



Identification of risk factors for respiratory complications in upper cervical spinal injured patients with neurological impairment

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Objective: Clinical features of respiratory complications in patients with upper cervical spine injuries (CSI) are unique due to the complex regional anatomy in the region. The objective of this study was to identify the risk factors for respiratory complications in the patients with upper CSI and cervical spinal cord injuries (C-SCI).

Methods: Ninety-two patients (out of 1593 spine injured patients) who met the inclusion criteria of upper CSI were admitted to our hospital from 1992 to 2010. Their records were retrospectively reviewed.

Results: Respiratory complications occurred in 16 patients (17.4%). In addition, ventilator-associated pneumonia played an important role in the respiratory complications, however, no pulmonary thromboembolism was found. Death rate in respiratory complication group (RCG, 31.3%) was significantly higher than that in non-respiratory complication group (NCG, 1.3%). In RCG, severe C-SCI (American Spinal Cord Injury Association Grades A and B, OR=34.401; 95% CI, 2.609-5.525) and hypoalbuminemia (OR=24.616; 95% CI, 1.492-6.182) were identified by logistic regression analysis as main risk factors for respiratory complications; whereas levels of neurological injury, quadriplegia, atlanto-axial fractures, smoking history, and electrolyte disturbances were not identified as risk factors (although statistically relevant to respiratory complications).

Conclusion: Severe C-SCI and hypoalbuminemia played important roles in predicting respiratory complications among the patients with upper CSI and neurological impairment. In addition, levels of neurological injury, quadriplegia, atlanto-axial fractures, smoking history, and electrolyte disturbances are also valuable indicators for these complications. Moreover, prevention of ventilator-associated pneumonia was crucial in the treatment of these patients. However, a screening for deep venous thrombosis was seemingly unnecessary in our patients.

Key words: Cervical spine; spine injury; spine surgery.

The upper cervical spine (occiput, C1, and C2) is unique because of its complex anatomy and weight-bearing function.^[1] Upper cervical spine injury (CSI) is varied and infrequently accompanied with cervical spinal cord injuries.^[2] Its rareness is attributable to the

relatively large diameter of the cervical spinal canal.^[1] However, severe cervical spinal cord injury (C-SCI) in this region can cause paralysis of the diaphragm (innervated by C3-C5 segments) and decreases the motion of the accessory respiratory muscles and consequently,

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pulmonary function is impaired.^[3] Complicating matters, the level of neurological impairment could increase due to bleeding and swelling of the spinal cord.^[3,4] Moreover, the imbalance between parasympathetic and sympathetic control causes an increase in airway tone and hypersecretion of bronchial mucus.^[5] Taken together, these factors cause various respiratory complications, such as respiratory failure, pneumonia, and atelectasis.^[6,7] In this situation, mortality rate is greatly enhanced and ventilatory support is frequently required.^[6,8,9] Therefore, prediction, prevention and timely treatment of these complications become crucial for an individual patient's prognosis.

Due to manifestations and complications of upper CSI, it has been recommended that pulmonary function should be monitored immediately after the injury occurs, however, assessment of respiratory functions using spirometry is often difficult and the results of blood gas analysis are unreliable,^[7,10] which has led to difficulties in treating patients and strained medical resources.^[11] Hence, identification of risk factors for respiratory complications will assist a practitioner in making therapeutic decisions. Researchers have previously concentrated on prediction of respiratory complications in cervical cord injured patients.^[4,12,13] However, studies concerning upper CSI are rare. Considering that patients of this type differ from those with other CSI, we estimated that the characteristics and risk factors for respiratory complications would be different. Therefore we aim to identify the risk factors for respiratory complications in the patients with upper CSI and neurological impairment.

