 176 (12.0)
SCI Type [12] <0.01
Tetra 531 (56.2) 776 (53.0)
Para 343 (36.3) 611 (41.7)
Cauda equina 71 (7.5) 77 (5.3)
Completeness [95] <0.001
Complete 566 (63.0) 1 012 (70.9)
Incomplete 332 (37.0) 416 (29.1)
Lesion Level & Completeness [52] <a></a>
Paraplegia, incomplete 283 (33.5) 479 (35.1)
Paraplegia, complete 235 (27.8) 288 (21.1)
Tetraplegia, incomplete 229 (27.1) 473 (34.7)
Tetraplegia, complete 97 (11.5) 125 (9.2)
ASIA Score [943] 0.75
AIS A 60 (28.6) 380 (29.8)
AIS B 24 (11.4) 160 (12.5)
AIS C 32 (15.2) 214 (16.8)
AIS D/E 94 (44.8) 521 (40.9)
Injury Severity* [1 292] n.a.
C1-C4 ABC - 108 (10.3)
C5-C8 ABC - 97 (9.3)
T1-S3 ABC 3 (3.1) 318 (30.5)
AIS D/E 94 (96.9) 521 (49.9)
Destination after discharge [69] 0.22
Private residence 709 (80.0) 1 146 (78.2)
Hospital 58 (6.5) 80 (5.5)
Nursing home/assisted living $89(10.0)$ 184 (12.6)
Other (e.g., notel) $4 (0.5) 13 (0.9)$
Death 26 (2.9) 43 (2.9)
Ventilator Assistance [73] 0.26
NO 881 (96.8) 1 379 (95.9)
Tes         ZY (3.2)         5Y (4.1)           Associated Injurica [4.954]         N.A.
Associated injulies [1 00 1] N.A.
- 321(30.3) No - 249(43.7)

\*\* p-value from chi-squared test or Kruskal-Wallis test; Abbreviations: SCI = Spinal cord injury; AIS = American Spinal Injury Association (ASIA) Impairment Scale (AIS)

		Univariable analysis	Multivariable analysis	
	Characteristic	Hazard Ratio (95% Cls)	Hazard Ratio (95% CIs)	P-value
	Sex			0.99
	Female	Reference	Reference	
	Male	1.38 (1.10-1.74)	1.00 (0.79-1.27)	
	Attained age			<0.001
	16-30	Reference	Reference	
	31-45	2.60 (1.36-4.98)	2.53 (1.32-4.85)	
	46-60	5.46 (2.93-10.19)	5.20 (2.77-9.77)	
	61-75	14.59 (8.03-26.52)	13.21 (7.14-24.43)	
	76+	43.15 (23.83-78.13)	38.27 (20.53-71.33)	
۵	Lesion Level			<0.001
One	Paraplegia	Reference	Reference	
el	Tetraplegia	2.03 (1.64-2.51)	1.74 (1.38-2.20)	
pol	Completeness			<0.001
$\geq$	Incomplete	Reference	Reference	
	Complete	1.00 (0.80-1.25)	2.08 (1.64-2.65)	
	Decade of SCI			0.51
	1990-1999	Reference	Reference	
	2000-2011	1.52 (1.14-2.02)	1.10 (0.82-1.47)	
	Cause of TSCI	- ( - )		<0.01
	Transport-related	Reference	Reference	
	Sports/Leisure activity	0.88 (0.59-1.31)	0.93 (0.62-1.39)	
	Fall	3 20 (2 41-4 25)	1 51 (1 12-2 04)	
	Other	2 51 (1 73-3 63)	1 66 (1 13-2 45)	
	Lesion Level &	2101 (1110 0100)		
Q	Completeness			<0.001
×⊢	Paraplegia, incomplete	Reference	Reference	
del	Paraplegia, complete	1.11 (0.80-1.53)	1.54 (1.11-2.14)	
Чõ	Tetraplegia, incomplete	2.04 (1.55-2.68)	1.50 (1.00-2.27)	
-	Tetraplegia, complete	2.34 (1.67-3.29)	4.27 (2.72-6.69)	
0	Injury Severity*			< 0.01
Jre	AIS D/F	Reference	Reference	
È	C1-C4 ABC	3.31 (1.83-5.98)	2.43 (1.29-4.58)	
de	C5-C8 ABC	2.09 (1.07-4.10)	3.27 (1.62-6.62)	
M	T1-S3 ABC	1.59 (0.96-2.64)	2.04 (1.18-3.52)	

# Table 2A. Univariable and multivariable hazard ratios from the flexible parametric survival model

\* Analyses including "Injury Severity" are restricted to 2000-2011 due to inadequate data prior to 2000. **Model** one is adjusted for: Current age, sex, decade of TSCI, cause of TSCI, lesion level, and completeness of injury; **Model two** is adjusted for: Current age, sex, decade of TSCI, cause of TSCI, and "Lesion level and completeness"; **Model three** is adjusted for: Current age, sex, injury severity, and cause of TSCI.

