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LITERATURE REVIEW

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Influence of severity and level of injury on the occurrence of complications during the subacute and chronic stage of traumatic spinal cord injury: a systematic review

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OBJECTIVE Secondary health conditions (SHCs) are long-term complications that frequently occur due to traumatic spinal cord injury (tSCI) and can negatively affect quality of life in this patient population. This study provides an overview of the associations between the severity and level of injury and the occurrence of SHCs in tSCI.

METHODS A systematic search was conducted in PubMed and Embase that retrieved 44 studies on the influence of severity and/or level of injury on the occurrence of SHCs in the subacute and chronic phase of tSCI (from 3 months after trauma). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.

RESULTS In the majority of studies, patients with motor-complete tSCI (American Spinal Injury Association [ASIA] Impairment Scale [AIS] grade A or B) had a significantly increased occurrence of SHCs in comparison to patients with motor-incomplete tSCI (AIS grade C or D), such as respiratory and urogenital complications, musculoskeletal disorders, pressure ulcers, and autonomic dysreflexia. In contrast, an increased prevalence of pain was seen in patients with motor-incomplete injuries. In addition, higher rates of pulmonary infections, spasticity, and autonomic dysreflexia were observed in patients with tetraplegia. Patients with paraplegia more commonly suffered from hypertension, venous thromboembolism, and pain.

CONCLUSIONS This review suggests that patients with a motor-complete tSCI have an increased risk of developing SHCs during the subacute and chronic stage of tSCI in comparison with patients with motor-incomplete tSCI. Future studies should examine whether systematic monitoring during rehabilitation and the subacute and chronic phase in patients with motor-complete tSCI could lead to early detection and potential prevention of SHCs in this population.

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KEYWORDS spinal cord injury; secondary complications; secondary health conditions; risk factors; rehabilitation; systematic review

Suffering a traumatic spinal cord injury (tSCI) is much more involved than just the physical impairments due to neurological damage. In addition to these permanent neurological deficits, systemic nonneurological complications can also occur in the long term. These so-called secondary health conditions (SHCs) are accessory conditions that occur as a result of having a primary disabling condition, such as a spinal cord injury (SCI). SHCs can occur during the acute and chronic phase and lead to increased morbidity, increased rehospitalization rates, higher healthcare costs, and even death in patients with tSCI.[1–5]

The incidence of SHCs is increasing, mainly because of improved survival in this population due to improvements

ABBREVIATIONS AIS = ASIA Impairment Scale; ASIA = American Spinal Injury Association; CIR = cumulative incidence rate; SCI = spinal cord injury; SHC = secondary health condition; SMR = standardized mortality ratio; tSCI = traumatic SCI.

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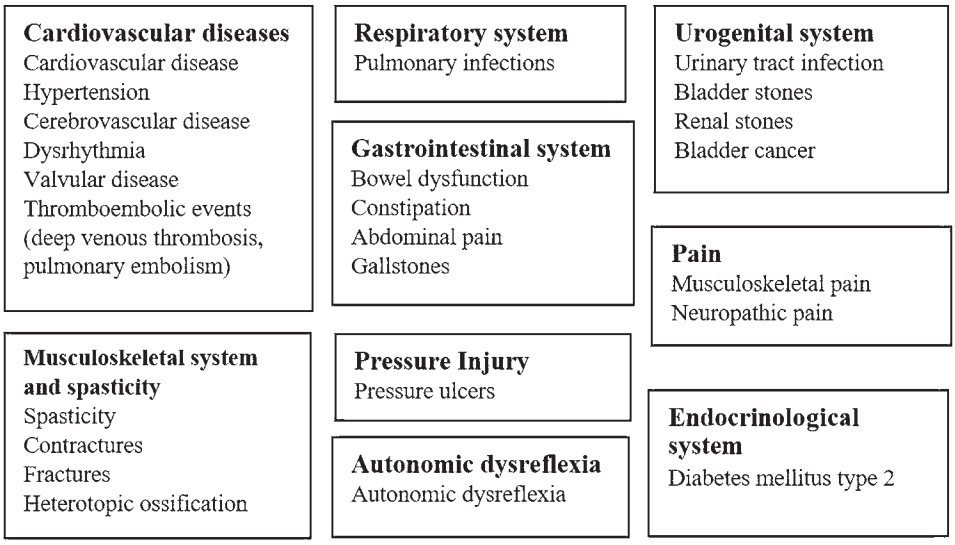

FIG. 1. Overview of included secondary health conditions.

in acute trauma care in the past several decades.[6,7] In addition to affecting neurological outcome, the initial severity and level of neurological injury also appear to be associated with the occurrence of several SHCs in the long term.[1,8] An overview presenting the extent of the association between severity and level of injury and each specific SHC is currently lacking. Such an overview is of great clinical importance for determining follow-up intensity for each individual with tSCI and for developing tailored follow-up care. Tailored follow-up care during the subacute and chronic phase could lead to early detection or potentially prevention of SHCs. The negative impact of SHCs on quality of life in the tSCI population and the heightened occurrence of these long-term complications emphasize the great urgency for tailored follow-up care for patients with tSCI.[9–11] Moreover, it can be used to inform this population in an early phase about the additional problems in the long term apart from the neurological sequelae.

Therefore, the aim of this systematic review was to provide an overview of the extent of associations between the severity and level of injury and the occurrence of SHCs in the subacute and chronic phase in patients with tSCI. The differences between occurrence of SHCs in patients with motor-complete and motor-incomplete tSCI were analyzed.

Methods

We performed a systematic review in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched the National Library of Medicine (PubMed) and the Excerpta Medica (Embase) databases on February 2, 2020, to identify all electronically available publications reporting on the association between severity or level of injury and occurrence of SHCs in adults with tSCI (*Appendix*). Additionally, we hand-searched the reference lists of all relevant reviews from this search to ensure that relevant studies were not missed. Backward and forward snowballing was performed on all included studies. Studies published in English were considered for inclusion. The Patient, Intervention, Comparison, Outcomes (PICO) framework was used to refine the search to the differences in occurrence of SHCs between patients with motor-complete and motor-incomplete tSCI, or tetraplegia and paraplegia.

Eligibility Criteria

The included SHCs were respiratory, gastrointestinal, musculoskeletal, urogenital, and endocrinological disorders; cardiovascular diseases; pain; pressure injury; autonomic dysreflexia; and other conditions caused by neurological deficit due to tSCI (Fig. 1). Studies containing a nontraumatic cause of SCI in more than 25% of the study population, fewer than 10 study participants, participants younger than 15 years of age, or a follow-up less than 3 months after injury in any of the study participants were excluded. A study population containing at least 75% of patients with tSCI was required because of the differences in long-term complication occurrences between tSCI and nontraumatic SCI.[10] In addition, studies that reported on secondary conditions in the acute stage of SCI, such as wound infections, cardiovascular instability, and thermodysregulation, were excluded. Studies published before 1990 and reviews were also excluded because of the improved acute management of tSCI in the last several decades and due to more accurate imaging techniques. The inclusion and exclusion criteria are listed in Table 1.

Data Extraction and Outcome Measures

Two raters (C.Y.A. and J.A.N.V.G.) independently reviewed and selected publications for analysis using a standardized form and data collection manual. Discrepancies were adjudicated by a third rater (P.V.T.W.). Studies were included when they contained analysis on the association between severity and/or level of injury and the occurrence of SHCs in the subacute and chronic phase of tSCI.

TABLE 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Clinical studied w/ a prospective, case-control, cross-sectional, or retrospective design	(Systematic) reviews, meta-analyses, case reports
Sample size ≥10 participants	Study population containing a nontraumatic cause of SCI for >25% of the cohort
Studies on the association btwn severity &/or level of injury & the occurrence of secondary health complications	Follow-up <3 mos
Secondary health complications during subacute & chronic stage	
Studies published after 1990	

Data obtained from the full texts included sample size, mean age of the study population at onset of injury, length of follow-up, and severity and level of injury of the participants. Multivariate analyses were preferred to minimize the influence of bias, and p values were extracted to investigate differences in SHCs for each subgroup. A p value < 0.05 was set as significant. To determine the impact of severity and level of injury on the occurrence of SHCs, prevalence, incidence, relative risk (RR), hazard ratio (HR), and odds ratio (OR) were extracted from the full texts or self-calculated and compared separately.

