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Mortality Rate and Predicting Factors of Traumatic Thoracolumbar Spinal Cord Injury; A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To estimate the summation of mortality rate and the contributing factors in patients with traumatic thoracolumbar spinal cord injuries (TLSCI).
Methods: A systematic search of observational studies that evaluated the mortality associated with TLSCI in MEDLINE and EMBASE was conducted. The study quality was evaluated using a modified quality assessment tool previously designed for observational studies.
Results: Twenty-four observational studies involving 11,205 patients were included, published between January 1, 1997, and February 6, 2016. Ten studies were of high quality, thirteen were of moderate quality, and one study was of low quality. Seventeen reports described risk factors for mortality and eleven of these studies used a multiple regression models to adjust for confounders.The reported mortality rate ranged from 0 to 37.7% overall and between 0 and 10.4% in-hospital. The sum of mortality for in-hospital, 6-month, and 12-month were 5.2%, 26.12%, 4.3%, respectively. The mortality at 7.7 years follow-up was 10.07% and for 14 years follow-up reports ranged from 13.47% to 21.46%. Associated data such as age at injury, male to female ratio, pre-existing comorbidities, concomitant injuries, duration of follow-up, and cause of death have been underreported in studies investigating the mortality rate after TLSCI.
Conclusion: Currently no study has accurately assessed mortality in the thoracolumbar spine, while there is general agreement that traumatic thoracolumbar spinal cord injuries are important,

Keywords: Thoracolumbar; Spinal cord injury; Mortality; Systematic review.

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Introduction

Traumatic thoracolumbar spinal cord injury (TLSCI) is an important healthcare issue that could affects thousands of individuals annually worldwide. The mortality rate is one of the important indicators of economic and social burdens of a disease. Treatment outcomes can also be evaluated using the rate of mortality. Additionally, more accurate data such as in-hospital mortality may be indicators of health system quality and play a major role in management decision making. Although the age and cause of injury are not different in thoracolumbar and cervical levels, complications and mortality rates are higher in cervical spinal cord injuries than thoracolumbar levels [1-6]. Thoracolumbar vertebral fractures occur most frequently between the levels of T12 to L2 [7] and associated neurological deficits are found with 15 – 20% of all thoracolumbar injuries [8]. Cardiovascular, infectious, and respiratory disorders had a great role in the mortality of patients with TLSCI. However, advances in medical care have led to a lower rate of the mortality in the 21st century [9]. The mortality rate associated with TLSCI in different countries is an important subject. However, there is no comprehensive study to show the global picture of the mortality of TLSCI.

According to the literature, the level of the lesion, the neurological status (complete or incomplete injury), age, gender, joint injuries, comorbidities, and time from injury to treatment are all factors affecting mortality in patients with spinal cord injury (SCI) [10]. In current work, we attempted to evaluate and, to the extent possible, pool all homogenous studies to estimate the overall mortality rate and contributing factors in patients with TLSCI. To the best of the authors' knowledge at the time of submission, this is the first systematic review that has explicitly evaluated mortality rate after thoracolumbar SCI.

Materials and Methods

Search Strategy

A systematic review of patients with TLSCI was performed to define mortality rate and its contributing factors. The review and its analysis were carried out in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11] and the search strategy was designed by a medical information specialist (Figure 1). The MEDLINE and EMBASE (via Ovid) databases were queried on February 6, 2016, without limitation for document type, or publication status. However, studies were excluded if not written in the English language or reported before 1997. Keywords were searched (Figure 2) as well as the review of the initial search results and citations of included articles. Because relevant outcome measures are not always mentioned in fields that may be queried for all reports, no specific issue term was used to augment the search results; instead, the outcomes were sought for after acquiring the full-text of the available results. The results of this query were then entered into Endnote X5 and sent to two independent reviewers.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: the study was conducted on patients with distinct, definite TLSCI as the main study group or sub-group; traumatic

A. EMBASE via Ovid SP

1. spinal cord injury/ or (("Spinal Cord" or "thoracolumbar Cord") adj (Trauma$ or Injur$)).ti,ab.
2. Cohort Analysis/ or Longitudinal Study/ or Follow up/ or Prospective Study/ or Retrospective Study/ or exp Case Control Study/ or (Cohort or Longitudinal or Follow Up or follow?up or Prospective or Retrospective or Case Control or Case Series or Case reports or Case studies).ti,ab.
3. 1 and 2
4. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
5. human/ or normal human/ or human cell/
6. 4 and 5
7. 4 not 6
8. 3 not 7
9. limit 8 to exclude medline journals

B. MEDLINE via Ovid SP

1. spinal cord injuries/ or (("Spinal Cord" or "thoracolumbar Cord") adj (Trauma$ or Injur$)).ti,ab.
2. exp Cohort Studies/ or exp Case-Control Studies/ or (Cohort or Longitudinal or Follow Up or follow?up or Prospective or Retrospective or Case Control or Case Series or Case reports or Case studies).ti,ab.
3. 1 and 2
4. (animals not (humans and animals)).sh.
5. 3 not 4

Fig. 1. Search strategy design.