Patients and methods

A retrospective review was performed in patients (age >20 years) with upper CSI and neurological impairment who were admitted to the Department of Orthopaedic Surgery in our institute from September 9, 1992 to February 8, 2010. A total of 92 patients were admitted within 20 days after injuries. Attending doctors in our department evaluated the patients' baseline conditions and injury severity. All patients received treatments according to their conditions. Clinical data were retrieved retrospectively by reviewing patients' records. Duration of follow up was from admission to discharge or death (4 to 41 days). Data collected on admission included age, gender, mechanism of the injury, completeness of the C-SCI according to International Standards for Neurological and Functional Classification of Spinal Cord Injury published by the American Spinal Cord Injury Association (ASIA).^[14] These classifications were as follows: Grade

A, no motor or sensory function is preserved; Grade B, sensory but not motor function is preserved; Grade C, some sensory and motor functions are preserved, and most key muscles have a muscle grade less than 3; Grade D, motor function is preserved, and most key muscles have a muscle grade greater than 3; Grade E, normal sensory and motor functions; the levels of the injury (according to the clinical manifestations and findings in the magnetic resonance images); the type of the injury (including atlanto-axial fractures and isolated fractures of the atlas or axis); type of the odontoid fractures (type I, II, III odontoid fractures according to Anderson-D'Alonzo standards); the type of paralysis (including quadriplegia and paraplegia); serum albumin and electrolyte concentration; smoking history and associated injuries; data obtained on discharge or death consisted of various complications during hospitalization, operations, tracheostomy, usage of mechanical ventilation, length of stay, time and cause(s) of death and significant neurological improvement. Steroids were administered intravenously as follows: (1) for those with duration before admission less than 8 hours, methyl prednisolone 30 mg/kg × 15 min + 5.4 mg/kg × 23 hours; (2) for those with duration before admission more than 8 hours, dexamethasone 20 mg × 3 days + declining dosage × 7 to 10 days.

We defined respiratory complications as pneumonia, respiratory failure, and atelectasis. Significant neurological improvement was defined as an increase in at least 1 clinical grade according to the ASIA grades. Diagnostic criteria were as follows: respiratory failure (dyspnea accompanied by partial pressure of oxygen <60 mmHg and/or partial pressure of carbon dioxide >50 mmHg on room air and/or the need for ventilatory support, without cardiogenic causes); pneumonia [should meet the principle diagnostic standard - new pulmonary infiltrative focus - and at least 2 secondary diagnostic standards]: (1) body temperature >38°C or <35.5°C, (2) leucocyte count >12,000/mm³ or <4000/mm³, (3) new purulent sputum or change of characteristics of sputum]; atelectasis (dyspnea, chest pain and characteristic radiographic signs); ventilator-associated pneumonia (evidence for respiratory infection after application of ventilation with a minimal time limit of 48 hours); electrolyte disturbances (serum potassium <3.5 mmol/L or >5.5 mmol/L; serum sodium <136 mmol/L or >145 mmol/L); and hypoalbuminemia (serum albumin <35 g/L).

The (RCG) patients who experienced respiratory complications were compared with those who did not (NCG), then univariate analysis was performed. Parametric data were analyzed using a t-test or

Cochran-Mantel-Haenszel (CMN) test, and categorical data using chi-square analysis or Fisher's exact test. The data were expressed as mean±SD. Statistical significance was defined as $p < 0.05$. Finally, statistically and clinically significant data were integrated into a multivariate logistic regression analysis and the risk factors were identified. All the data were analyzed using SAS software version 9.1.

Results

A total of 1593 patients with spinal injuries were admitted to our hospital during 18 years, including 343 patients with the upper CSI, of whom there were 172 patients with odontoid fractures (50.1%). Within the upper CSI patients, there were 92 (26.8%) patients with C-SCI, all of whom suffered from blunt injuries. In terms of the level of neurological injury, we found 47 (51.1%) with high C-SCI (C5 and above segments). The mean age of the patients with neurological impairment was 49.5 ± 4.9 years. The most common causes of injury were motor vehicle accidents (58.7%), followed by falls (25.0%). High energy motor vehicle accidents (69.0%) occurred mostly among youths between 20-40 years of age, while falls (38.3%) were usually found in elders (60-70 years of age). We found that respiratory complications occurred in 16 patients (17.4%), 12 had pneumonia (13.0%), 8 had respiratory failure (8.7%) and one had atelectasis (1.1%). Patients with compromised traumatic airways were not observed.