The primary outcome was the difference in occurrence of SHCs between patients with motor-complete and motor-incomplete injury. In cases in which a study compared complete and incomplete tSCI, it will explicitly be described in the results. Severity of injury was defined according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS) or similar scores, with AIS grade A defined as complete injury and AIS grades B, C, and D defined as incomplete injury.[12] Motor-complete injury was equal to AIS grade A and B, motor-incomplete injury was equal to AIS grades C and D.[12] To describe the level of injury, paraplegia was defined as spinal cord damage below the level of C8 resulting in (partial) functional loss in the trunk and/or the lower extremities, and tetraplegia was defined as spinal cord damage at or above C8 resulting in (partial) impairment of the upper and lower extremities.[13] The subacute stage was defined as equal to or more than 3 months after trauma to ensure that acute complications were excluded from this analysis. The chronic stage is attained 12 months after tSCI.[13]

Results

The search strategy identified 10,514 publications, of which 8596 unique publications remained after removing the duplicates. Of these, 44 studies were suitable for inclusion (Fig. 2). The study size varied from 31 to 45,486 participants. The range of mean age at injury of the included participants was 25–55 years. Length of follow-up was between 3 months and 25 years. An overview of the studies is shown in Tables 2 and 3.

Cardiovascular Diseases

Four studies reported on cardiovascular diseases after tSCI, which showed an inconsistent association.[14–17] Hypertension was investigated in 3 studies, which all demonstrated lower rates of hypertension in tetraplegic patients compared to patients with paraplegia (RR 0.22, 95% confidence interval [CI] 0.09–0.5; OR 0.56, 95% CI 0.39–0.80; 18% vs 45%, p < 0.001).[16,18,19] Furthermore, 1 study with 545 participants showed that people with tetraplegia were more prone to develop cerebrovascular disease (RR 5.1, 95% CI 1.2–21), dysrhythmia (RR 3.9, 95% CI 2.5–6.4) or valvular disease (RR 3.3, 95% CI 1.6–6.7) in at least 20 years after injury compared to people with paraplegia.[16] The strength of evidence is low.

Thromboembolic Events

Four studies investigated the occurrence of venous thromboembolism during the chronic stage of tSCI.[14,20–22] Two studies reported higher prevalence of venous thromboembolism in motor-complete injury compared to motor-incomplete injury.[21,22] Regarding level of injury, 1 study found a higher prevalence in people with paraplegia compared to people with tetraplegia,[22] whereas 1 study found higher rates of venous thromboembolism in complete paraplegia compared to complete tetraplegia (OR 1.8, 95% CI 1.4–2.3).[20] The remaining study did not find an association between venous thromboembolism and injury characteristics.[14] The strength of evidence is low.

Respiratory System

Five studies reported on pulmonary infections during the chronic phase of tSCI.[14,15,19,21,23] Of these 5 studies, 2 prospective cohorts indicated an association between motor-complete injury and a higher occurrence of pulmonary infections, both showing a comparable increased risk (OR 3.5, 95% CI 1.7–7.2; RR 3.4, 95% CI 2.1–5.5).[14,23] One study found an increased prevalence of pulmonary infections in patients with complete tetraplegia in comparison to other injuries (9.8% vs 1.1%–3.8%, p < 0.01).[21] Moreover, a decreased rate of pulmonary infections in patients with paraplegia is shown in 2 studies.[14,15] The strength of evidence is medium to low.

Gastrointestinal System

Five studies reported on neurogenic bowel dysfunction,[19,24–27] 3 of which showed an association between neurogenic bowel dysfunction and motor-completeness.[25–27] One study even demonstrated an up to 13 times increased risk in AIS grade A patients compared to AIS grade D patients.[27] With regard to level of injury, 1 study found an association between bowel dysfunction and tetraplegia, with a lower occurrence of bowel dysfunction in persons with tetraplegia (OR 0.70, 95% CI 0.52–0.84).[19] Other studies did not show significant associations between level of injury and bowel dysfunction or abdominal pain.[28]

Constipation was investigated in 1 study with 291 participants, where a lower prevalence of constipation was observed in patients with incomplete paraplegia compared to patients with complete tetraplegia (OR 0.33, 95% CI 0.13–0.84).[25] One retrospective study with 439 participants

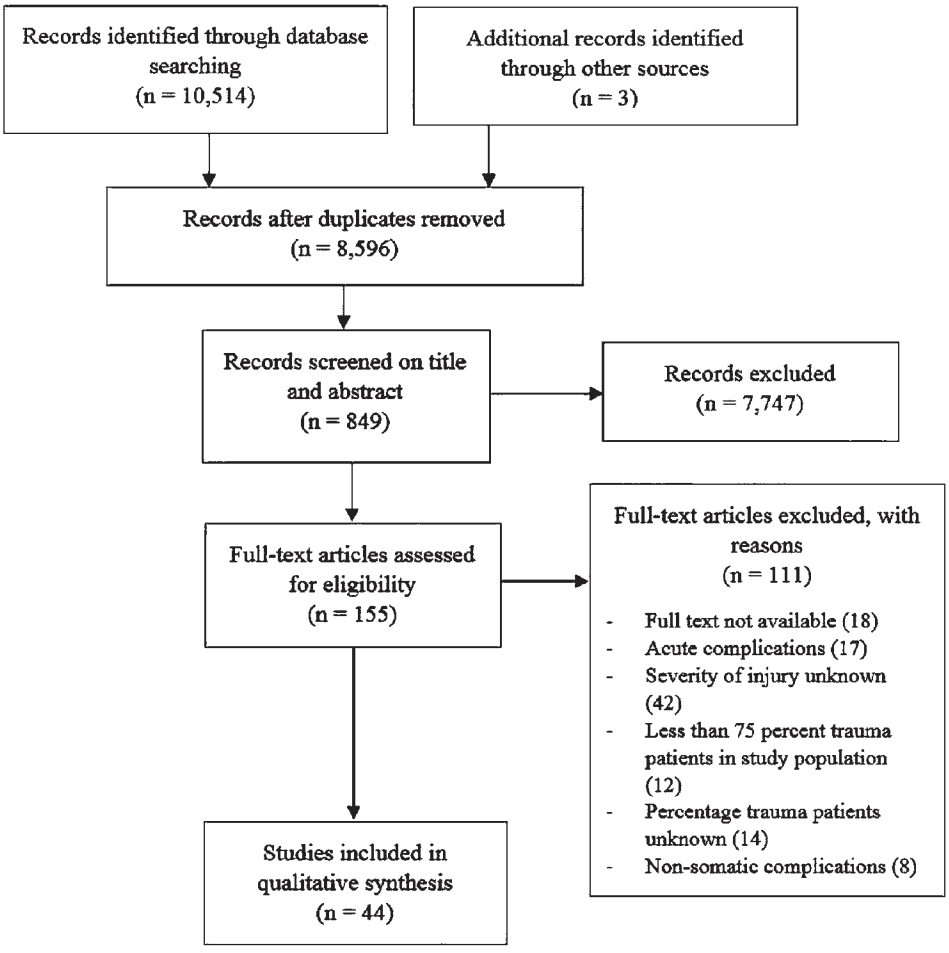

FIG. 2. PRISMA flowchart describing screening and review process. Data added to the PRISMA template [from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 6(7): e1000097] under the terms of the Creative Commons Attribution License.

demonstrated an increased risk of gallstones in motor-complete injury in comparison to motor-incomplete injury (OR 1.7, 95% CI 1.0–2.6).[29] The strength of evidence is low.

Urogenital System

Six of 7 studies demonstrated a higher prevalence of urinary tract infections in patients with motor-complete injury compared to patients with motor-incomplete injury, with an increased risk between 1.3 and 2.8 and a prevalence between 36%–67% and 19%–39%, respectively.[14,15,19,22,30–32] Bladder stone prevalence was reported in 3 studies, 2 of which showed a higher prevalence in complete injuries in comparison to incomplete injuries (5-year cumulative incidence rate [CIR] AIS grade A = 16 vs AIS grade D = 3.1, $p = 0.001$; 68% vs 32%, $p < 0.0001$).[33–35] Renal stone formation was reported in 3 studies, 2 of which found higher rates of renal stone formation in motor-complete injury in comparison to motor-incomplete tSCI.[21,34] One study even found a 4 times higher risk of renal stones in motor-complete injury in comparison to motor-incomplete injury.[34] The remaining study showed that patients with AIS grade A, B, or C tetraplegia had a 1.9 times higher risk of developing renal stones in comparison to patient with AIS grade D injury.[36]

Finally, 2 studies investigated the presence of bladder cancer in the tSCI population. Both studies observed that people with tSCI are more likely to die of bladder cancer compared to the general population (standardized mortality ratio [SMR] between 6.7 and 71).[37,38] One of these studies, including 45,496 tSCI participants, reported that people with motor-complete injuries are more at risk to die from bladder cancer compared to patients with motor-incomplete injuries (SMR = 13–15 vs 1.4).[37] Additional findings were a calculated 15-fold higher risk of developing bladder cancer in people with tSCI compared to the general population and the fact that bladder cancer seems to appear at a younger age in the tSCI population in comparison to the general population.[38] The strength of evidence is medium to low.