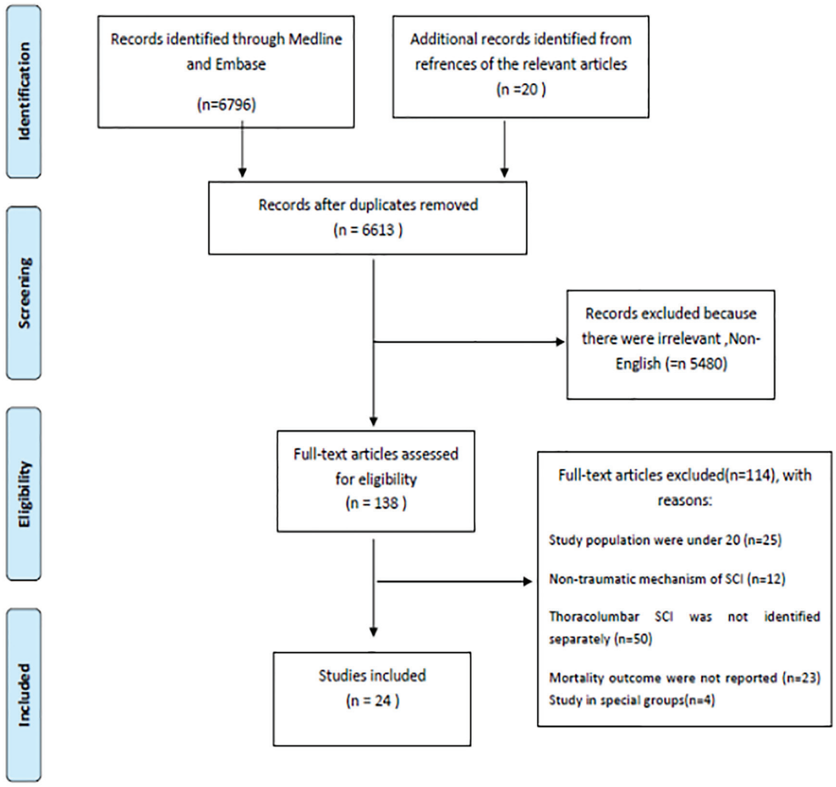

Fig. 2. Flowchart of Studies Excluded and Included for Systematic Review

status was established; death was considered as an outcome, and the cohort consisted of at least 20 patients. Studies with age, gender, and functional limitations and those conducted on a particular population were excluded. Reports not written in the English language and those where only the abstract was available were excluded. Studies carried out on January 1, 1997, were excluded.

Data Extraction

The titles, abstracts, and full-texts of available reports were checked by two independent reviewers against the criteria as mentioned earlier. Any disagreements on article selection were solved through discussion. Where the records were unclear or incompetent, attempts were made to contact the authors by email. There was only one response to our emails. Two reviewers separately assessed the quality of the selected studies according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group [12], which was designed for observational studies and used in previous systematic reviews [13-16] (Table 1). The studies were categorized into quality levels according to the methodological quality score (Table 2). Two independent reviewers extracted data including the study type and duration, demographics, male to female ratio, mean age at the time of injury, and assessment period. Because any potentially confounding factors affecting mortality are peculiar to the particular study, these factors (comorbidities and coexisting injuries) were included, similar to previous systematic reviews [17, 18]. Reports examining the association between risk factors and mortality were found. Since the essential characteristics were not homogenous across all studies, a meta-analysis was not performed. However, the mean number of death for studies with similar follow-up period was calculated.

Results

The search strategy yielded 6796 records. After screening the titles and abstracts, 138 articles were selected for full-text assessment; 114 of these were excluded. After application of all inclusion and exclusion criteria, a total of 24 studies were selected for systematic review (Figure 3). The characteristics of the selected studies are shown in Table 3. The articles were published from January 1, 1997, to February 6, 2016. The population sizes ranged from 22 subjects to 4042 patients. Eight studies were from North America (6 from the United States, two from Canada), one from Latin America (Brazil), three from Oceania (Australia), five from European countries, four from the African region, and three from Asian countries. Concomitant traumatic injuries and comorbidities were stated in just 8 and four reports, respectively; however, in all of these reports, these factors were described for the total study population and not for the thoracolumbar patients exclusively.

The quality of the studies is shown in Table 4. All studies had predefined patient inclusion criteria. In 13 studies, the contributing factors for mortality were analyzed. Also in 13 studies, mortality for patients with TLSCI was assessed according to age, gender,

Table 1. Criteria for Assessment of the Methodological Quality of Observational Studies

Item	Criterion	Score
Study population	Sample size ≥50 and participation rate≥ 80%	1
Patient selection	For cohort studies: cases and controls draw from the same population; for cross-sectional and case-series studies: selected group was representative of the TLSCI[a] population	1
Study design	Cohort design	2
	Retrospective case-series or cross-sectional design	1
	Reported the duration of follow-up	1
	Study withdrawal rate ≤20%	1
Analysis and data presentation	Appropriate analysis techniques were used	1
	Multivariate analysis performed	1
	Frequencies of most important outcomes were given	1

[a]Thoracolumbar spinal cord injury.

