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# Risk factors for respiratory failure with tetraplegia after acute traumatic cervical spinal cord injury

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**Abstract. – OBJECTIVE: To analyze risk factors for respiratory failure with tetraplegia after acute traumatic cervical spinal cord injury (CSCI).**

**PATIENTS AND METHODS: Total 180 tetraplegia cases after acute traumatic CSCI treated in Shanghai Changzheng Hospital from 2001 to 2011 were reviewed retrospectively and the frequency of respiratory failure in these patients were analyzed against the factors including age, gender, cause of injury, level/severity of injury, high-dose methylprednisolone (MP) therapy, and surgery intervention, using Chi-square test to look into the correlations of the prevalence of respiratory failure to those factors.**

**RESULTS: Of the 180 tetraplegia with acute traumatic CSCI, 29 patients (16.11%) developed respiratory failure. The factors, including age, level and severity of injury, high-dose MP therapy, and surgery intervention, were found to significantly correlate with the appearance of respiratory failure in tetraplegia after acute traumatic CSCI ($p < 0.05$), while no significant correlation was found between the other factors: gender and cause of injury and the frequency of respiratory failure.**

**CONCLUSIONS: Age, level/severity of injury, high-dose MP therapy, and surgery intervention are the four major relevant factors of respiratory failure in patients with acute traumatic CSCI. The appropriate and timing treatments involving high-dose MP therapy and surgical decompression and reconstruction can substantially increase the rates of clinical improvements and reduce the frequency of respiratory failure.**

*Key Words:*
Cervical spinal cord injury, Respiratory failure, Tetraplegia, Relevant factor.

## Introduction

With the development of economy and transportation industry, the incidence of traumatic cervical spinal cord injury (CSCI) is rising in recent years in China as in other countries in trend. The incidence of traumatic CSCI varies globally from 10.4 to 83.0 per million population per year[1-3]. Most cases of disability and mortality occurred in the early stage of CSCI[4], mainly due to neurologic dysfunction, systemic inflammation, concomitant injuries, treatments to prevent and ameliorate secondary injury, and prolonged immobilization[5]. Apart from those who died on the spot, more victims developed quadriplegia or paraplegia. And the paralysis of acute CSCI is a potentially catastrophic event causing major impact at both a personal and societal level for which there is no effective treatment.

Respiratory complications are the leading causes for morbidity and mortality in both acute and chronic stages of CSCI[6-8]. Pulmonary complications seen after acute tetraplegia progressively increase over the first 5 days[9], and respiratory failure is a common consequence of tetraplegia following CSCI[10]. However, to date, the relevant factors remain poorly characterized for appearance of respiratory failure in tetraplegia with acute traumatic CSCI. In the present study, we retrospectively reviewed the clinical data of 180 patients with acute tetraplegia who received treatments in the same treatment group in Shanghai Changzheng Hospital from 2001 to 2011, and analyzed the relevant factors against the frequency of respiratory failure in these patients to see whether there were close correlations present. The better understanding of the characters of tetraplegia after CSCI may lead to the better manners to prevent the appearance of respiratory failure and better therapies after injury.

## Patients and Methods

### Patients

Included in this study were 180 patients with tetraplegia (153 male and 27 female) following CSCI who received treatments in the same treat-

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ment group in Shanghai Changzheng Hospital from 2001 to 2011. Patients were considered ineligible if they (1) had serious co-morbidities at admission or specific conditions that might affect treatment assessment, (2) previously had a spinal cord injury, (3) had a penetrating CSCI, (4) had received steroids prior to admission, (5) were pregnant, (6) were aged under 14 years. They ranged in age from 14 to 86 years with a mean of 39.41±13.99 years. All patients were admitted in the first 24 hours after injury. All patients in our center received specialized care, including secretions clearing, bronchodilators, postural drainage, emergent intubation, tracheostomy, et al.

### Methods

The clinical data of these patients were stratified with respect to age (< 40-year and ≥ 40-year groups), gender, cause of injury (road traffic accidents, falls from height, and other causes), severity of injury according to the American Spine Association (ASIA) Impairment Scale (Grade A, B, C, and D), the level of injury (above C4 and C5-C8), high-dose MP therapy, surgery, and nutritional status during the course of treatment to explore their correlations with the occurrence of respiratory failure with tetraplegia after acute traumatic CSCI.