Pain

Eight studies reported on chronic pain after tSCI.[14,15,19,39–43] Four of 8 studies indicated higher rates of pain in motor-incomplete tSCI in comparison to motor-complete in-

TABLE 2. Overview of included studies on the association between severity of injury and SHCs

Authors & Year	Study Design	No. of Pts	Mean Age at Injury (SD/ range), yrs	AIS Grades: No.		FU/Time Postinjury (SD/range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Cardiovascular disease											
Haisma et al., 2007[14]	Pro	212	40 (14)	A: 95	BCD: 117	1 yr after discharge rehab center	Comp vs incomp	Multi	OR	0.60 (0.19–1.9)	NS
Adriaansen et al., 2013[15]	Pro	139	40 (14)	A: 79	BCD: 60	5 yrs after discharge rehab center	Comp vs incomp	Multi	OR	0.70 (0.22–2.3)	NS
Groah et al., 2001[16]	Pro	545	27 (9)	ABC: 384	D: 161	20 yrs	AIS ABC vs AIS D	Uni	RR	0.80 (0.58–1.1)	NS
Lee et al., 2006[17]	CSS	47	30 (9)	AB: 24	CD: 23	16 (2) yrs	Motor-comp tetra	Uni	Chi-square	85%	NA
							Motor-in-comp tetra			63%	
							Motor-comp para			55%	
							Motor-in-comp tetra			50%	
Hypertension											
Groah et al., 2001[16]	Pro	545	27 (9)	ABC: 384	D: 161	20 yrs	AIS ABC vs AIS D	Uni	RR	1.4 (0.85–2.2)	NS
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	A: 270	BCD: 511	14 (1–60) yrs	Comp vs incomp	Multi	OR	0.78 (0.52–1.2)	NS
Adriaansen et al., 2017[18]	CSS	282	26 (20–33)	A: 194	BCD: 88	22 (17–30) yrs	Comp vs incomp	Uni	Chi-square	68% vs 69%	NS
Cerebrovascular disease											
Groah et al., 2001[16]	Pro	545	27 (9)	ABC: 384	D: 161	20 yrs	AIS ABC vs AIS D	Uni	RR	3.1 (0.38–25)	NS
Dysrhythmia											
Groah et al., 2001[16]	Pro	545	27 (9)	ABC: 384	D: 161	20 yrs	AIS ABC vs AIS D	Uni	RR	2.5 (1.2–5.6)	NA
Valvular disease											
Groah et al., 2001[16]	Pro	545	27 (9)	ABC: 384	D: 161	20 yrs	AIS ABC vs AIS D	Uni	RR	2.5 (0.62–2.7)	NS
Thromboembolic events											
Jones et al., 2005[20]	Retro	16,240	45 (21)	A: 2235	BCD: 13,003	1 yr	Comp tetra	Multi	OR	1.0 (ref)	<0.01
							Comp para			1.8 (1.4–2.3	
							Incomp tetra			0.80 (0.60–1.1)	
							Incomp para			1.2 (0.8–1.7)	
Haisma et al., 2007[14]	Pro	212	40 (14)	A: 95	BCD: 117	1 yr after discharge rehab center	Comp vs incomp	Multi	OR	1.8 (0.6–5.7)	NS

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TABLE 2. Overview of included studies on the association between severity of injury and SHCs

Authors & Year	Study Design	No. of Pts	Mean Age at Injury (SD/range), yrs	AIS Grades: No.		FU/Time Postinjury (SD/range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Cardiovascular disease (*continued*)											
Thromboembolic events (*continued*)											
McKinley et al., 1999[21]	Pro	6594	NA	A: 3165	BCD: 3429	1–20 yrs	Comp tetra	Uni	Chi-square	2.7%	<0.001
							Comp para			3.2%	
							Incomp tetra			1.4%	
							Incomp para			1.2%	
Noreau et al., 2000[22]	CSS	482	29 (12)	AB: 300	CD: 182	14 (12) yrs	Motor-comp vs motor-incomp	Uni	Chi-square	6.1% vs 2%	<0.0001
Respiratory system											
Pulmonary infection											
Aarabi et al., 2012[23]	Pro	109	43 (17)	AB: 64	CD: 45	1 yr	Motor-comp vs motor-incomp	Multi	RR	3.4 (2.1–5.5)	<0.001
Adriaansen et al., 2013[15]	Pro	139	40 (14)	A: 79	BCD: 60	5 yrs after discharge rehab center	Comp vs incomp	Multi	OR	1.9 (0.65–5.3)	NS
Haisma et al., 2007[14]	Pro	212	40 (14)	A: 95	BCD: 117	1 yr after discharge rehab center	Comp vs incomp	Multi	OR	3.5 (1.7–7.2)	NA
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	A: 270	BCD: 511	14 (1–60) yrs	Comp vs incomp	Multi	OR	0.97 (0.62–1.5)	NS
McKinley et al., 1999[21]	Pro	5406	NA	A: NA	BCD: NA	1–20 yrs	Comp tetra	Uni	Chi-square	9.8%	<0.01
							Comp para			2.0%	
							Incomp tetra			3.8%	
							Incomp para			1.1%	
Gastrointestinal system											
Bowel dysfunction											
Han et al., 1998[24]	CSS	72	38 (12)	AB: 47	CD: 25	3 (4) yrs	Motor-comp vs motor-incomp	Uni	Chi-square	55% vs 68%	>0.05
Tate et al., 2016[25]	CSS	291	31 (13)	AB: 178	CD: 113	20 (11) yrs	Motor-comp tetra	Multi	Logistic regression (β)	1.0 (ref)	
							Motor-comp para			−1.6 (−2.7 to −0.45)	0.016
							Motor-incomp tetra			−1.5 (−2.8 to −0.28)	0.007
							Motor-incomp para			−1.9 (−3.5 to −0.33)	0.018
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	A: 270	BCD: 511	14 (1–60) yrs	Comp vs incomp	Multi	OR	0.92 (0.67–1.3)	NS
Adriaansen et al., 2015[26]	CSS	258	24 (29–65)	A: 181	BCD: 77	24 (10–47) yrs	Comp vs incomp	Multi	OR	2.0	0.046

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TABLE 2. Overview of included studies on the association between severity of injury and SHCs

Authors & Year	Study Design	No. of Pts	Mean Age at Injury (SD/ range), yrs	AIS Grades: No.		FU/Time Postinjury (SD/range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Gastrointestinal system (*continued*)											
Bowel dysfunction (*continued*)											
Liu et al., 2010[27]	CSS	142	45 (18–84)	A: 38	BCD: 104	1 to ≥10 yrs	AIS D	Multi	OR	1.0 (ref)	0.001
							AIS A			13 (3.3–50)	
							AIS B			1.7 (0.8–5.3)	
							AIS C			1.3 (3.3–50)	
Constipation											
Tate et al., 2016[25]	CSS	291	31 (13)	AB: 178	CD: 113	20 (11) yrs	Motor-comp tetra	Multi	OR	1.0 (ref)	NA
							Motor-comp para			0.39 (0.11–1.5)	
							Motor-in-comp tetra			0.45 (0.17–1.2)	
							Motor-in-comp para			0.33 (0.13–0.84)	
Abdominal pain											
Finnerup et al., 2008[28]	CSS	193	26 (13)	A: 116	BCD: 77	22 (9.1) yrs	Comp vs incomp	Uni	Pearson chi-square	NA	NS
Gallstones											
Moonka et al., 1999[29]	Retro	439	53 (13)	AB: 255	CD: 184	18 (13) yrs	Motor-comp vs motor-incomp	Multi	OR	1.7 (1.0–2.6)	NA
Urogenital system											
Urinary tract infection											
Noreau et al., 2000[22]	CSS	482	29 (12)	AB: 300	CD: 182	14 (12) yrs	Motor-comp vs motor-incomp	Uni	Chi-square	67% vs 38%	<0.0001
Wahman et al., 2019[32]	Pro	31	55 (17)	A: 13	BCD: 32	18 mos	Comp vs incomp	Uni	Fisher exact	50% vs 37%	NS
Stillman et al., 2018[30]	Pro	147	41	AB: 72	CD: 75	1 yr after discharge rehab center	Motor-comp vs motor-incomp	Uni	CIR	36% vs 19%	0.040
Adriaansen et al., 2013[15]	Pro	139	40 (14)	A: 79	BCD: 60	5 yrs after discharge rehab center	Comp vs incomp	Multi	OR	2.8 (1.7–4.8)	NA
Haisma et al., 2007[14]	Pro	212	40 (14)	A: 95	BCD: 117	1 yr after discharge rehab center	Comp vs incomp	Multi	OR	1.8 (1.3–2.6)	NA
Herruzo Cabrera et al., 1994[31]	Pro	121	31	AB: NA	CD: NA	6 mos	Motor-comp vs motor-incomp	Multi	OR	2.8 (1.0–7.8)	NA
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	A: 270	BCD: 511	14 (1–60) yrs	Comp vs incomp	Multi	OR	2.3 (1.7–3.2)	NA