Table 2. Criteria for Assessment of Quality of the Included Studies

Item	Level	Criteria for Inclusion
Level of studies	High-quality studies	Multivariate analysis performed and had a quality score ≥7
	Moderate-quality studies	Multivariate analysis performed, but had a quality score <7
		No multivariate analysis performed and had a quality score ≥4
	Low-quality studies	No multivariate analysis performed and had a quality score <4

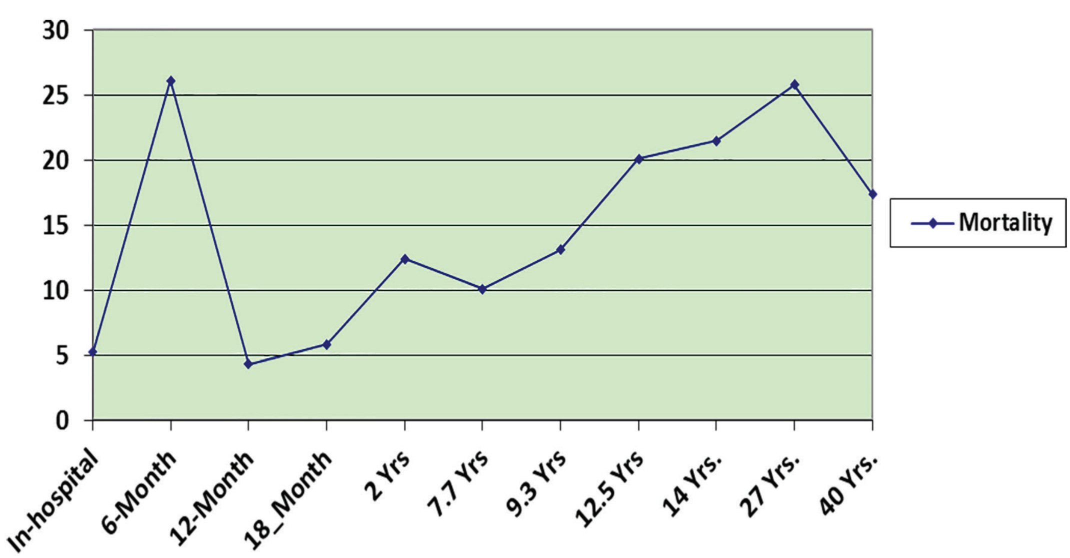

Fig. 3. The mortality rate in Thoracolumbar Spinal Cord Injury studies with determined post-injury follow-up

ASIA (American Spinal Injury Association) grade, Frankel grade, and level of thoracolumbar spine

Table 3. Characteristics of the Selected Studies

Studies	Country	Study period	Design	Sample size	M/F	Mean age(years)	Co-injuries	PECs[q]	Mortality	SMR[r]
Krause 1997 [37]	United States	1985-1996	Prospective cohort	141	4.3/1[a]	24.5±10.9[a]	NA[b]	NA[b]	13.5%	NA[b]
Levy 1998 [19]	Zimbabwe	1988_1994	Retrospective case-series	67	7.4/1	NA[b]	NA[b]	NA[b]	19.4%	NA[b]
Yeo 1998 [6]	Australia	1955-1994	Retrospective cohort	650	4.5/1[a]	NA[b]	NA[b]	NA[b]	17.4%	1.9(1.5-2.3)
O'Connor2005 [5]	Australia	1986-1997	Cohort study	1355	4.01/1	NA[b]				
Lidal 2007[9]	Norway	1961-1982	Retrospective	205	3.54:1	25.3			37%	Men:1.3 women:3.3
Leal-Filho 2008 [38]	Brazil	1995_2002	Prospective cohort	189	6.3/1[a]	NA[b]	NA[b]	NA[b]	0	NA[b]

Furlan 2009 [23]	Canada	1996-2007	Retrospective cohort	87	2.7/1 [a]	52.1 [a]	NA[b]	Mean CCI[s], Mean CIRS[t], Mean number of ICD-9[o] codes	2.3%	NA[b]
Divanoglou 2010 [30]	Sweden Greece	2006-2007	Prospective Population-Based Study	48	NA[b]	NA[b]	Extra-spinal Injuries (Skull, Thorax, Pelvis)	CVD[e], Spinal stenosis, AS[h], Degenerative	6.3%	NA[b]
Furlan 2010 [25]	Canada	NA	Prospective cohort	136	5.3/1 [a]	NA	GCS[m]	NA[b]	4.4%	NA[b]
Hagen 2010 [20]	Norway	1952_2001	Retrospective cohort	188	4.7/1 [a]	35.2	NA[b]	NA[b]	31.4%	1.94 (1.51, 2.51)
Ning 2011 [39]	China	2004-2008	Retrospective	248	5.6/1	46			0	
Varma 2010 [10]	United States	1993-2003	Retrospective cohort	715	3/1 [a]	Median age:41[a]	TBI[g], ISS[l]	NA[b]	10.3%	NA[b]
Ahoniemi 2011 [1]	Finland	1976-2007	Retrospective	811	3.77:1	Male:34.5 female: 33.2			4.06%	2.97
Krause 2011 [27]	United States	1998-2008	Prospective cohort	402	2.9:1 [a]	31.1±13.5[a]	NA[b]	NA[b]	20.9%	NA[b]
Krause 2011 [28]	United States	1995-2006	Retrospective cohort	3990	3.9:1 [a]	NA[b]	NA[b]	NA[b]	10%	NA[b]
Kawu 2011 [32]	Nigeria	1997-2007	Retrospective cohort	94	4.6/1 [a]	37.2±14.2 [a]	GCS[m]	NA[b]	34%	NA[b]
Grossman 2012 [40]	United states	2005-2010	Prospective cohort	56	3.7:1 [a]	44.6±17.1 [a]	GCS[m], AIS[p]	HT[j], Diabetes mellitus, hepatitis C	0	NA[b]
Middleton 2012 [41]	Australia	1955 -2006	Retrospective cohort	938	4.5:1 [a]	34±17.4 [a]	NA[b]	NA[b]	21.3%	1.7
Cao 2013 [42]	United States	1995-2006	Cohort	4042	3.88:1 [a]	NA[b]				
Nwankwo 2013 [26]	Nigeria	2009-2012	Retrospective case-series	40	4.3:1 [a]	34.8±3.3 [a]	Chest lesion/ long bone fx/ head injury/ abdomen lesion	NA[b]	7.5%	NA[b]
Sabre 2013 [24]	Estonia	1997 -2011	Retrospective cohort	205	NA[b]	NA[b]	Head injury, ATI[d]	NA[b]	21.5%	NA[b]
Löfvenmark 2014 [43]	Botswana	2011 2013	Descriptive cross-sectional	20	2.5:1 [a]	80% ≤45 years [a]	fractures in upper and lower extremities, as well as ribs, abdominal injuries and head trauma.	HIV hypertension	27.2%	NA[b]
Barman 2014 [29]	India	1981 -2011	Retrospective cohort	367	8.6:1 [a]	Median age:31 [a]	NA[b]	NA[b]	25.3%	NA[b]