<b>Table 2D.</b> Risk factors according to follow-up period. Multivariable results from hexible parametric survival mod	Table 2B. F	Risk factors accordin	a to follow-up period	: Multivariable results	from flexible i	parametric survival m	odel
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	Characteristic	Inpatient Rehabilitation	P-value	<1 year post-discharge	P-value	≥1 year post-discharge	P-value
	Sex		0.66		0.71		0.74
	Female	Reference		Reference		Reference	
	Male	1.13 (0.65-1.96)		1.11 (0.64-1.95)		0.95 (0.70-1.28)	
	Attained age		<0.001		<0.001		<0.001
	16-30	Reference		Reference		Reference	
	31-45	1.99 (0.44-8.94)		2.48 (0.61-10.07)		2.85 (1.18-6.90)	
	46-60	6.60 (1.77-24.53)		6.02 (1.60-22.63)		5.14 (2.15-12.30)	
	61-75	14.81 (4.16-52.72)		12.41 (3.41-45.19)		13.75 (5.85-32.32)	
	76+	63.75 (17.78-228.52)		27.68 (7.34-104.41)		39.03 (16.46-92.59)	
Ð	TSCI type		0.03		<0.01		<0.001
ő	Paraplegia	Reference		Reference		Reference	
<u>e</u>	Tetraplegia	1.92 (1.05-3.50)		2.49 (1.38-4.49)		1.57 (1.18-2.09)	
po	Completeness		<0.001		<0.01		<0.001
Σ	Incomplete	Reference		Reference		Reference	
	Complete	2.71 (1.57-4.67)		2.53 (1.40-4.59)		1.97 (1.46-2.67)	
	Decade of SCI		0.09		0.75		0.07
	1990-1999	Reference		Reference		Reference	
	2000-2011	0.64 (0.39-1.08)		1.10 (0.60-2.03)		1.53 (0.95-2.45)	
	Cause of TSCI		0.99		0.15		<0.01
	Transport-related	Reference		Reference		Reference	
	Sports/Leisure activity	1.13 (0.46-2.80)		0.57 (0.20-1.64)		1.01 (0.61-1.67)	
	Fall	1.06 (0.54-2.06)		1.09 (0.54-2.21)		1.81 (1.24-2.64)	
	Other	1.01 (0.34-3.01)		1.94 (0.82-4.61)		1.76 (1.08-2.84)	
0	TSCI type		<0.001		<0.001		<0.001
≥	Paraplegia, incomplete	Reference		Reference		Reference	
	Paraplegia, complete	1.74 (0.69-4.40)		0.82 (0.30-2.26)		1.71 (1.17-2.51)	
ро	Tetraplegia, incomplete	1.36 (0.60-3.09)		1.33 (0.68-2.59)		1.42 (1.00-2.01)	
Σ	Tetraplegia, complete	4.52 (1.91-10.74)		6.91 (3.22-14.83)		3.36 (2.10-5.37)	
e e	Injury Severity*	· · · · · · · · · · · · · · · · · · ·	0.34		<0.001		0.35
<u>h</u> re	AIS D/E	Reference		Reference		Reference	
Ť	C1-C4 ABC	3.00 (0.79-11.48)		7.10 (1.92-26.30)		1.47 (0.53-4.06)	
ъdе	C5-C8 ABC	2.04 (0.37-11.23)		15.86 (4.17-60.35)		2.49 (0.84-7.41)	
Ĕ	T1-S3 ABC	2.61 (0.67-10.16)		6.20 (1.91-20.16)		1.25 (0.59-2.65)	

\* Note: Model Three including "Injury Severity" only includes cases of TSCI post-2000. The model used for estimating hazard ratios in Model Three including follow-up time less than one year post-discharge specifies 2 knots, rather than the 3 knots used in all other models, as well as attained age as a continuous variable to aid in model convergence.