### Statistical Analysis

Statistical analysis was performed with SPSS13.0 software (SPSS Inc., Chicago, IL, USA). Measurement data were expressed as mean ± standard deviation and represented by proportion or percentage. Inter-group comparisons were performed by Chi-square test. $p$ value less than 0.05 was considered to be of significant difference.

## Results

All patients in our Center received specialized care, including secretions clearing, bronchodilators, postural drainage, emergent intubation, tracheostomy, et al. To get the accurate statistical analysis, we excluded the patients with serious comorbidities at admission such as brain trauma, multiple fracture, and chest abdomen joint injury since these sever complications are high risk factors of respiratory. Of the 180 subjects with tetraplegia after acute traumatic CSCI, 29 patients (16.11%) were complicated by respiratory failure. The statistical analysis of these data with the method described above (Chi-square test) was conducted against the factors: age, gender, cause of injury, level/severity of injury, high-dose MP therapy, and early surgery intervention (surgical decompression and reconstruction) to explore the relevance of these factors to the frequency of respiratory failure after acute traumatic CSCI.

Age: The frequency of traumatic CSCI complicated with respiratory failure increased with age. Since all the patients were Chinese, we divided all the patients into young (< 40 years old) and old (≥ 40 years old) group by age according to the Chinese criteria. In the 180 patients of this study, 95 patients were younger than 40 years, in whom the prevalence of respiratory failure was 7.37% (7/95); 85 patients were 40 years or older, in whom the prevalence of respiratory failure was 25.88% (22/85). The difference in the prevalence of respiratory failure between the two age groups was statistically significant ($p = 0.0007$).

Gender: We assessed the gender difference in the occurrence of respiratory failure in tetraplegia after acute traumatic CSCI. The analysis showed that the differences between male (153) and female (27) patients was not significant ($p > 0.05$).

Level/severity of injury: The prevalence of respiratory failure was 26.92% (14/52) in patients with injuries above C4 and 11.71% (15/128) in those with C5-C8 injuries. According to Grade A, Grade B, Grade C and D, the prevalence of respiratory failure in the 180 patients of our series was 39.34% (24/61), 15% (3/20), 5.56% (3/36) and 1.59% (1/63) respectively. There was significant difference between different level and severity of injury ($p < 0.05$).

High-dose MP therapy: MP is the effective drug for acute CSCI. Among the 180 cases in this study, the percentage of respiratory failure was 11.50% (13/113) in patients who received early (within 8 hours of injury) high-dose MP therapy, and 23.88% (16/67) in those without that treatment, which shows the significant difference between with and without high-dose MP therapy ($p < 0.05$) group.

Surgery intervention: In this study, 129 of 180 cases were treated by decompression and reconstruction surgery in three ways (anterior cervical spine surgery, posterior cervical spine surgery, combined anteroposterior cervical spine surgery) with 6 days (3.2 ± 0.6 days) after injury because the pronounced spinal instability and/or spinal cord compression were observed in these patients and the surgery was allowed based on the comprehensive health check result: 99 subjects received anterior surgery, 15 received pos-

terior surgery and another 15 received combined anteroposterior surgery. Note that the patient received indirect decompression through temporary skull traction was not included in the study. Comparing the prevalence of respiratory failure in the surgical (6.98%, 9/129) and non-surgical (39.22%, 20/51) groups, it's obvious that there was statistically significant difference between the two groups ($p < 0.0001$).

Cause of injury: The acute traumatic CSCI could be caused by road accidents, falls from height, and other reasons. Through the risk factor analysis, the difference in the occurrence of respiratory failure after acute traumatic CSCI was not statistically significant ($p > 0.05$) among three groups of patients by road accidents, falls from height, and other reasons.