Hossain 2015 [44]	Bangla-desh	2011-2014	Mixed ret-rospective-prospective cohort	201	8,5 1:1 [a]	34 (25–44) [a]	NA[b]	NA[b]	12.43%	NA[b]

[a] The data for all patients with cervical and thoracolumbar spinal cord injury; [b]NA: not available; [c]CHI: closed head injury; [d]ATI: associated traumatic injury; [e]CVD: cardiovascular disease; [f]PD: pulmonary disease; [g]TBI: traumatic brain injury; [h]AS: ankylosing spondylitis; [i]OPLL: ossification of posterior longitudinal ligament; [j]HT: hypertension; [k]OA: osteoarthritis; [l]ISS: Injury Severity Score; [m]GCS: Glasgow Coma Scale; [n]GI disease: gastrointestinal disease; [o]ICD-9 codes: international classification of disease-ninth revision; [p]AIS: Abbreviated Injury Scale; [q]PECs: Preexisting co-morbidity; [r]SMR: standardized mortality ratio; [s]CCI: Charlson Comorbidity Index; [t]CIRS: Cumulative Index Rating Scale; [u]AS: Ankylosing Spondylitis.

Table 4. Quality Assessment of the Selected Studies

No.	Studies	Study Population	Patient Selection	Study Design	Analysis and Data Presentation	Total Score	Level of Studies
1	Krause 1997	0	1	4	3	8	High
2	Levy 1998	1	1	2	0	4	Low
3	Yeo 1998	1	1	3	1	6	Moderate
4	O'Connor 2005	1	1	3	3	8	High
5	Lidal 2007	1	1	3	2	7	moderate
6	Leal-Filho 2008	1	1	3	1	6	Moderate
7	Furlan 2009	1	1	3	3	8	High
8	Divanoglou 2010	1	1	3	1	6	Moderate
9	Furlan 2010	1	1	4	3	9	High
10	Hagen 2010	1	1	3	3	8	High
11	Ning 2010	1	1	3	1	6	Moderate
12	Varma 2010	1	1	3	3	8	High
13	Ahoniemi 2011	1	1	3	1	6	Moderate
14	Krause 2011	1	1	3	3	8	High
15	Krause 2011	1	1	4	3	9	High
16	Kawu 2011	1	1	3	1	6	Moderate
17	Grossman 2012	1	1	3	2	7	Moderate
18	Middleton 2012	1	1	4	2	8	Moderate[a]
19	Cao 2013	1	1	4	3	9	High
20	Nwankwo 2013	1	1	2	1	5	Moderate
21	Sabre 2013	1	1	2	2	6	Moderate
22	Löfvenmark 2014	0	1	3	2	6	moderate
23	Barman2014	1	1	3	3	8	High
24	Hossain 2015	1	1	4	2	8	Moderate[a]

[a]Multivariate analysis has been performed; ** Multivariate analysis has not been performed

injury. In eight studies survival rate and four studies, life expectancy was reported as separate outcomes. In just one study, causes of mortality were reported separately for patients with TLSCI. According to methodological quality (Table 1), three studies had nine points, nine studies had eight points, two studies had seven points, eight studies had six points, one study had 5 points, and one study had four points. Therefore, ten studies were high-quality (41.6% of studies), 13 studies were moderate quality (54.2 %), and one study was low-quality (4.2%) (Table 5).

Demographic Data

Although all studies reported male to female ratio (M/F), M/F was reported for the TLSCI subgroup specifically in just one study [19] while in the other studies M/F was presented for the SCI patients overall. Generally speaking, men were more often affected by SCI. In the study that specifically mentioned M/F in TLSCI patients, it was reported as 7.37 [19]. The mean age was reported in twelve studies and just one study [20] reported the mean age for the thoracolumbar subgroup (35.2 years). One study was performed only among the elderly population [21] and one study was in children [22].