Comparisons were made in baseline condition and severity of injuries between RCG and NCG. We found

that male patients accounted for the majority of both RCG (87.5%) and NCG (90.8%) (Table 1), however, no statistical difference was found ($p = 0.69$, chi-square analysis). In addition, the mean ages of the two groups were similar (Table 1, RCG: 44.9 ± 11.1 years, NCG: 40.4 ± 12.1 years; $p = 0.69$, chi-square analysis).

Among all the patients, the incidence of respiratory complications in different age groups were as follows: 12.5% (20 to 35 years), 14.7% (35 to 50 years) and 26.9% (50 years and above). However, there was no significant difference among different age groups ($p = 0.92$, CMH test). The association between respiratory complications and quadriplegia in RCG was found to be statistically significant (Table 1, $p < 0.001$, chi-square analysis). There was a strong correlation between respiratory complications and atlanto-axial fractures (Table 1, $p < 0.001$, chi-square analysis) in the RCG. Besides, hypoalbuminemia was found to be significantly related to respiratory complications as well (Table 1, $p < 0.001$, Fisher's exact test). However, no correlation was found between odontoid fracture types and respiratory complications (Table 1, $p = 0.41$, chi-square analysis). Serum electrolyte disturbances (mainly hyponatremia and hypopotassaemia, $p = 0.01$, Fisher's exact test) and smoking history were strongly correlated with respiratory complications (Table 1, $p < 0.001$, chi-square analysis). By contrast, no significant difference was found in the incidence of associated injuries between RCG and NCG ($p = 0.39$, chi-square analysis). The associated injuries included injuries to other portions of the spine (levels except for upper cervical spine injuries), craniocerebral trauma,

Table 1. Summary of demographic characteristics, severity of injuries and associated complications for patients with and without respiratory complications.

Variables	RCG (n=16)	NCG (n=76)	Statistical test	p value
Male sex	14 (87.5%)	69 (90.8%)	Chi-square analysis	0.69
Age (yr) (means±SD)	44.9±11.1	40.4±12.1	"t" test	0.17
ASIA scale				
Grade A	6 (37.5%)	–	–	–
Grade B	4 (25.0%)	2 (2.6%)	–	–
Grade C	3 (18.8%)	8 (10.1%)	–	–
Grade D	3 (18.8%)	66 (87.3%)	–	–
Type II odontoid fracture	4 (25.0%)	28 (36.8%)	Chi-square analysis	0.41
Smoking history	12 (75.0%)	19 (25.0%)	Chi-square analysis	<0.001
Quadriplegia	14 (87.5%)	19 (25.0%)	Chi-square analysis	<0.001
High level C-SCI	14 (87.5%)	32 (42.1%)	Chi-square analysis	0.001
Atlanto-axial fractures	11 (68.8%)	24 (31.6%)	Chi-square analysis	<0.001
Associated injuries	3 (18.8%)	22 (28.9%)	Chi-square analysis	0.39
Hypoalbuminemia	7 (43.8%)	3 (3.9%)	Fisher's exact test	<0.001
Electrolyte disturbances	7 (43.8%)	11 (14.5%)	Fisher's exact test	0.01

AISA: American Spinal Cord Injury Association; C-SCI: cervical spinal cord injury; NCG: non-respiratory complications group; RCG: respiratory complications group

fractures of long bones or the pelvis and contusion of the internal organs (the lung and kidney). In addition, similar arrhythmia rates were also seen in patients in both RCG (18.8%) and NCG (18.4%).

Next, we examined the correlation between respiratory complications and severity of the C-SCI. Our data showed that respiratory complications were positively correlated with the severity (Table 2, ASIA grades A and B, $p < 0.001$, CMH test) and level of C-SCI (Table 1, C1-C4, $p = 0.001$, chi-square analysis) in RCG.