From the above statistical analysis, it's obvious that age ($p = 0.007$), level/severity of injury ($p = 0.0119$), early surgery intervention ($p = 0.0001$), and high-dose MP therapy ($p = 0.0290$) were significant relevant factors for respiratory failure in tetraplegia after acute traumatic CSCI. Gender and cause of injury could more or less affect the appearance of respiratory failure with tetraplegia after acute traumatic CSCI, but not significantly.

## Discussion

Current treatment options for acute traumatic CSCI include the use of high dose methylprednisolone (MP), a corticosteroid, surgical interventions to stabilize and decompress the spinal cord, intensive multisystem medical management, and rehabilitative care[11,12]. To date, effects of these interventions after acute traumatic CSCI have been limited and as a result, pulmonary complications after acute tetraplegia progressively increase over the first 5 days[9], and respiratory failure is one of the common consequences of tetraplegia following CSCI[10]. Thus, it's critical to figure out the relevant factors to the prevalence of respiratory failure and initiate the prevention of respiratory immediately after the acute traumatic CSCI to achieve better therapeutic result.

The impact of age on functional recovery among survivors of traumatic CSCI still remains unclear. However, it's been reported respiratory failure increased from the mean age at 30.23 to 45.77 in a retrospective study with a total 553 individuals with CSCI[13]. In-hospital and 60-day mortality rates were significantly greater among older people following spine trauma in a popula-

**Table I.**

| Factors | Cases | ARDS/MODS (n=) | Prevalence (%) | $\chi^2$ value | *p* value |
|---|---|---|---|---|---|
| Age | | | | 11.38 | 0.0007* |
| <40 yr. | 95 | 7 | 7.37 | | |
| ≥40 yr. | 85 | 22 | 25.88 | | |
| Gender | | | | 1.78 | 0.1821 |
| Male | 153 | 27 | 17.65 | | |
| Female | 27 | 2 | 7.41 | | |
| Cause of injury | | | | 4.64 | 0.0982 |
| Road accidents | 63 | 13 | 20.63 | | |
| Falls from height | 70 | 6 | 8.57 | | |
| Others | 47 | 10 | 31.30 | | |
| Severity of injury (ASIA) | | | | 64 | <0.0001* |
| Grade A | 61 | 24 | 39.34 | | |
| Grade B | 20 | 3 | 15.00 | | |
| Grade C | 36 | 1 | 5.56 | | |
| Grade D | 63 | 1 | 1.59 | | |
| Level of injury | | | | 6.32 | 0.0119* |
| Above C4 | 52 | 14 | 26.92 | | |
| C5~8 | 128 | 15 | 11.71 | | |
| Surgery Intervention | | | | 28.11 | 0.0001* |
| Yes | 129 | 9 | 6.98 | | |
| No | 51 | 20 | 39.22 | | |
| High-dose MP therapy | | | | 4.77 | 0.0290* |
| Yes | 113 | 13 | 11.50 | | |
| No | 67 | 16 | 23.88 | | |

tion-based study that included 10,002 spinal cord-injured individuals[14]. The animal experiment showed that the young (4-week-old) mice had better functional recovery and lower pro-inflammatory cytokines or chemokine during the acute phase of CSCI, and highlighted age-related differences in pro-inflammatory properties of microglial cells that contribute to the amplification of detrimental inflammatory responses after CSCI[15]. Our findings indicated that the percentage of respiratory failure after CSCI was significantly higher among older people than in younger. The reasons could be slower rates of recovery and immunity in older patients, who are more likely to develop respiratory, cardiovascular and endocrine diseases, and to tolerate and cope with various attacks and surgical stress.

The potential clinical impact of gender on prevalence of respiratory failure in tetraplegia after acute traumatic CSCI has received little attention. We found that in the patients with tetraplegia, the appearance of respiratory failure after CSCI appeared not to be related to gender. Women had higher rates of reactive depression and deep venous thrombosis, but taking the treatment duration, treatment costs, and outcomes of patients with CSCI, gender was not a significant factor in functional outcome of CSCI patients after rehabilitation[16]. Although the women with motor-incomplete high tetraplegia (C1-4 levels) had higher discharge functional independence measure motor scores than that of similarly affiliated men, no differences were observed between men and women at other levels of motor incomplete CSCI[17]. All these previous studies revealed the consistent result from out study: gender is not a significant factor in functional outcome of CSCI patients after rehabilitation.