Mortality Rate

Table 6 demonstrates the mortality rate of all patients with TLSCI and the related causes of death during follow-up. Mortality causes for TLSCI cases were identified in only two studies; the reported mortality rate ranged from 0% to 37.7% disregarding follow-up duration. None of the articles reported the pre-hospital mortality rate. Four reports mentioned the short-term and long-term mortality; eight reported short including in-hospital mortality, and 11 described long-term and post-discharge mortality. In studies relating the in-hospital mortality rate, the duration of hospitalization was not reported (one study mentioned this was less than three months), and the reported death rates ranged from 0 to 10.34 percent. Excluding the pediatric study, four studies

Table 5. Reported Follow-up and Causes of Death in Included Thoracolumbar Spinal Cord Injury Studies

Studies	No. patients	Duration of shorter follow up period	Mortality during shorter follow up period	Duration of longer follow-up Period	Mortality during of longer follow-up period	No. deaths
Krause 1997	141	-	-	14.3±7.8 yr.post-injury 11 yr. follow-up	19	19
Levy 1998	67	-	-	Hospital discharge - >1year	13	13
Yeo 1998	650	<18 months	35	>18 months	78	113
O'Connor 2005	1355			10-year	92	92
Lidal 2007	205	-	-	median 27 years (range 20–39 years)	53	53
Leal-Filho 2008	189	(In-hospital)	0	-	-	0
Furlan 2009	87	(In-hospital)	2	-	-	2
Divanoglou 2010	48	-	-	After 1st week to 1 year	3	3
Furlan 2010	136	-	-	In the 1st year	6	6
Hagen 2010	188	-	-	Mean 33 years (7-56)	59	59
Ning 2010	248	In-hospital	0	-	-	0
Varma 2010	715	(In-hospital)	74	-	-	74
Krause2011	402	-	-	minimum of 1 yr. post injury (Mean mortality follow-up: 10.4±7.3)	84	84
Krause2011	3990	-	-	Average of 7.7 yrs. post-injury (>1 yr.)	402	402
Ahoniemi 2011	811	-	-	The median length of follow-up was 12.5 years (interquartile range (IQR) 5.5–19.8 years).	163	163
Kawu 2011	94	<6 months	32	-	-	32
Grossman 2012	56	In hospital	0	-	-	0
Middleton.2012	938	≤12M	38	>12M	162	200
Cao 2013	4042	-	-	7.7 years posst inury with the average follow-up 9.3 years	530	530
Nwankwo 2013	40	≤6 months	3	-	-	3
Sabre2013	205	<12M	12	12M-2yr >2yr	3 29	44
Löfvenmark 2014	20	In-hospital	1	-	-	1
Barman2014	367	-	-	NA[a]	93	93
Hossain 2015	201	In-hospital	2	2-year	23	25
Total	11205		197		977	1174

[a]NA: not available

evaluated mortality rates after initial hospital admission including 1047 cases; among them 76 patients (7.2%) died. Furlan *et al.*, [23] reported an in-hospital mortality rate of 5.7% of the overall SCI population and 2.3% of patients with TLSCI.

Table 7 shows Mortality in Thoracolumbar Spinal Cord Injury according to the duration of follow-up. Three studies (16%) reported long-term mortality without explicitly stating the follow-up period. In one study, the follow-up duration was between one week and one year after injury with 6.2% mortality. In three studies including 1279 patients, the mean 1-year mortality was 4.3% (56 patients) [24-26]. In another recent study, among 147 patients with TLSCI region, the mortality rate of thoracic cases was 5% [21]. Krause *et al.*, [27] reported the long-term outcomes of a cohort of patients with average follow-up duration 14.3 (±7.8) months post-injury and the maximum of 11 years; there were 19 deaths in 141 patients (13.5 %).

Risk Factors for Mortality

In 13 of the 24 studies, contributing factors for mortality were reported. In all of these studies, the risk factors were assessed for all SCI patients and not for each thoracolumbar subgroup distinctively. Seven studies developed multivariate regression models to adjust for the effects of confounding

Table 6. Mortality in Thoracolumbar Spinal Cord Injury according to the duration of follow-up

Duration	Death/SCI Number (%)	Author year (Number of studies)
In hospital	79/1516 (5,21) F F H: 2/201 (1.0)	(Furlan 2005, Furlan 2009, Hossain 2015, Varma 2010, Leal-filho 2008 Löfvenmark 2014)
<6mo.	35/134 (26.12)	Mean (2) (Nwankwo 2013, Kawn 2011
<12mo.	55/1279 (4.30)	Mean (2) (Midelton 2012, Sabre 2013, Furlan 2010)
Hospital discharge – 1-year	13/45 (28.89)	Levy 1998
<18mo.	35/650 (5.4)	Yeo 1998
from H. discharge to 34.4 month **12month-2year**	23/195(11.8) 3/193(1.5)	Hossain 2015 Sabre 2013
1y- 5.6y (4.6y=55.6m.- median)	23/180## (12.8)	Garshick 2005
10 yrs. 6.5 y (Mean)	92/1355 (6.8)	O'Connor 2005
7.7yrs.	402/3990 (10.07)	Krause 2011
9.3 yrs.	530/4042(13.1)	Cao 2013
10.4 yrs.	84/402 (20.89)	Krause 2011
12.5 yrs.	163/811(20.09)	Ahoniemi 2011
14 yrs.	44/205 (21.46)	Sabre 2013
14.3 yrs.	19/141 (13.47)	Krause 1997
27 yrs.	53/205(25.8)	Lidal 2007
15yrs.[b]	92/337 (27.3)	Barman 2014
From 1.5y to 30yrs.	78/650-X[a] (24.0)	Yeo 1998
32 yrs.	59/188 (31.38)	Hagen[c] 2010

[a]Unknown number of cases with lost to follow-up; [b]Mean follow-up is 15 years for study between 1981 and 2011; [c]2001-1952-50; evaluation of individuals with SCI was performed at August 2008 (after 7yrs); Mean follow-up of (25+7=) yrs.32; ## others: Lumbosacralo