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TABLE 2. Overview of included studies on the association between severity of injury and SHCs

Authors & Year	Study Design	No. of Pts	Mean Age at Injury (SD/range), yrs	AIS Grades: No.		FU/Time Postinjury (SD/range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Urogenital system (*continued*)											
Bladder stones											
Ku et al., 2006[34]	Retro	140	23 (18–53)	AB: 34	CD: 106	17 (1–37) yrs	Motor-comp vs motor-incomp	Multi	OR	1.4 (0.56–3.3)	NS
Chen et al., 2001[33]	Retro	1336	32 (18–80)	A: 628	BCD: 708	6 (1–24) yrs	AIS A	Multi	5-yr CIR	16	<0.0001
							AIS B			7.8	
							AIS C			6.0	
							AIS D			3.1	
Favazza et al., 2004[35]	Retro CC	218	38 (23–84)	A: 118	BCD: 100	21 (0.5–55) yrs	Comp vs incomp	Uni	Student t-test	68% vs 32%	<0.0001
Renal stones											
Chen et al., 2000[36]	Retro	8314	15–80	A: 3824	BCD: 4490	3 yrs (7 mos–13 yrs)	Para AIS ABC vs AIS D	Multi	RR	1.4 (0.8–2.7)	NS
							Tetra AIS ABC vs AIS D			1.9 (1.0–3.6)	NA
Ku et al., 2006[34]	Retro	140	23 (18–53)	AB: 34	CD: 106	17 (1–37) yrs	Motor-comp vs motor-incomp	Multi	OR	4.1 (1.3–13)	NA
McKinley et al., 1999[21]	Pro	3581	NA	A: NA	BCD: NA	1–20 yrs	Comp tetra vs other injury types	Uni	Chi-square	20% vs unknown	<0.0014
Bladder cancer											
Nahm et al., 2015[37]	Retro	45,486	33 (17)	ABC: 29,731	D: 10,379	13 (10) yrs	Tetra AIS A, B, & C vs non-SCI		SMR	15 (10–21)	NA
							Para AIS A, B, & C vs non-SCI			13 (9.3–17)	NA
Groah et al., 2002[38]	Retro	3670	30	A: 2385	BCD: 1285	20 (12–40) yrs	Comp vs incomp	Multi	Cox regression	NA	NS
Pain											
Musculoskeletal pain											
Klotz et al., 2002[39]	CSS	1363	30 (13)	AB: 723	CD: 640	13 (11) yrs	Motor-comp vs motor-incomp	Uni	Pearson chi-square	70% vs 77%	0.003
Cardenas et al., 2004[40]	CSS	2879	25 (9.4)	A: 1411	BCD: 1468	1–6 yrs	Comp vs incomp	Multi	Logistic regression	NA	NS
Modirian et al., 2010[41]	CSS	1295	22 (6.4)	A: 1165	BCD: 130	14 (3) yrs	Comp vs incomp	Uni	Chi-square	65% vs 84%	0.013
Iorio-Morin et al., 2018[42]	CSS	1051	30 (18–71)	AB: 578	CD: 473	19 (1–75) yrs	Motor-comp vs motor-incomp	Uni	Student t-test	NA	NS
Adriaansen et al., 2013[15]	Pro	139	40 (14)	A: 79	BCD: 60	5 yrs after discharge rehab center	Comp vs incomp	Multi	OR	0.76 (0.40–1.5)	NS

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TABLE 2. Overview of included studies on the association between severity of injury and SHCs

Authors & Year	Study Design	No. of Pts	Mean Age at Injury (SD/ range), yrs	AIS Grades: No.		FU/Time Postinjury (SD/range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Pain (*continued*)											
Musculoskeletal pain (*continued*)											
Haisma et al., 2007[14]	Pro	212	40 (14)	A: 95	BCD: 117	1 yr after discharge rehab center	Comp vs incomp	Multi	OR	0.73 (0.48–1.1)	NS
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	A: 270	BCD: 511	14 (1–60) yrs	Comp vs incomp	Multi	OR	1.1 (0.81–1.5)	NS
Demirel et al., 1998[43]	CSS	47	31 (11)	A: 15	BCD: 32	126 days	Comp vs incomp uni	Uni	Fisher exact test	50% vs 60%	<0.05
Neuropathic pain											
Haisma et al., 2007[14]	Pro	212	40 (14)	A: 95	BCD: 117	1 yr after discharge rehab center	Comp vs incomp	Multi	OR	0.57 (0.29–1.1)	NS
Adriaansen et al., 2013[15]	Pro	139	40 (14)	A: 79	BCD: 60	5 yrs after discharge rehab center	Comp vs incomp	Multi	OR	1.2 (0.54–2.7)	NS
Nakipoglu et al., 2013[44]	CSS	69	38 (11)	A: 25	BCD: 44	>6 mos	Comp vs incomp	Uni	Student t-test	NA	NS
Wahman et al., 2019[32]	Pro	31	55 (17)	A: 13	BCD: 32	18 mos	Comp vs incomp	Uni	Fisher exact test	42% vs 42%	NS
Musculoskeletal disorders & spasticity											
Spasticity											
Noreau et al., 2000[22]	CSS	482	29 (12)	AB: 300	CD: 182	14 (12) yrs	Motor-comp vs motor-incomp	Uni	Chi-square	43% vs 35%	NS
Wahman et al., 2019[32]	Pro	31	55 (17)	A: 13	BCD: 32	18 mos	Comp vs incomp	Uni	Fisher exact test	57% vs 30%	NS
Holtz et al., 2017[45]	Pro	465	43 (18)	AB: NA	CD: NA	125 days	Motor-comp vs motor-incomp	Uni	t-test	NA	<0.001
Haisma et al., 2007[14]	Pro	212	40 (14)	A: 95	BCD: 117	1 yr after discharge rehab center	Comp vs incomp	Multi	OR	0.95 (0.6–1.5)	NS
Adriaansen et al., 2013[15]	Pro	139	40 (14)	A: 79	BCD: 60	5 yrs after discharge rehab center	Comp vs incomp	Multi	OR	1.1 (0.66–2.0)	NS
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	A: 270	BCD: 511	14 (1–60) yrs	Comp vs incomp	Multi	OR	1.0 (0.73–1.49)	NS
Contractures											
Klotz et al., 2002[39]	CSS	1363	30 (13)	AB: 723	CD: 640	13 (11) yrs	Motor-comp vs motor-incomp	Uni	Pearson chi-square	28% vs 35%	<0.001
Fractures											
Gifre et al., 2014[46]	Retro	63	36 (20)	A: 34	BCD: 29	10 yrs	Comp vs incomp	Multi	RR	4.0 (1.1–24)	0.037

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TABLE 2. Overview of included studies on the association between severity of injury and SHCs