Our data indicated that a higher level and a more severity of injury can bring about higher prevalence of respiratory failure. The occurence of respiratory dysfunction is related to the injured level and severity of injury. The respiratory complications of CSCI at the level of C5 and above may include diaphragm dysfunction, retained airway secretions, recurrent aspiration, nocturnal hypoventilation, and respiratory failure [6]. The reason could be the diaphragm plays a leading role in quiet breathing and is the main driving force for respiratory movements providing 65% of the tidal volume during normal breathing[18-20]. The diaphragm is innervated by the phrenic nerve, and the phrenic nucleus is located in the center of C4 anterior column. Axons emitting from motor neurons main travel across C4-5 nerve roots (also possibly C3 anterior nerve root), form the trunk above the lateral border of anterior scalene muscle, and run downward along the anterior scalene muscle. When high-level (C1-C4) CSCI occurs, the phrenic nerve is involved, causing loss of spontaneous respiration and respiratory failure. Kang et al[21] reported that patients with complete cervical spinal cord injury at and above C3 level may die of respiratory failure at the very moment of injury or shortly after injury due to denervation of the phrenic nerve and intercostal nerve.

It has been well known that MP is the effective drug for acute CSCI, but the mechanism still need to be further understood. Primary spinal cord injury refers to the injury caused by external forces at the very moment of injury and is often irreversible. Secondary spinal cord injury refers to a series of injuries after the primary spinal cord injury, including hemorrhage, edema, microcirculatory dysfunction, and per-oxidative response. The consequence of secondary spinal cord injury is more serious, and early high-dose MP therapy can mitigate re-injury from secondary spinal cord injury. The effect of high-dose MP therapy for acute cervical spinal cord injury through the inhibition of inflammatory response is definite, but the poor side-effect profiles including gastrointestinal bleeding or delayed wound healing can occur. But the risk of such complication is not significant with using high-MP[26]. It is, therefore, important to use high-MP as specified and take positive measures to prevent complications from occurring.

There are controversies around whether surgery is necessary and the timing of surgical decompression and reconstruction for patients with acute traumatic CSCI[27]. Some clinical studies demonstrated the early surgery would increase the risk of nerve injury and patients with early surgical decompression had similar outcomes to patients who received a delayed decompression operation[28]. However, other non- and clinical studies argued the early surgery intervention could decompress the spinal cord and restore spine stability, which was damaged in CSCI, to prevent re-injury of the spinal cord from repeated movement of unstable bony elements[29-32]. In addition, the increasing evidences have suggested that early surgical decompression is safe and feasible, and can improve clinical and neurological outcomes, which could further reduce health care cost[30,33,34]. In this case, the surgery was beneficial and the appearance of the respiratory failure after acute

CSCI decreased significantly after surgery (from 39.22% to 6.98%). Surgery-treated patients generally had more confidence in keel over, pat on the back, exercise the function of the leaving respiratory muscles, and carry-out of fibrotic bronchoscope and bronchial lavage for effective secretion clearance[35,36]. However, the feasibility of surgery in patients with severe spinal cord injury is quite limited due to various conditions, such as severe post-traumatic infection and death from organ failure before surgery. Although a consensus regarding the optimal timing of surgical decompression for CSCI has not been reached, the preclinical and clinical evidence, as well as a recent international survey of spine surgeons, advocates performing early surgery intervention after injury[37]. The positive surgical decompression and reconstruction of spinal stability should be considered and operated in patients with evident cervical spinal instability and compression if their health status allows.

The acute traumatic CSCI could be caused by road accidents, falls from height, and other reasons. Through the risk factor analysis, the difference in the appearance of respiratory failure after acute traumatic CSCI was not statistically significant ($p > 0.05$) among three groups of patients, the injury of which were caused by road accidents, falls from height, and other reasons indicating that the cause of injury is not a major risk factor for the development of respiratory failure in CSCI.