Table 7. Risk Factors for Mortality in Spinal Cord Injury Studies

Studies	Risk Factor	Comparison	Significance	Risk Factors Adjusted for- Confounding factors
Krause 1997	Male Age(continuous) Complete Economic Satisfaction Employment Status	Female - Incomplete	NS[b] p=≤ 0.001 P=≤0.05 NS[b] P=≤ 0.05	No
Furlan 2009	Male Age (continuous) duration of the initial hospitalization ASIA Scale Charlson Co-morbidity Index Number of ICD-9[d] codes Cumulative Illness Rating Scale	Female	NS[b] P=0.0002 NS[b] 0.01 P= 0.005 NS[b] NS[b]	Yes
Divanoglou 2010	Male Mean age mortality cases Complete Transportation-related injury Serious extra spinal injuries Comorbid spinal disease Surgery	Female Mean age survival cases incomplete No Transportation-related injury No Serious extra spinal injuries No Comorbid spinal disease No surgery	NS[b] P= 0.003 NS[b] NS[b] NS[b] P= 0.04 NS[b]	No

Furlan 2010	Male	Female	NS[b]	No
	Age(continuous)		P=<0.0001	
	Complete	incomplete	P=0.02	
	White	Non-white	NS[b]	
	MVA	Not MVA	NS[b]	
	GCS[f]		NS[b]	
	Drug intervention (placebo or drug)	No Drug intervention (placebo or drug)	NS[b]	
	Co-intervention (surgical or conservative management)	No Co-intervention (surgical or conservative management)	NS[b]	
Hagen 2010	Female	Male	P=0.002	Yes
	Complete	Incomplete	P=<0.001	
	Age(per 10 year increase)		P=<0.001	
	Time period (Per 10 year increase.)		NS[b]	
Varma 2010	Male	Female	P= 0.016	Yes
	Age in <20y age group		NS[b]	
	Age in >20y age group		P<0.0001	
	Frankel A	Frankel B	P=0.015	
	white	No white	NS[b]	
	number of comorbidities (1,2&3)	0	P<0.0001	
	ISS[h] :severe	ISS :mild-moderate	P= 0.012	
	TBI[i]	No TBI	P=< 0.0001	
	Trauma center level 1	Trauma center level 2	P=0.026	
Krause 2011	Male	Female	NS[b]	yes
	Age (continuous)		P=<0.0001	
	Injury severity:			
	In cervical	Ambulatory	P=<0.0001	
	In non-cervical	ambulatory	NS[b]	
	Years since injury	-	NS[b]	
	PUs[j]/YES	never get them	P=<0.0001	
	PMD[d]/YES	NO	P=0.0009	
	Hospitalizations ≥1	NO	P=0.0006	
Kawu 2011	Mean age mortality cases	Mean age survival cases	P=0.001	No
	Frankel A	-	P=0.001	
	GCS[f]<9	-	P=0.001	
Grossman 2012	Mean age mortality cases	Mean age survival cases	P=0.038	NO
	concurrent morbidities/YES	NO	P=0.01	
Krause 2012	Male	Female	CI:1.05–1.46	YES
	35-39	18–34 Y	CI :1.36–2.39	
	40-44	18–34 Y	CI :1.74–2.95	
	45-49	18–34 Y	CI :2.40–4.00	
	50-54	18–34 Y	CI :3.21–5.44	
	55-59	18–34 Y	CI :3.96–7.01	
	60-64	18–34 Y	CI :4.22–8.01	
	65-69	18–34 Y	CI :7.33–13.60	
	70-74	18–34 Y	CI :10.98–20.86	
	75-79	18–34 Y	CI :17.57–36.37	
	>80	18–34 Y	CI :23.70–52.14	
	C1–C4	Non-cervical	CI :2.09–3.06	
	C5–C8	Non-cervical	CI :1.74–2.41	
	White	other	CI :1.00–1.74	
	Black	other	CI :1.24–1.87	
	Violence & other	MVC/FL/Sp[c]	NS[b]	
	AIS[k]/Frankel A	AIS[k]/Frankel D/E	CI :1.37–2.37	
	AIS[k]/Frankel B & c	AIS[k]/Frankel D/E	NS[b]	
	Low Income	High Income	CI :1.76–3.02	
	Middle Income	High Income	CI :1.23–2.12	
	Education >Bachelors	< High School	CI :0.45–0.71	
	Education High School/Associates	< High School	CI :0.69–0.96	