Authors & Year	Study Design	No. of Pts	Mean Age at Injury (SD/range), yrs	AIS Grades: No.		FU/Time Postinjury (SD/range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Musculoskeletal disorders & spasticity (*continued*)											
Fractures (*continued*)											
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	A: 270	BCD: 511	14 (1–60) yrs	Comp vs incomp	Multi	OR	1.7 (0.94–3.1)	NS
Heterotopic ossification											
Citak et al., 2012[47]	CCS	264	46 (17)	A: 171	BCD: 93	125 days–1 yr	Comp vs incomp	Uni	OR	5.8 (3.2–11)	NA
Coelho & Beraldo, 2009[50]	Retro CC	66	29	A: 45	B: 21	6 (3–9) mos	Comp vs incomp	Uni	OR	1.5 (0.5–4.9)	NS
Krauss et al., 2015[48]	Retro	575	43 (17–79)	AB: 385	CD: 190	154 days	Motor-comp vs motor-incomp	Uni	Fisher exact test	64% vs 8.5%–19%	0.048
Wittenberg et al., 1992[49]	Pro	356	35	AB: 143	CD: 213	≥2 yrs	Motor-comp vs motor-incomp	Uni	Student t-test	42% vs 13%	<0.05
Haisma et al., 2007[14]	Pro	212	40 (14)	A: 95	BCD: 117	1 yr after discharge rehab center	Comp vs incomp	Multi	OR	2.5 (1.3–4.7)	NA
Adriaansen et al., 2013[15]	Pro	139	40 (14)	A: 79	BCD: 60	5 yrs after discharge rehab center	Comp vs incomp	Multi	OR	1.6 (0.62–3.9)	NS
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	A: 270	BCD: 511	14 (1–60) yrs	Comp vs incomp	Multi	OR	1.0 (0.57–1.8)	NS
Pressure ulcers											
Noreau et al., 2000[22]	CSS	482	29 (12)	AB: 300	CD: 182	14 (12) yrs	Motor-comp vs motor-incomp	Uni	Chi-square	38% vs 11%	<0.0001
Klotz et al., 2002[39]	CSS	1363	30 (13)	AB: 723	CD: 640	13 (11) yrs	Motor-comp vs motor-incomp	Uni	Pearson chi-square	19% vs 8%	<0.01
McKinley et al., 1999[21]	Pro	1073	NA	A: NA	BCD: NA	1–20 yrs	Comp tetra	Uni	Chi-square	25%	<0.005
							Comp para			28%	
							Incomp tetra			18%	
							Incomp para			15%	
Chen et al., 2005[51]	Pro	3361	31 (14)	AB: 2238	CD: 1109	5 (4) yrs	AIS A vs AIS D	Multi	OR	8.0 (5.6–11)	<0.001
							AIS B vs AIS D			6.0 (4.1–8.8)	
							AIS C vs AIS D			3.0 (2.1–4.4)	
Krishnan et al., 2017[52]	Retro	1748	37 (16)	A: 765	BCD: 983	≥3 mos	AIS A vs AIS B, AIS C & AIS D	Uni	Mann-Whitney U-test	64% vs 16%–23%	<0.001

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TABLE 2. Overview of included studies on the association between severity of injury and SHCs

Authors & Year	Study Design	No. of Pts	Mean Age at Injury (SD/ range), yrs	AIS Grades: No.		FU/Time Postinjury (SD/range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Pressure ulcers (*continued*)											
Haisma et al., 2007[14]	Pro	212	40 (14)	A: 95	BCD: 117	1 yr after discharge rehab center	Comp vs incomp	Multi	OR	1.7 (1.2–2.6)	NA
Adriaansen et al., 2013[15]	Pro	139	40 (14)	A: 79	BCD: 60	5 yrs after discharge rehab center	Comp vs incomp	Multi	OR	3.3 (1.9–5.8)	NA
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	A: 270	BCD: 511	14 (1–60) yrs	Comp vs incomp	Multi	OR	2.6 (1.9–3.7)	NA
Correa et al., 2006[53]	CC	41	35 (12)	AB: 25	CD: 16	7 (4) yrs	Motor-comp para vs other injuries	Multi	OR	6.6 (1.7–25)	NA
Recurrence of pressure ulcers											
Guihan et al., 2008[54]	CSS	64	35	A: 48	BCD: 16	22 (1–53) yrs	AIS A vs AIS B, C & D	Uni	Fisher exact test	42% vs 25%	>0.05
Paker et al., 2018[55]	Retro	39	38 (6.7)	AB:	CD:	33 (12–288) mos	Motor-comp vs motor-incomp	Uni	OR	0.654 (0.13–3.1)	NS
Autonomic dysreflexia											
Haisma et al., 2007[14]	Pro	212	40 (14)	A: 95	BCD: 117	1 yr after discharge rehab center	Comp vs incomp	Multi	OR	2.4 (1.3–4.4)	NA
Adriaansen et al., 2013[15]	Pro	139	40 (14)	A: 79	BCD: 60	5 yrs after discharge rehab center	Comp vs incomp	Multi	OR	3.1 (1.4–6.7)	NA
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	A: 270	BCD: 511	14 (1–60) yrs	Comp vs incomp	Multi	OR	2.3 (1.6–3.4)	NA
Endocrinological system											
Diabetes mellitus type 2											
Lai et al., 2014[56]	Retro	35,043	52	AB: NA	CD: NA	6 yrs	Tetra vs non-SCI	Multi	HR	1.2 (1.1–1.4)	<0.01
							Motor-comp para vs non-SCI			2.4 (1.1–5.2)	<0.0001
							Motor-comp para vs non-SCI			1.6 (1.3–1.9)	<0.05

CC = case-control; comp = complete; CSS = cross-sectional study; FU = follow-up; incomp = incomplete; Multi = multivariate; NA = not applicable; NS = nonsignificant; para = paraplegia; Pro = prospective; Pts = patients; rehab = rehabilitation; Retro = retrospective; tetra = tetraplegia; Uni = univariate.

jury, with up to 84% of those with motor-incomplete tSCI suffering from pain.[39,41–43] The level of injury was associated with pain as well, as 2 studies showed an increased occurrence of pain in patients with paraplegia compared to people with tetraplegia (46%–78% vs 62%–84%, $p < 0.001$).[41,43] Three studies did not report an association between chronic pain and level or severity of injury.[14,15,19] Four studies reported on neuropathic pain, 2 of which demonstrated higher rates of neuropathic pain in patients with tetraplegia in comparison to patients with paraplegia (57% vs 10%, OR 0.34, 95% CI 0.13–0.89).[14,15,32,44] The strength of evidence is low.

TABLE 3. Overview of included studies on the association between level of injury and SHCs

Authors & Year	Design	No. of Pts	Mean Age at Injury (SD/ range), yrs	Tetraplegia/ Paraplegia (n)		FU/Time Postinjury (SD/ range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Cardiovascular disease				Tetra	Para						
Haisma et al., 2007[14]	Pro	212	40 (14)	138	74	1 yr after discharge rehab center	Para vs tetra	Multi	OR	0.90 (0.31–2.6)	NS
Adriaansen et al., 2013[15]	Pro	139	40 (14)	50	89	5 yrs after discharge rehab center	Para vs tetra	Multi	OR	2.3 (0.57–9.3)	NS
Groah et al., 2001[16]	Pro	545	27 (9)	99	285	20 yrs	Tetra ABC vs para ABC	Uni	RR	0.30 (0.13–0.70)	NS
Lee et al., 2006[17]	CSS	47	30 (9)	24	23	16 (2) yrs	Motor-comp tetra	Uni	Chi-square	85%	<0.05
							Motor-in-comp tetra			63%	
							Motor-comp para			55%	
							Motor-in-comp tetra			50%	
Hypertension											
Groah et al., 2001[16]	Pro	545	27 (9)	99	285	20 yrs	Tetra ABC vs para ABC	Uni	RR	0.22 (0.09–0.5)	NA
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	358	423	14 (1–60) yrs	Tetra vs para	Multi	OR	0.56 (0.39–0.80)	0.002
Adriaansen et al., 2017[18]	CSS	282	26 (20–33)	124	158	22 (17–30) yrs	Tetra vs para	Uni	Chi-square	18% vs 45%	<0.001
Cerebrovascular disease											
Groah et al., 2001[16]	Pro	545	27 (9)	99	285	20 yrs	Tetra ABC vs para ABC	Uni	RR	5.1 (1.2–21)	NA
Dysrhythmia											
Groah et al., 2001[16]	Pro	545	27 (9)	99	285	20 yrs	Tetra ABC vs para ABC	Uni	RR	3.9 (2.5–6.4)	NA
Valvular disease											
Groah et al., 2001[16]	Pro	545	27 (9)	99	285	20 yrs	Tetra ABC vs para ABC	Uni	RR	3.3 (1.6–6.7)	NA
Thromboembolic events											
Jones et al., 2005[20]	Retro	16,240	45 (21)	8613	6625	1 yr	Comp tetra	Multi	OR	1.0 (ref)	<0.01
							Comp para			1.8 (1.4–2.3)	
							Incomp tetra			0.80 (0.60–1.1)	
							Incomp para			1.2 (0.8–1.7)	
Haisma et al., 2007[14]	Pro	212	40 (14)	138	74	1 yr after discharge rehab center	Para vs tetra	Multi	OR	1.4 (0.42–4.3)	NS

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TABLE 3. Overview of included studies on the association between level of injury and SHCs