## Conclusions

Age, level/severity of injury, high-dose MP therapy, and surgery intervention are the four major relevant factors (statistically significant) in relevance with the incident of respiratory failure in patients with acute traumatic CSCI. The patient with older age, higher level (above C4) and more severe injury has higher occurrence of respiratory failure following acute traumatic CSCI regardless of gender. However, our study also indicates that high-dose MP therapy within 5 hr after injury and the appropriate surgical, if allowed, can substantially increase the rates of clinical improvements and reduce complication. Even it's not essential, from our clinical case load, patient can benefit more or less from the clinical nutritional support for recovery and complication reduction. This study could be a valuable reference for the clinical practice in treatment of spinal trauma.

### Conflict of Interest

The Authors declare that there are no conflicts of interest.

## References


1) Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey? Spinal Cord 2006; 44: 523-529.
2) DeVivo MJ, Krause JS, Lammertse DP. Recent trends in mortality and causes of death among persons with spinal cord injury. Arch Phys Med Rehabil 1999; 80: 1411-1419.
3) DeVivo MJ, Go BK, Jackson AB. Overview of the national spinal cord injury statistical center database. J Spinal Cord Med 2002; 25: 335-338.
4) Jones L, Bagnall A. Spinal injuries centres (SICs) for acute traumatic spinal cord injury. Cochrane Database Syst Rev 2004; 4: CD004442.
5) Stein DM, Menaker J, McQuillan K, Handley C, Aarabi B, Scalea TM. Risk factors for organ dysfunction and failure in patients with acute traumatic cervical spinal cord injury. Neurocrit Care 2010; 13: 29-39.
6) Porth SC. Recognition and management of respiratory dysfunction in children with tetraplegia. J Spinal Cord Med 2004; 27(Suppl 1): S75-79.
7) Zimmer MB, Nantwi K, Goshgarian HG. Effect of spinal cord injury on the respiratory system: basic research and current clinical treatment options. J Spinal Cord Med 2007; 30: 319-330.
8) Jackson AB, Groomes TE. Incidence of respiratory complications following spinal cord injury. Arch Phys Med Rehabil 1994; 75: 270-275.
9) Berlly M, Shem K. Respiratory management during the first five days after spinal cord injury. J Spinal Cord Med 2007; 30: 309-318.
10) Winslow C, Bode RK, Felton D, Chen D, Meyer PR, Jr. Impact of respiratory complications on length of stay and hospital costs in acute cervical spine injury. Chest 2002; 121: 1548-1554.
11) Schilero GJ, Spungen AM, Bauman WA, Radulovic M, Lesser M. Pulmonary function and spinal cord injury. Respir Physiol Neurobiol 2009; 166: 129-141.
12) Baptiste DC, Fehlings MG. Update on the treatment of spinal cord injury. Prog Brain Res 2007; 161: 217-233.
13) McCammon JR, Ethans K. Spinal cord injury in Manitoba: a provincial epidemiological study. J Spinal Cord Med 2011; 34: 6-10.
14) Irwin ZN, Arthur M, Mullins RJ, Hart RA. Variations in injury patterns, treatment, and outcome for spinal fracture and paralysis in adult versus geriatric patients. Spine (Phila Pa 1976) 2004; 29: 796-802.
15) Kumamaru H, Saiwai H, Ohkawa Y, Yamada H, Iwamoto Y, Okada S. Age-related differences in cellular and molecular profiles of inflammatory responses after spinal cord injury. J Cell Physiol 2011; 227: 1335-1346.

16) Furlan JC, Krassioukov AV, Fehlings MG. The effects of gender on clinical and neurological outcomes after acute cervical spinal cord injury. J Neurotrauma 2005; 22: 368-381.

17) Sipski ML, Jackson AB, Gomez-Marin O, Estores I, Stein A. Effects of gender on neurologic and functional recovery after spinal cord injury. Arch Phys Med Rehabil 2004; 85: 1826-1836.

18) Ledsome JR, Sharp JM. Pulmonary function in acute cervical cord injury. Am Rev Respir Dis 1981; 124: 41-44.