Complications and treatment of the patients during hospitalization were listed in Table 3. The mean length of stay was 26.8 ± 5.7 days in RCG and 13.3 ± 4.9 days in NCG ($p = 0.03$, CMH test). Operation rate in RCG was 68.8%, which was significantly lower than that of 78.9% in NCG ($p < 0.001$, Fisher's exact test). The surgical approaches included anterior, posterior and anterior-posterior approaches. Due to the difference in severity of the injuries, the rate of significant neurological improvement in the two groups was also different, the rate in NCG was approximately 6 folds higher than that in RCG (Table 3, $p < 0.001$, chi-square analysis). The total mortality rate was 6.5%, and death rate in RCG was markedly higher than NCG (Table 3, $p < 0.001$, Fisher's exact test). Time from injury to death was 9 ± 2.3 days. All of the severely injured patients (Table 2, $n = 12$, 13.0%) underwent tracheostomy (7, 43.8%) or ventilation (9, 56.3%). In the ventilation group, 2 incomplete C-SCI patients weaned from ventilation on discharge while 5 patients became ventilator-dependent, and 2 patients deceased. There were 7 patients in RCG with

Table 2. Summary of the severity of injuries and respiratory complications.

	Degree of neurological deficit (ASIA scale)			
	Grade A	Grade B	Grade C	Grade D
NCG – n (%)	–	2 (33.3)	8 (72.7)	66 (95.7)
RCG – n (%)	6 (100.0)	4 (66.7)	3 (27.3)	3 (4.3)
% in RCG*	37.5	25.0	18.8	18.8

ASIA: American Spinal Cord Injury Association; NCG: non-respiratory complication group; RCG: respiratory complication group. *% of patients with the same degree of injury severity in RCG.

ventilator-associated pneumonia, accounting for 43.8% of respiratory complications. No patients in NCG received tracheostomy or ventilation. With regard to the interactions among various respiratory complications, ventilator-associated pneumonia accounted for 87.5% in patients with respiratory failure, increasing the risk of mortality. In addition, there were 5 patients initially presenting with pneumonia, and one of them suffered from respiratory failure during hospitalization.

Additionally, we also found that the prognosis of the patients in RCG was poor, and the mean length of stay in RCG was 26.8 ± 5.7 days (Table 3), which was significantly longer than that in NCG (Table 3, 13.3 ± 4.9 days, $p = 0.03$, CMH test). Of all the patients who underwent operation, 18.2% of the patients in RCG and only 1.3% in the NCG manifested postoperative complications including dysphagia, serum electrolyte and acid-base disturbances, airway obstruction

Table 3. Summary of treatment and prognosis of the patients.

	RCG (n=16)	NCG (n=76)	Statistical test	p value
Length of stay in hospital-day (means \pm SD)	26.8 ± 5.7	13.3 ± 4.9	CMH test	0.03
Surgical treatment	11 (68.8%)	75 (98.7%)	Fisher's exact test	<0.001
Surgical approach				
Anterior	5 (45.5%)	30 (40.0%)	–	–
Posterior	4 (36.4%)	36 (48.0%)	–	–
Anterior-posterior	2 (18.2%)	9 (12.0%)	–	–
*Significant neurological improvement	2 (12.5%)	60 (78.9%)	Chi-square analysis	<0.001
*Postoperative complications	2 (18.2%)	1 (1.3%)	–	–
*Complications associated with glucocorticoid	–	–	–	–
Death	5 (31.3%)	1 (1.3%)	Fisher's exact test	<0.001
Tracheostomy	7 (43.8%)	–	–	–
Ventilator	9 (56.3%)	–	–	–
Length of use of ventilator-day (means \pm SD)	10.3 ± 4.2	–	–	–
DVT	–	1 (1.3%)	–	–
Bedsore	3 (18.8%)	–	–	–

DVT: deep venous thrombosis; NCG: non-respiratory complications group; RCG: respiratory complications group. *Significant neurological improvement was defined as increase of at least 1 clinical grade according to the ASIA classification system. *Postoperative complications included bucking, airway obstruction and arrhythmias aroused by hypotassaemia. *Complications associated with glucocorticoid included peptic ulcer, upper gastrointestinal bleeding, perforation of digestive tract and urinary tract infection.

and ventricular tachycardia. Only one patient (1.1%) was diagnosed with deep venous thrombosis (DVT), however no pulmonary embolism was observed. Glucocorticoids were included in the therapy protocol for every patient, however, the previously reported relevant complications were not seen in this study.^[15]

To further identify potential risk factors, a logistic regression analysis was performed. Bedsores were excluded due to the small number of patients who experienced this complication. Age, gender, types of odontoid fractures and associated injuries were also excluded, because no significance was seen in the univariate analysis. Therefore, the severity, level and types of injury, serum albumin and electrolyte concentration, length of stay and smoking history were included in the logistic regression analysis. The main risk factors identified were severe C-SCI (OR=34.401; 95% CI, 2.609-5.525) and hypoalbuminemia (OR=24.616; 95% CI, 1.492-6.182).