Authors & Year	Design	No. of Pts	Mean Age at Injury (SD/ range), yrs	Tetraplegia/ Paraplegia (n)		FU/Time Postinjury (SD/ range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Cardiovascular disease (*continued*)				Tetra	Para						
Thromboembolic events (*continued*)											
McKinley et al., 1999[21]	Pro	6594	NA	NA	NA	1–20 yrs	Comp tetra	Uni	Chi-square	2.7%	<0.001
							Comp para			3.2%	
							Incomp tetra			1.4%	
							Incomp para			1.2%	
Noreau et al., 2000[22]	CSS	482	29 (12)	211	271	14 (12) yrs	Tetra vs para	Uni	Chi-square	0.9% vs 7.3%	0.03
Respiratory system											
Pulmonary infection											
Adriaansen et al., 2013[15]	Pro	139	40 (14)	50	89	5 yrs after discharge rehab center	Para vs tetra	Multi	OR	0.18 (0.06–0.52)	NA
Haisma et al., 2007[14]	Pro	212	40 (14)	138	74	1 yr after discharge rehab center	Para vs tetra	Multi	OR	0.26 (0.13–0.53)	NA
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	358	423	14 (1–60) yrs	Tetra vs para	Multi	OR	1.2 (0.82–1.8)	NS
McKinley et al., 1999[21]	Pro	5406	NA	NA	NA	1–20 yrs	Comp tetra	Uni	Chi-square	9.8%	<0.01
							Comp para			2.0%	
							Incomp tetra			3.8%	
							Incomp para			1.1%	
Gastrointestinal system											
Bowel dysfunction											
Tate et al., 2016[25]	CSS	291	31 (13)	161	130	20 (11) yrs	Motor-comp tetra	Multi	Logistic regression (β)	1.0 (ref)	
							Motor-comp para			−1.6 (−2.7 to −0.45)	0.016
							Motor-in-comp tetra			−1.5 (−2.8 to −0.28)	0.007
							Motor-in-comp para			−1.9 (−3.5 to −0.33)	0.018
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	358	423	14 (1–60) yrs	Tetra vs para	Multi	OR	0.70 (0.52–0.84)	0.016
Constipation											
Tate et al., 2016[25]	CSS	291	31 (13)	161	130	20 (11) yrs	Motor-comp tetra	Multi	OR	1.0 (ref)	NA
							Motor-comp para			0.39 (0.11–1.5)	
							Motor-in-comp tetra			0.45 (0.17–1.2)	
							Motor-in-comp para			0.33 (0.13–0.84)	

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TABLE 3. Overview of included studies on the association between level of injury and SHCs

Authors & Year	Design	No. of Pts	Mean Age at Injury (SD/ range), yrs	Tetraplegia/ Paraplegia (n)		FU/Time Postinjury (SD/ range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Urogenital system											
Urinary tract infection											
Noreau et al., 2000[22]	CSS	482	29 (12)	211	271	14 (12) yrs	Tetra vs para	Uni	Chi-square	53% vs 58%	<0.0001
Wahman et al., 2019[32]	Pro	31	55 (17)	32	13	18 mos	Tetra vs para	Uni	Fisher exact test	52% vs 20%	NS
Adriaansen et al., 2013[15]	Pro	139	40 (14)	50	89	5 yrs after discharge rehab center	Para vs tetra	Multi	OR	0.69 (0.41–1.2)	NS
Haisma et al., 2007[14]	Pro	212	40 (14)	138	74	1 yr after discharge rehab center	Para vs tetra	Multi	OR	0.52 (0.36–0.75)	NA
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	358	423	14 (1–60) yrs	Tetra vs para	Multi	OR	0.84 (0.62–1.1)	NS
Renal stones											
Chen et al., 2000[36]	Retro	8314	15–80	2600	3249	3 yrs (7 mos–13 yrs)	Para AIS ABC vs AIS D	Multi	RR	1.4 (0.8–2.7)	NS
							Tetra AIS ABC vs AIS D			1.9 (1.0–3.6)	NA
McKinley et al., 1999[21]	Pro	3581	NA	NA	NA	1–20 yrs	Comp tetra vs other injury types	Uni	Chi-square	20% vs unknown	<0.0014
Bladder cancer											
Nahm et al., 2015[37]	Retro	45,486	33 (17)	14,763	14,968	13 (10) yrs	Tetra AIS A, B & C vs non-SCI		SMR	15 (10–21)	NA
							Para AIS A, B & C vs non-SCI			13 (9.3–17)	NA
Pain											
Musculoskeletal pain											
Cardenas et al., 2004[40]	CSS	2879	25 (9.4)	1116	1416	1–6 yrs	Tetra vs para	Multi	Chi-square	78% vs 84%	<0.001
Modirian et al., 2010[41]	CSS	1295	22 (6.4)	120	1175	14 (3) yrs	Tetra vs para	Uni	Chi-square	46% vs 62%	0.0001
Adriaansen et al., 2013[15]	Pro	139	40 (14)	50	89	5 yrs after discharge rehab center	Para vs tetra	Multi	OR	0.76 (0.40–1.5)	NS
Haisma et al., 2007[14]	Pro	212	40 (14)	138	74	1 yr after discharge rehab center	Para vs tetra	Multi	OR	0.66 (0.43–1.0)	NS

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TABLE 3. Overview of included studies on the association between level of injury and SHCs

Authors & Year	Design	No. of Pts	Mean Age at Injury (SD/ range), yrs	Tetraplegia/ Paraplegia (n)		FU/Time Postinjury (SD/ range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Pain (*continued*)											
Musculoskeletal pain (*continued*)											
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	358	423	14 (1–60) yrs	Tetra vs para	Multi	OR	0.76 (0.57–1.0)	NS
Demirel et al., 1998[43]	CSS	47	31 (11)	11	36	126 days	Tetra vs para	Uni	Fisher exact test	40% vs 60%	<0.001
Neuropathic pain											
Haisma et al., 2007[14]	Pro	212	40 (14)	138	74	1 yr after discharge rehab center	Para vs tetra	Multi	OR	0.86 (0.44–1.7)	NS
Adriaansen et al., 2013[15]	Pro	139	40 (14)	50	89	5 yrs after discharge rehab center	Para vs tetra	Multi	OR	0.34 (0.13–0.89)	NA
Wahman et al., 2019[32]	Pro	31	55 (17)	32	13	18 mos	Tetra vs para	Uni	Fisher exact test	57% vs 10%	0.02
Musculoskeletal disorders & spasticity											
Spasticity											
Noreau et al., 2000[22]	CSS	482	29 (12)	211	271	14 (12) yrs	Tetra vs para	Uni	Chi-square	46% vs 36%	0.00
Wahman et al., 2019[32]	Pro	31	55 (17)	32	13	18 mos	Tetra vs para	Uni	Fisher exact test	29% vs 45%	NS
Holtz et al., 2017[45]	Pro	465	43 (18)	NA	NA	125 days	Tetra vs para	Uni	t-test	NA	<0.001
Haisma et al., 2007[14]	Pro	212	40 (14)	138	74	1 yr after discharge rehab center	Para vs tetra	Multi	OR	0.13 (0.08–0.23)	NA
Adriaansen et al., 2013[15]	Pro	139	40 (14)	50	89	5 yrs after discharge rehab center	Para vs tetra	Multi	OR	0.53 (0.30–0.93)	NA
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	358	423	14 (1–60) yrs	Tetra vs para	Multi	OR	2.3 (1.7–3.3)	<0.0001
Fractures											
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	358	423	14 (1–60) yrs	Tetra vs para	Multi	OR	0.62 (0.34–1.2)	NS
Heterotopic ossification											
Haisma et al., 2007[14]	Pro	212	40 (14)	138	74	1 yr after discharge rehab center	Para vs tetra	Multi	OR	0.80 (0.42–1.5)	NS

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TABLE 3. Overview of included studies on the association between level of injury and SHCs