Table 3. Marginally a	diusted survival	probabilities	according to	time since iniurv

		1-year	5- year	10-year	15-year	20-year
	Overall	91.5 (89.6-93.5)	86.2 (84.4-88.1)	81.2 (79.4-83.1)	77.1 (75.0-79.2)	73.7 (71.2-76.3)
	Sex					
	Male	91.5 (89.5-93.5)	86.2 (84.3-88.2)	81.2 (79.2-83.2)	77.1 (74.8-79.4)	73.7 (71.0-76.5)
	Female	91.5 (89.2-93.9)	86.3 (83.8-88.9)	81.3 (78.4-84.3)	77.2 (73.9-80.6)	73.8 (70.0-77.8)
	Attained age					
	16-30	98.8 (98.1-99.5)	97.9 (96.7-99.1)	96.9 (95.1-98.7)	95.9 (93.6-98.2)	95.0 (92.1-97.9)
ne	31-45	97.1 (95.9-98.2)	94.8 (93.1-96.6)	92.3 (90.0-94.7)	90.0 (87.0-93.1)	87.8 (84.2-91.6)
Ō	46-60	94.1 (92.0-96.1)	89.7 (86.9-92.5)	84.9 (81.3-88.7)	80.6 (76.2-85.2)	76.7 (71.5-82.3)
pde	61-75	85.7 (81.6-90.0)	76.1 (71.3-81.2)	66.6 (61.2-72.5)	58.7 (52.8-65.4)	52.3 (45.7-59.7)
Ĕ	76+	64.3 (56.2-73.6)	46.6 (39.0-55.6)	32.9 (26.2-41.3)	23.9 (17.9-31.8)	17.9 (12.6-25.5)
	SCI Type					
	Tetraplegia	89.2 (86.7-91.8)	82.8 (80.3-85.3)	76.8 (74.1-79.6)	72.0 (68.9-75.3)	68.1 (64.5-72.0)
	Paraplegia	93.4 (91.6-95.2)	89.0 (87.0-91.0)	84.7 (82.5-86.9)	81.0 (78.5-83.6)	77.9 (75.0-80.9)
	Completeness					
	Incomplete	92.9 (91.2-94.6)	88.3 (86.6-90.1)	84.0 (82.1-85.9)	80.3 (78.1-82.6)	77.3 (74.7-80.0)
	Complete	86.8 (83.7-90.0)	79.7 (76.7-82.9)	73.5 (70.3-76.8)	68.6 (65.2-72.2)	64.8 (61.0-68.8)
	Lesion Level & Completeness					
ΤŇ	Paraplegia, incomplete	93.3 (91.4-95.3)	89.0 (86.7-91.3)	84.8 (82.2-87.6)	81.4 (78.4-84.5)	78.6 (75.3-82.0)
- 	Paraplegia, complete	90.3 (87.5-93.2)	84.5 (81.3-87.9)	79.3 (75.7-83.1)	75.1 (71.2-79.2)	71.7 (67.6-76.2)
100	Tetraplegia, incomplete	91.9 (89.9-94.0)	86.9 (84.7-89.1)	82.2 (79.7-84.8)	78.4 (75.5-81.4)	75.3 (71.9-78.7)
2	Tetraplegia, complete	80.6 (76.0-85.6)	71.6 (66.7-76.8)	64.2 (59.1-69.8)	58.7 (53.2-64.7)	54.3 (48.6-60.8)
ee ee	Injury Severity*					
odel Thre	C1-C4 ABC	93.1 (89.3-97.1)	85.0 (78.9-91.6)	78.7 (70.8-87.6)	74.4 (65.0-85.2)	71.0 (60.4-83.5)
	C5-C8 ABC	91.0 (85.9-96.4)	81.2 (73.4-89.8)	74.0 (64.4-85.0)	69.2 (58.2-82.1)	65.5 (53.5-80.2)
	T1-S3 ABC	94.1 (91.3-97.1)	87.0 (82.7-91.5)	81.3 (75.5-87.4)	77.2 (70.1-85.0)	74.0 (65.8-83.3)
Σ	AIS D/E	96.8 (95.2-98.5)	92.6 (90.0-95.2)	88.8 (85.2-92.4)	85.9 (81.2-90.8)	83.5 (77.8-89.6)

Notes: \* Analyses including "Injury Severity" are restricted to 2000-2011 due to inadequate data prior to 2000. **Model one** is adjusted for: Current age, sex, decade of TSCI, cause of TSCI, lesion level, and completeness of injury; **Model two** is adjusted for: Current age, sex, decade of TSCI, cause of TSCI, cause of TSCI, cause of TSCI, and "Lesion level and completeness"; **Model three** is adjusted for: Current age, sex, injury severity, and cause of TSCI.