Figure 1 presents the tendency towards respiratory complications among patients with severe spinal injuries (ASIA grade A and B) combined with hypoalbuminemia, where all of these patients suffered from respiratory complications, however, when hypoalbuminemia was absent in the severely injured patients, 71.4% of these patients had respiratory complications. Among patients with minor injuries, hypoalbuminemia alone indicated a 50% likelihood of respiratory complications. When hypoalbuminemia was absent in this group, 5.3% of the patients experienced respiratory complications.

Discussion

In the present study, we have identified risk factors for respiratory complications among patients with upper CSI and neurological impairment.

In our patients, the major cause of injury was high energy motor vehicle accidents (most frequently seen in the youths) and falls (the main cause in the elderly). Our findings were consistent with previous reports.^[16, 17] The incidence of C-SCI in patients with upper CSI were reported to be 18%-26%, and similarly, the incidence in our patients was 26.8%.^[18,19] The types and frequency of respiratory complications were consistent with previous findings.^[10,12] However, the number of severely injured patients were low (n=12, 13.0%), and it was attributable to the relatively poor on-spot treatment in China, which may increase mortality rate on arrival. If we were able to add more severely injured patients to the study, the incidence of respiratory complications would be much higher.^[1] Although traumatic airway compromise and pulmonary embolism have previously been reported in cervical spine injured patients, no patient in our study manifested these complications.^[2,20]

Risk factors for respiratory complications in patients with C-SCI have been studied previously, however, few studies concentrated on identification of risk factors in patients with upper CSI.^[3,4,10] Well identified risk factors include severe C-SCI (ASIA grades A and B), high levels of injuries and smoking history.^[4,15,17,21,22] However, the

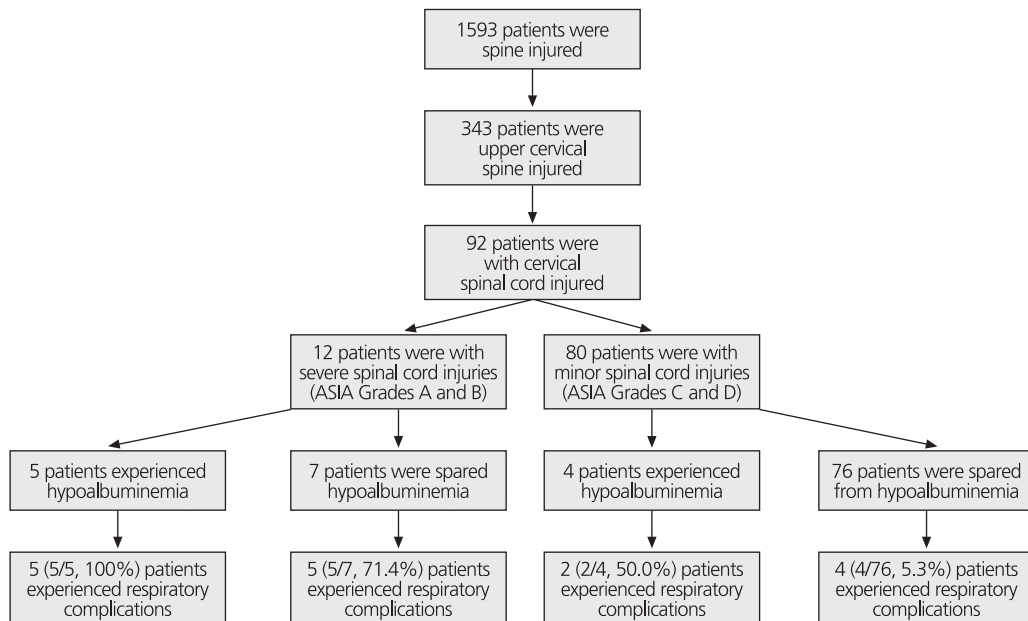


Fig. 1. A flow chart showing hypoalbuminemia, apart from severe cervical spinal injury, increased the tendency of respiratory complications in all patients.