Authors & Year	Design	No. of Pts	Mean Age at Injury (SD/ range), yrs	Tetraplegia/ Paraplegia (n)		FU/Time Postinjury (SD/ range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Musculoskeletal disorders & spasticity (*continued*)											
Heterotopic ossification (*continued*)											
Adriaansen et al., 2013[15]	Pro	139	40 (14)	50	89	5 yrs after discharge rehab center	Para vs tetra	Multi	OR	0.87 (0.35–2.2)	NS
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	358	423	14 (1–60) yrs	Tetra vs para	Multi	OR	0.63 (0.35–1.1)	NS
Pressure ulcers											
Noreau et al., 2000[22]	CSS	482	29 (12)	211	271	14 (12) yrs	Tetra vs para	Uni	Chi-square	28% vs 28%	NS
McKinley et al., 1999[21]	Pro	1073	NA	NA	NA	1–20 yrs	Comp tetra	Uni	Chi-square	25%	<0.005
							Comp para			28%	
							Incomp tetra			18%	
							Incomp para			15%	
Haisma et al., 2007[14]	Pro	212	40 (14)	138	74	1 yr after discharge rehab center	Para vs tetra	Multi	OR	0.53 (0.36–0.78)	NA
Adriaansen et al., 2013[15]	Pro	139	40 (14)	50	89	5 yrs after discharge rehab center	Para vs tetra	Multi	OR	0.70 (0.40–1.2)	NS
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	358	423	14 (1–60) yrs	Tetra vs para	Multi	OR	0.95 (0.68–1.3)	NA
Correa et al., 2006[53]	CC	41	35 (12)	8	33	7 (4) yrs	Motor-comp para vs other injuries	Multi	OR	6.6 (1.7–25)	NA
Autonomic dysreflexia											
Haisma et al., 2007[14]	Pro	212	40 (14)	138	74	1 yr after discharge rehab center	Para vs tetra	Multi	OR	0.14 (0.07–0.27)	NA
Adriaansen et al., 2013[15]	Pro	139	40 (14)	50	89	5 yrs after discharge rehab center	Para vs tetra	Multi	OR	0.20 (0.10–0.42)	NA
Hitzig et al., 2008[19]	CSS	781	37 (18–92)	358	423	14 (1–60) yrs	Tetra vs para	Multi	OR	3.0 (2.0–4.4)	NA

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Musculoskeletal Disorders and Spasticity

Six studies reported on spasticity in tSCI.[14,15,19,22,32,45] Five studies showed that level of injury was associated with spasticity, whereas in 3 studies significantly higher rates of spasticity were observed in patients with tetraplegia in comparison to paraplegia. The remaining 2 studies demonstrated that patients with paraplegia less commonly experienced spasticity compared to patients with tetraplegia (OR 0.53, 95% CI 0.30–0.93; OR 0.13, 95% CI 0.08–0.23).[14,15,19,22,45] One study demonstrated higher rates of spasticity in more severe injuries.[45]

Only 1 study described the prevalence of contractures

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TABLE 3. Overview of included studies on the association between level of injury and SHCs

Authors & Year	Design	No. of Pts	Mean Age at Injury (SD/ range), yrs	Tetraplegia/ Paraplegia (n)		FU/Time Postinjury (SD/ range)	Analysis	Uni- or Multivariate Analysis	Comparison	Outcome (95% CI)	p Value
Endocrine system											
Diabetes mellitus type 2											
Lai et al., 2014[56]	Retro	35,043	52	28,696	23,626	6 yrs	Tetra vs non-SCI	Multi	HR	1.2 (1.1–1.4)	<0.01
							Motor-comp para vs non-SCI			2.4 (1.1–5.2)	<0.0001
							Motor-comp para vs non-SCI			1.6 (1.3–1.9)	<0.05

in the tSCI population.[39] This study, with 1668 participants, reported a significant difference in the prevalence of contractures between incomplete tetraplegia and complete paraplegia (35% vs 28%, $p < 0.001$).

Two studies reported on the presence of osteoporotic fractures after tSCI.[19,46] One study with 63 participants observed higher rates of fractures in patients with complete tSCI compared to people with incomplete tSCI (24% vs 6.9%, RR 4.0, 95% CI 1.1–24, $p = 0.037$).[46] However, the other study with 781 participants did not find an association between the rate of fractures and severity or level of injury.[19]

Four of 7 studies that reported on heterotopic ossification after tSCI demonstrated a higher prevalence in motor-complete tSCI in comparison to motor-incomplete injury.[14,47–49] One study even found an almost 6 times increased risk in complete injury.[47] The remaining 3 studies did not find an association between heterotopic ossification and severity or level of injury.[15,19,50] The strength of evidence is low.

Pressure Ulcers

All 9 studies that reported on pressure ulcers in chronic tSCI showed higher rates of pressure ulcers in motor-complete tSCI in comparison to motor-incomplete tSCI.[14,15,19,21,22,39,51–53] Of these, 1 study demonstrated a 6 to 8 times higher risk of developing pressure ulcers in motor-complete tSCI in comparison to AIS grade D injuries.[51] Another study showed an increased risk of pressure ulcers in patients with complete tetraplegia in comparison to other injuries.[53] With regard to level of injury, 1 study demonstrated a decreased rate of pressure ulcers in patients with paraplegia.[14] There was no association between the recurrence of pressure ulcers and level or severity of injury.[54,55] The strength of evidence is medium to low.

Autonomic Dysreflexia

Three studies on autonomic dysreflexia demonstrated higher prevalence of autonomic dysreflexia in motor-complete tSCI (OR 3.1, 95% CI 1.4–6.7; OR 2.4, 95% CI 1.3–4.4; OR 2.3, 95% CI 1.6–3.4).[14,15,19] Two of these studies additionally observed that autonomic dysreflexia was less common in people with paraplegia in comparison to people with tetraplegia.[14,15] The remaining study showed a higher rate of autonomic dysreflexia in people with tetraplegia (OR 3.0, 95% CI 2.0–4.4).[19] The strength of evidence is medium to low.

Endocrine System

One study with 35,141 participants reported that people with tSCI are at higher risk of developing diabetes mellitus type 2 compared to the normal population, with thoracic motor-complete tSCI causing the highest risk of developing diabetes mellitus type 2 (HR 2.4, 95% CI 1.1–5.2, $p < 0.0001$).[56] The strength of evidence is low.

Discussion

Based on this analysis, patients with motor-complete injury are more prone to respiratory and urogenital complications, musculoskeletal disorders, pressure ulcers, and autonomic dysreflexia during the subacute and chronic phase of tSCI, while chronic pain was more prevalent in patients with motor-incomplete injury. Moreover, patients with tetraplegia are more prone to pulmonary infections, spasticity, and autonomic dysreflexia in comparison to patients with paraplegia, and patients with paraplegia report higher rates of hypertension, venous thromboembolism, and pain compared to people with tetraplegia during the subacute and chronic phase.

Motor-Complete Injury

This analysis shows that patients with motor-complete injury are more prone to SHCs during the subacute and chronic stage of tSCI than patients with motor-incomplete injury. A direct cause of this increased occurrence of SHCs is, in all probability, the extended neural damage in motor-complete injury that indirectly leads to a more profound

immobility and inactivity in patients with motor-complete injury.[14,27,57,58] Immobility has many consequences. While the increased occurrence of pressure ulcers in these patients can partially be explained by the loss of sensation and awareness of pressure ulcers, immobility remains the major risk factor for pressure ulcer development.[51,59] Moreover, immobility affects mineral metabolism due to excessive bone loss resulting in hypercalciuria, which in turn can result in an increased risk of renal stone formation.[36,60] In addition to immobility, another cause of renal stone formation can be the use of bladder catheterization,[21] which is also an important risk factor for urinary tract infection.[21,61] Finally, another consequence of immobility is an increased occurrence of pulmonary infections. Moreover, recent literature stated that metabolic changes and inflammatory processes due to pulmonary as well as urinary infections can lead to heterotopic ossifications.[49] This review seems to support this as higher rates of heterotopic ossification as well as of pulmonary infections and urinary tract infections were observed in patients with motor-complete injury compared to patients with motor-incomplete injury in the majority of included studies.

An additional finding of this analysis was an increased occurrence of bladder cancer in the tSCI population with a younger age at onset and a heightened mortality due to bladder cancer in comparison to the general population.[37,38] It was suggested that the use of indwelling catheters caused this increased occurrence of bladder cancer. However, other studies contradict this and suggest that an inactive, neurogenic bladder leads to prolonged exposure of the urothelium to a high volume of urine with activated carcinogens, which possibly accelerates the development of bladder cancer.[62,63] Evidence for both etiological explanations for bladder cancer in patients with tSCI is limited and therefore more research is needed.

These differences in SHC prevalence between motor-complete and motor-incomplete injury are substantial and require attention. However, no firm conclusions can be drawn from this study due to the lack of statistical tests.