Rabadi 2013	Male	Female	NS[b]	YES
	Age (continuous)		P=<0.0001	
	Ethnicity (White/Black/American Indian/ Hispanic)		NS[b]	
	Duration since SCI[a]		NS[b]	
	Spinal injury level		NS[b]	
	Severity of injury (AIS Grade)		NS[b]	
	Etiology of SCI[a]		NS[b]	
	Hypertension/DM[l]		NS[b]	
	Hyperlipidemia		P=0.01	
	Vascular risk factors		NS[b]	
	Myocardial infarction		P=0.006	
	Congestive heart failure		NS[b]	
	Depression		P=0.005	
	Pressure ulcers		NS[b]	
	Neurogenic bowel /bladder		NS[b]	
Sabre 2013	Male	Female	NS[b]	NO
	Age at injury(continuous)	-	P=<0.001	
≤2 years	Year of injury	-	NS[b]	
after TSCI	Assault/Traffic accident/falls	Sport	NS[b]	
	Preinjury alcohol consumption/YES	NO	NS[b]	
	Concomitant injury/YES	NO	NS[b]	
	Head injury/YES	NO	P=0.005	
	C1–4 & C5–8	T1–S5	P=<0.001	
	Incomplete	complete	P=<0.001	
	Operation in 6 weeks/YES	NO	P=<0.001	
	Methylprednisolone in acute phase/YES	NO	NS[b]	
	Complication in acute phase/YES	NO	0.004	
>2 years	Male	Female	NS[b]	
after TSCI	Age at injury(continuous)	-	P=<0.001	
	Year of injury	-	NS[b]	
	Assault/Traffic accident	Sport	NS[b]	
	Falls	sport	P=0.004	
	Preinjury alcohol consumption/YES	NO	NS[b]	
	Concomitant injury/YES	NO	NS[b]	
	Head injury/YES	NO	NS[b]	
	C1–4 & C5–8	T1–S5	NS[b]	
	Incomplete	complete	NS[b]	
	Operation in 6 weeks/YES	NO	NS[b]	
	Methylprednisolone in acute phase/YES	NO	NS[b]	
	Complication in acute phase/YES	NO	NS[b]	
Barman 2014	Male	Female	NS[b]	YES
	Age(continuous)		NS[b]	
	Fall	MVC	CI:1.16-3.18	
	others	MVC	CI:1.56-5.15	
	C1-4	L1-S5	CI:1.87-8.15	
	C5-8	L1-S5	CI:1.01-4.05	
	T1-6	L1-S5	CI:1.05-4.02	
	T7-12	L1-S5	NS[b]	
	AIS[k] grade A	D	CI:3.23-168.15	
	AIS[k] grade B	D	CI:2.73-148.91	
	AIS[k] grade C	D	NS[b]	

[a]SCI: spinal cord injury; [b]NS=not significant; [c]MVC/FL/Sp =motor vehicle crash/fall/sports; [d]PMD= probable major depression; [e]ICD-9: International Statistical Classification of Diseases and Related Health Problems-9th revision; [f]GCS: Glasgow Coma Scale; [g]PEC: Preexisting co-morbidity; [h]ISS: injury severity score; [i]TBI: traumatic brain injury; [j]PUs: pressure ulcers; [k]AIS: American Spinal Injury Association Impairment Scale; [l]DM: diabetes mellitus.

factors.

Age and Gender

In 14 studies, the association of mortality and gender was assessed; there was no significant association except three studies [10, 27, 28]. In one of these studies [27], the female gender and in two studies [10, 28], the male gender were predominant. In the study by Varma *et al.*, [10] gender was not significant by univariate analysis however after adjustment for confounders by multivariable logistic regression modeling, a 60 percent higher chance of death in males compared with females was seen (OR=1.6). In all studies, the association of higher age and mortality was assessed which showed a significant relationship in all except one [29]; this study compared patients less than 20 years old with older subjects.

The Level of Lesion and Neurologic Status

Severity of injury as complete or incomplete neurologic deficit or Frankel and ASIA classes was evaluated in 10 studies. Five studies reported completeness of neurologic deficit and the association with death. In all except one study 30, the association was significant. In this study, two groups of 61 and 30 patients were enrolled from Greece and Sudan, respectively; lack of significance may be due to the small sample populations. In the study by Hagen *et al*., [20], Patients with complete traumatic spinal cord injury had higher standardized mortality ratio (SMR) in comparison to incomplete injuries (4.23 vs. 1.25). This higher SMR was also true for spinal lesions at cervical and thoracolumbar level subgroups (3.07 vs. 1.13). In the study by Sabre *et al*., [24], the completeness of lesions was only related to mortality in the first two years after injury. In the other five studies, the severity was assessed by ASIA and Frankel Grades, and its association with mortality was reported. In these studies, the mortality rate was higher in those with Grade A neurological injury.

Time Passed from Injury

The association of duration of time since injury and mortality was evaluated in 3 studies which did not find any significance [20, 21, 27].

Comorbidities

The association of comorbidities with mortality was assessed in 5 studies with significant associations in all studies. One study [23] evaluated comorbidities using three methods including the Charlson Comorbidity Index, some diagnostic ICD-9 codes assigned, and the Cumulative Illness Rating Scale (CIRS); only the Charlson Comorbidity Index exhibited a significant association. One study assessed the incidence of comorbidities [10] and one report assessed mortality [21] according to each risk factor separately; one hyperlipidemia reached significance. In one study, only comorbidities related to spinal diseases was considered [30].

Associated Injuries

Traumatic co-injuries were assessed in three studies [24, 25, 30] and in one study, a concomitant head injury was significant just within the first two years after injury [24]. The association of treatment method with mortality was assessed in three studies [24, 25, 30] and was significant in one [24]. In this study, the death rate in the first two years after injury was lower in those who underwent operations within the first six weeks after injury. The other risk factors are presented in Table 7.

We did not consider the data of Levy 1998 because of unknown period for mortality (13/67), the significant number of non-responder patients with SCI and discrepancy between information in the text and figure [19].