main risk factors identified in the present study were severe C-SCI and hypoalbuminemia. Respiratory complications mainly occurred in the patients with high C-SCI levels, and the incidence was 17.4% (including 13.0% pneumonia; 8.7% respiratory failure; and 1.1% atelectasis). Previous studies have demonstrated that sex differences play a role in respiratory recovery in rats with high C-SCI. After the injury occurs, female rats preserve better pulmonary function and prognosis than males.^[23] These findings imply that female patients with high C-SCI may benefit from estrogen in terms of respiratory prognosis, resulting in a lower incidence of respiratory complications. In our study, this phenomenon was not observed; we attribute it to the small number of female patients, differences between the mechanisms of injury (our patients suffered from blunt injuries instead of trans-actions) and the discrepancy between humans and rats.

On the other hand, it is known that serum albumin can last as long as 3 weeks in vivo, which provides stable and valuable evidence for patients' status since injury occurred. In our study, measurement of blood albumin was taken on admission (less than 20 days after injury), and it indicated an early change in the whole disease process, and avoided distinct interference caused by medication. Notably, hypoalbuminemia has been reported to be common either in acute or chronic SCI (with its reasons unclear).^[24,25] Furthermore, hypoalbuminemia is more than an indicator for malnutrition since it could further impair the respiratory muscle function so as to enhance the risk of respiratory failure and other respiratory complications.^[7,26,27] However, hypoalbuminemia may be neglected by the clinicians since maintenance of vital signs are deemed priority in treating such patients. Therefore, more attention should be paid to patients' albumin level since it may indicate the tendency toward fatal respiratory complications among traumatic cervical spine injured patients.

Apart from high C-SCI levels, other factors significantly related to respiratory complications are quadriplegia, electrolyte disturbances, atlanto-axial fractures and smoking history (Table 1). Simultaneous atlanto-axial fractures may well indicate the severity of injuries, and may increase the incidence of neurological impairment, resulting in respiratory complications. Additionally, the insignificant correlation between age and respiratory complications was attributable to the limited number of elderly patients (≥ 60 years, $n=6$, 6.5%).

In the present study, we also found that associated injuries occurred in 27.2% of patients, and had significant correlation with mortality rate, however, we did not find an association with respiratory complications

($p=0.39$, chi-square analysis).^[17] Although the incidence of DVT was low (1.1%), it could be much higher since most patients would not have relevant clinical manifestations.^[20] Due to the potential risk for pulmonary embolism, some researchers have recommended screening for DVT in the spinal cord injured population.^[20] Nevertheless, based on our findings, we do not think it is necessary for our patients.

With regard to the therapy, the operation rate was low in RCG, for patients in this group frequently had poor health status. Tracheostomy and ventilatory support were only performed among severely injured patients. Postoperative complications took place in three patients (3.3%), and were more common in RCG (18.2%). Moreover, postoperative complications in RCG were fatal (airway obstruction and arrhythmias caused by hypotassaemia). The rate of significant neurological improvement in RCG was low, since most patients in this group were severely injured.^[28]

Administration of glucocorticoids to complete C-SCI patients is controversial.^[15] In this study, glucocorticoid therapy was administered to all patients, however, none of the patients manifested relevant complications. This possibly was attributable to the proper use of steroids according to the duration before admission. One limitation of this study is that it was a single center retrospective study. Furthermore, many patients died prior to arrival at the hospital, resulting in a loss of information. Moreover, the small number of the patients due to rareness of the disease and the short length of follow up might have introduced bias.

In summary, identification of risk factors for respiratory complications in patients with upper CSI and neurologic deficits is crucial for a practitioner's therapeutic decision making. The main risk factors among our patients were severe C-SCI and hypoalbuminemia. Meanwhile, completeness and levels of neurologic injury, quadriplegia, atlanto-axial fractures, smoking history and electrolyte disturbances were also valuable indicators. Prevention of ventilator-associated pneumonia is crucial in treatment of the patients. DVT will increase the risk of pulmonary embolism, however, in our patients, a routine screening was unnecessary.

Conflicts of Interest: No conflicts declared.

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