Motor-Incomplete Injury

Large cohorts included in this analysis suggest that chronic pain is more prevalent in patients with motor-incomplete injury in comparison to patients with motor-complete injury.[39,41–43] A combination of biochemical cascades causing loss of balanced sensory pathways, spinal inhibitory mechanisms, and synaptic plasticity will result in changes in neuronal activity that will eventually lead to chronic pain.[64] However, because of the extended number of processes that occur SCI, it is difficult to determine which processes specifically contribute to the development of chronic pain after tSCI. Another factor that can explain this difference is the chronic overuse of the upper extremity in motor-incomplete injury, for example, due to wheelchair use. This could lead to overload, while patients with motor-complete injury receive more help in daily activities by caregivers or assistant devices that relieve the upper extremity. In contrast, other studies noted divergent results on the impact of severity or level on pain.[65,66] Nevertheless, severe musculoskeletal and neuropathic pain negatively influence quality of life in the tSCI population.[67] Therefore, special attention to chronic pain in SCI is important. Extra monitoring of chronic pain can be considered in patients suffering a motor-incomplete injury, especially when at risk for overload of the upper extremity. Additionally, due to the negative impact on the quality of life of SHCs, focus on optimization of the treatment of chronic pain in the tSCI population in future research appears warranted.

Level of Injury

An increased risk of autonomic dysreflexia in motor-complete tetraplegic patients is to be expected due to interruption of descending sympathetic pathways above spinal segment T6 that regulate vasomotor tone, resulting in dangerous episodic hypertension.[68] A higher occurrence of hypertension in patients with paraplegia is a common finding.[16,18,19] It is suggested that increased immobility leads to functional and structural changes in the vasculature below the level of injury.[69] These physiological changes in vasculature in combination with aging probably lead to hypertension.[69] Moreover, it is demonstrated that after the spinal shock phase, blood pressure is set lower in comparison to the blood pressure before injury with inverse proportionality: a higher level of injury results in a lower blood pressure.[70] This could explain why hypertension is solely found in people with paraplegia. Therefore, frequent monitoring and adequate regulation of blood pressure seem warranted to diminish cardiovascular diseases in patients with paraplegia.

Notably, 1 study found a 5-fold higher risk of developing cerebrovascular disease in patients with tetraplegia in comparison to patients with paraplegia.[16] Current evidence demonstrates that immobility is also an important risk factor for stroke in the tSCI population because it leads to overweight, diabetes mellitus, and dyslipidemia.[71] Patients with tetraplegia are more immobilized than patients with paraplegia and thus could be more prone to stroke in comparison to patients with paraplegia. Additionally, this study also found an increased risk of dysrhythmia and valvular disease in people with tetraplegia in comparison to people with paraplegia, which generally are risk factors for stroke.[16] The enumeration of these factors can lead to an additional increased risk of stroke for patients with tetraplegia. Another finding was the association between paraplegia and heightened risk of venous thromboembolism found in most of the included studies.[20–22] Until now, its pathophysiology remains unclear.

Finally, 1 study noted an increased risk of diabetes mellitus in patients with tSCI.[56] Especially in complete thoracic tSCI, the risk of developing diabetes mellitus was more than doubled in comparison to the non-SCI group. A higher prevalence of diabetes mellitus in the tSCI population is caused by body composition changes due to immobility that negatively influence carbohydrate and lipid metabolism, leading (for example) to insulin resistance.[72] However, the reason that complete thoracic tSCI patients are more likely to be diagnosed with diabetes mellitus compared to other subgroups remains unclear. Nevertheless, the fact that all patients with tSCI suffer an increased risk of diabetes mellitus is clinically relevant. Therefore, it seems warranted to implement preventive treatment for diabetes mellitus in follow-up care.

Study Limitations

Systematic reviews are unavoidably limited by publication bias. It should be taken into account that the included studies are limited by heterogeneity and small sample size. Often, heterogeneity is caused due to conflicting methodologies, differences in mean age, and wide variation between follow-up periods. Also, the wide range of clinical expression of SCI and the divergent health problems that were investigated in the included studies complicated this analysis. It is important to state that the search strategy of this study was focused on publications investigating multiple SHCs instead of a single SHC. This was done to obtain an overarching overview of all different SHCs and to ensure the feasibility of this analysis. Therefore, some studies might have been excluded in this search. In addition, studies on mental health as SHCs are also excluded as this study focused on somatic SHCs. To reduce the influence of the heterogeneity of the SHCs, the articles were clustered per subject and compared within these subcategories. Because of conflicting methodologies, meta-analyses were not possible. Part of the included studies only performed univariate analysis instead of multivariate analysis, which increases the risk of bias. To obtain clarity on the applicability of the results of each individual study, the type of analysis is mentioned in Table 2. Furthermore, the wide range of mean ages between studies should also be taken into account as aging is a risk factor for the development of SHCs in tSCI patients.[73] Due to these limitations, the conclusions of this systematic review should be interpreted with caution.

Nevertheless, this study provides a useful overview of subgroups, based on severity and level of injury, at risk for specific SHCs during the subacute and chronic stage of tSCI. This is a first step to obtain patient-specific information about the prognosis of SHCs in people with tSCI leading to the prevention of long-term complications due to tailored follow-up care. With elucidation of these risk factors, morbidity and mortality could potentially be decreased, resulting in less frequent rehospitalization, a decrease of healthcare costs, and improvement of quality of life in the tSCI population.[2,4,8,74,75] Additionally, due to tailored follow-up care, SHCs will be detected in an early stage and worsening of these conditions may potentially be prevented.

Currently, international guidelines for rehabilitation and postrehabilitation care of chronic tSCI containing unambiguous recommendations about the follow-up of this population are lacking. Based on this analysis, it can be suggested that suffering motor-complete tSCI is a very important risk factor for SHCs and will require follow-up evaluations more frequently than with motor-incomplete tSCI, with focus on respiratory and urogenital systems, musculoskeletal disorders, pressure ulcers, and autonomic dysreflexia, to potentiate early detection of these SHCs. For the development of such an evidence-based guideline, large prospective cohorts with adequate follow-up are required to gain an optimal overview of subgroups at risk for specific SHCs as well as the influence of systematic screening, improvement of mobility, or neurological recovery on the prevention of SHCs in the tSCI population.

Conclusions

Patients with motor-complete tSCI are more prone to develop SHCs compared to patients with incomplete tSCI. Moreover, the level of injury influences the development of some SHCs as well, such as pneumonia, spasticity, autonomic dysreflexia, hypertension, and chronic pain. Additional monitoring in these subgroups for each specific SHC appears warranted, especially in patients suffering motor-complete tSCI. This review may contribute to the prioritizing of preventive treatment strategies during long-term care of tSCI patients.

Appendix

Search Syntax

PubMed Search

((((“spinal cord injuries/complications”[Mesh] OR “spinal cord”[tiab] OR “spinal cord injuries”[Mesh] OR “Spinal Cord Injuries/complications”[MAJR])) AND (“complications”[tiab] OR “complications”[Subheading] OR “consequences”[tiab])) AND (“long-term”[tiab] OR “secondary”[tiab] OR “late complications”[tiab] OR “Risk factors”[tiab] OR “Risk factors”[Mesh])) NOT (“carcinoma”[tiab] OR “malign*”[tiab] OR “tumor”[tiab] OR “metastases”[tiab] OR “aneurysms”[tiab]) AND ((“1990/01/01”[PDat]: “3000/12/31”[PDat]))

Embase Search

(‘spinal cord injury’/exp OR ‘spinal cord injury’ OR ‘spinal cord’/exp OR ‘spinal cord’ OR ‘spinal cord injur*’:ab,ti) AND (‘complication’/exp OR ‘complication’ OR complication:ab,ti OR ‘consequences’/exp OR ‘consequences’ OR consequences:ab,ti) AND (secondary:ab,ti OR ‘late complications’:ab,ti OR ‘long term’:ab,ti OR ‘long-term’:ab,ti OR ‘risk factor’/exp OR ‘risk factor’ OR ‘risk factors’:ab,ti) NOT (‘carcinoma’/exp OR ‘carcinoma’ OR carcinoma:ab,ti OR ‘malignant neoplasm’/exp OR ‘malignant neoplasm’ OR malign*:ab,ti OR ‘aneurysm’/exp OR ‘aneurysm’ OR ‘metastasis’/exp OR ‘metastasis’) (AND [1990-2020]/py)

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Adegeest, ter Wengel. Acquisition of data: Adegeest. Analysis and interpretation of data: Adegeest, van Gent, Stolwijk-Swüste, Post, ter Wengel. Drafting the article: Adegeest. Critically revising the article: Stolwijk-Swüste, Post, Vandertop, Öner, Peul, ter Wengel. Reviewed submitted version of manuscript: Adegeest. Administrative/technical/material support: Adegeest.

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