Discussion

The goal of this systematic review was to evaluate the rate of mortality and its contributing factors in patients with TLSCI. In another systematic review, we assess mortality in the cervical region and by comparing the results of both systematic reviews we could have a better understanding of epidemiology and burden of traumatic spinal cord injury. Due to the heterogeneity of the studies on factors such as follow-up duration and cohort size, it is not possible to form a general conclusion. Also, because of a general dearth of reports on pre-hospital mortality and the fact that only subjects who survived the trauma were included, the mortality rate is lower than the real rate. The reported mortality rate ranges from 0% to 37.7%. This wide range is due to inhomogeneity between study designs. Studies with higher mortality had longer follow-up periods in general and, because the exact cause of death was typically not mentioned, it may not be due to TLSCI itself. Nonetheless, the SCI does affect the function of many other organ systems in the long run as indicated by reports of accelerated cardiovascular disease in SCI patients.

In studies reporting in-hospital mortality, the overall mortality rate was 5.2%; in studies reporting 6-month mortality, the overall rate was 26.12%, and in studies reporting 1-year mortality, the overall rate was 4.3%. In a systematic review by Chamberlain *et al*., the pooled in-hospital mortality rate among all traumatic SCI patients was 8% [31]. The significant differences between overall rates for in-hospital, 6-month and 1-year mortality may be because the 6-month mortality reports were from underdeveloped countries, which emphasizes the role of health system quality in mortality. In the studies from more developed countries with more advanced medical systems, mortality rates were lower. For example, comparing two studies with a similar follow-up period, the report from Nigeria (1997-2007) reported a 34% mortality rate after 6-months follow-up [32] while a study from the USA (1998-2008) reported 20% mortality with a minimum follow-up period of 1 year [27]. Although the cause of death was reported, in those with TLSCI the cause was available only in two studies. For a thorough assessment of the effects of the treatment on mortality, it is recommended that future studies report the cause of death during hospital admission and long-term follow-up.

Age at admission was described in all report. The association of age with mortality was significant in all except one study which reported higher but nonsignificant hazard ratio (HR) with increasing age. The authors hypothesized this was due to a higher severity of injury in the younger subjects and lower severity in older patients. In a meta-analysis by Chamberlain et al., pooled estimates of HRs and ORs of 1.06 (1.05–1.07; I2=78.2%) and 1.06 (1.03–1.09; I2=94.6%) for age at injury for all traumatic spinal cord injuries showed moderate-to-high heterogeneity, indicating that mortality risk increases on average by 6% with increasing age [31]. Although injury of a higher spinal level is associated with higher mortality rates, the studies did not differentiate between thoracic and lumbar injuries. The study by Cotton *et al*. involving 596 patients with thoracic SCI revealed that patients with high-thoracic SCI have 1.5-fold higher mortality probability compared with SCI of lower thoracic region and 3.45-fold higher compared with lumbar SCI [33].

There is also increased mortality in complete versus incomplete lesions. For example, Hagen et al. reported 23% and 38.6% mortality in incomplete and complete TLSCI, respectively. This study evaluated all individuals with SCI however and not TLSCI specifically. Duration of time after injury showed no significant association with mortality [20, 21, 27]. Considering the effects of comorbidities and associated injuries in patients with spinal injuries may help in defining mortality risk factors. These factors were related to higher mortality rates in some studies, and it seems in-hospital mortality in TLSCI may be more dependent on associated injuries and comorbidities than cervical SCI.

The presence or count of comorbidities by diagnostic code was not useful in differentiating mild and severe injuries. Tools such as the premorbid illnesses criteria and the Charlson Comorbidity Index were more useful for comparison purposes and are recommended for further studies. Divanoglou 2010 performed a cohort of population based study from 1-week to 1-year and found related mortalities [30]. We did not consider their study in our figure because of the inhomogeneous time interval of 1-week to 1-year.

In the systematic review (SR) of van den Berg et al., they assessed survival of patients with SCI, there were 11 out of 16 studies with traumatic SCI, four with non-traumatic and one both [34]. Therefore, the SR was a mixture of traumatic and non-traumatic patients with involvement of all cervical, thoracic and lumbar levels [34]. In the traumatic SCI population, survival rates up to 5 years post-injury ranged from 94.6% to 99.0% (mean 5-year survival rate 97.0±1.85) [34]. In another SR, Wilson et al., have combined three components of outcome to include survival, functional and neurological recovery [35]. They included traumatic SCI. However, they did not perform analysis for survival or mortality and did not extract the data of patients with thoracolumbar levels from all patients with SCI.

The most significant limitation of this systematic review is that no study exclusively assessed mortality rate and causes of death and risk factors in TLSCI patients. Some other limitations include: 1) the systematic review of observational studies is controversial [15, 16]. Despite the use of some criteria for quality assessment in some recent systematic reviews [15, 16, 36], their choice status is not clear yet; 2) observational studies are sensitive to selection, detection, confounders, performance bias, and publication bias; 3) Non-English reports were excluded which may result in the omission of some relevant studies; and 4) Types of treatment, severity of injury, patients medical status, mechanism of traumatic injury, and follow-up duration differed across the selected studies. These variations, especially in follow-up time, may contribute to the discrepancies in outcomes of the studies. In our review, a meta-analysis was not performed due to the limited number of selected studies, varying definitions of short- and long-term follow-up, and the general absence of reports on the mean follow-up duration.

Conclusion

Despite the importance of TLSCI, related epidemiological data such as mortality and contributing factors remain unclear. Although there is general agreement that traumatic thoracolumbar spinal cord injuries are important, no study was found that accurately assessed mortality in the thoracolumbar spine. It is recommended that well-designed prospective observational studies be conducted to determine the mortality rate and exact causes of death in thoracolumbar injuries.

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