19) Lanig IS, Peterson WP. The respiratory system in spinal cord injury. Phys Med Rehabil Clin N Am 2000; 11: 29-43, vii.

20) Winslow C, Rozovsky J. Effect of spinal cord injury on the respiratory system. Am J Phys Med Rehabil 2003; 82: 803-814.

21) Kang SW, Shin JC, Park CI, Moon JH, Rha DW, Cho DH. Relationship between inspiratory muscle strength and cough capacity in cervical spinal cord injured patients. Spinal Cord 2006; 44: 242-248.

22) Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, Fehlings MG, Herr DL, Hitchon PW, Marshall LF, Nockels RP, Pascale V, Perot PL Jr, Piepmeier J, Sonntag VK, Wagner F, Wilberger JE, Winn HR, Young W. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. J Neurosurg 1998; 89: 699-706.

23) Bracken MB. Treatment of acute spinal cord injury with methylprednisolone: results of a multicenter, randomized clinical trial. J Neurotrauma 1991; 8(Suppl 1): S47-50; discussion S41-42.

24) Hall ED, Braughler JM. Glucocorticoid mechanisms in acute spinal cord injury: a review and therapeutic rationale. Surg Neurol 1982; 18: 320-327.

25) Bracken MB. Methylprednisolone and acute spinal cord injury: an update of the randomized evidence. Spine (Phila Pa 1976) 2001; 26(24 Suppl): S47-54.

26) Sun T, Xu S, Huang H. High-methylprednisolone treatment in acute cervical spinal cord injury without fracture and dislocation. Zhonghua Wai Ke Za Zhi 1997; 35: 735-737.

27) McKinley W, Meade MA, Kirshblum S, Barnard B. Outcomes of early surgical management versus late or no surgical intervention after acute spinal cord injury. Arch Phys Med Rehabil 2004; 85: 1818-1825.

28) Kawano O, Ueta T, Shiba K, Iwamoto Y. Outcome of decompression surgery for cervical spinal cord injury without bone and disc injury in patients with spinal cord compression: a multicenter prospective study. Spinal Cord 2010; 48: 548-553.

29) Ng WP, Fehlings MG, Cuddy B, Dickman C, Fazl M, Green B, Hitchon P, Northrup B, Sonntag V, Wagner F, Tator CH. Surgical treatment for acute spinal cord injury study pilot study #2: evaluation of protocol for decompressive surgery within 8 hours of injury. Neurosurg Focus 1999; 6: e3.

30) Furlan JC, Noonan V, Cadotte DW, Fehlings MG. Timing of decompressive surgery of spinal cord after traumatic spinal cord injury: An evidence-based examination of pre-clinical and clinical studies. J Neurotrauma 2010; 28: 1371-1399.

31) Fehlings MG, Arvin B. The timing of surgery in patients with central spinal cord injury. J Neurosurg Spine 2009; 10: 1-2.

32) Wang D, Teddy PJ, Henderson NJ, Shine BS, Gardner BP. Mobilization of patients after spinal surgery for acute spinal cord injury. Spine (Phila Pa 1976) 2001; 26: 2278-2282.

33) Bagnall AM, Jones L, Duffy S, Riemsma RP. Spinal fixation surgery for acute traumatic spinal cord injury. Cochrane Database Syst Rev 2008; CD004725.

34) Kishan S, Vives MJ, Reiter MF. Timing of surgery following spinal cord injury. J Spinal Cord Med 2005; 28: 11-19.

35) McBride DQ, Rodts GE. Intensive care of patients with spinal trauma. Neurosurg Clin N Am 1994; 5: 755-766.

36) Claxton AR, Wong DT, Chung F, Fehlings MG. Predictors of hospital mortality and mechanical ventilation in patients with cervical spinal cord injury. Can J Anaesth 1998; 45: 144-149.

37) Wilson JR, Fehlings MG. Emerging approaches to the surgical management of acute traumatic spinal cord injury. Neurotherapeutics 2011; 8: 187-194.

38) Cook N. Respiratory care in spinal cord injury with associated traumatic brain injury: bridging the gap in critical care nursing interventions. Intensive Crit Care Nurs 2003; 19: 143-153.