



## Research article

# Vertebral fracture and dislocation patterns, location of injuries, and 6-month clinical outcomes in cats: A retrospective study

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## Abstract

This study investigates the vertebral fracture and dislocation patterns, spinal cord segment injury location, paretic grading, and the 6-month outcome in cats at a university veterinary hospital. The medical records and radiographs of cats with traumatic injuries were reviewed from October 2016 to December 2019. Eighty-nine cats were diagnosed with vertebral fracture and dislocation. The most damaged location was T3–L3 (36/89, 40.45%), followed by L4–L7 (33/89, 37.07%), S1–S3 (18/89, 20.22%), C1–C5 (1/89, 1.12%), and C6–T2 (1/89, 1.12%). The patterns of vertebral damage could be classified as burst/compression (24/89, 26.96%), subluxation (19/89, 21.35%), complete luxation (16/89, 17.97%), combined fracture, and luxation (19/89, 21.35%), transverse fracture (10/69, 11.23%), and hyperextension (1/89, 1.12%). No hyperflexion-damaged pattern was detected in 89 cats. The T3–L7 lesion data was thoroughly examined (69 cats). Most of them preferred non-surgical treatment (33/69, 47.83%). Only 30 cats in the non-surgical group and 4 cats in the surgical group had tracking information. Six months after treatment, 60% of cats in the non-surgical group had better outcomes (18/30), while 66.67% of cats in the surgical group had better outcomes (4/6). Two cats in the surgical group had died of parvovirus infection. The mortality rate increased from 16.67% (6/36) at 3 months to 25% (9/36) at 6 months after treatment. All cats with paretic grade 5 had a poor prognosis. Most cats with paretic grades 1–4 receiving treatment had better clinical outcomes within 6 months and gradually improved. Follow-up should be performed for >6 months.

**Keywords:** Mortality rate, Outcome, Spinal fracture, Spinal luxation, Traumatic spinal cord injury

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**Article history;** received manuscript: 21 February 2022,  
 revised manuscript: 8 March 2022,  
 accepted manuscript: 1 April 2022,  
 published online: 11 April 2022

**Academic editor;** Korakot Nganvongpanit



## INTRODUCTION

Vertebral fracture and dislocation, which result in spinal cord injury, are common disorders in dogs and cats. The most common causes of spinal fracture and dislocation include trauma induced by vehicle accidents, penetrating wounds, animal-animal interaction, animal abuse, and fall from height (Shores, 1992; Bagley, 2000; Jeffery, 2010; Olby, 2010). Traumatic lesions of spinal fracture can cause complete or partial damage to the spinal cord functions, with almost 60% of the affected area being thoracic and lumbar sections in both dogs and cats (Bruce et al., 2008; Bali et al., 2009). Additionally, back pain, knuckling, limb weakness, ataxia, and paralysis are some of the clinical signs observed (Fluehmann et al., 2006; Simpson et al., 2009; Ali, 2013).

Spinal fracture and spinal cord injury (SCI) have been reported in several countries worldwide (Phillips, 1979; Grasmueck and Steffen, 2004; Simpson et al., 2009; Ali, 2013). According to a study in the UK, 4.2% of cats encountered road traffic accidents that resulted in spinal and internal organ trauma (Conroy et al., 2019). Therefore, vertebral damage and SCI are significant conditions that veterinarians must be prepared to manage professionally.

Because there have been few studies on the patterns of damaged vertebrae and a small sample size of cats throughout the world, the outcome of spinal fracture and/or dislocation after treatment is rarely studied. Therefore, the author investigates the patterns of damaged vertebrae and paretic grading, focusing on the thoracic and lumbar areas and the results after treatment at a specific time.

## MATERIALS AND METHODS

### Case selection and data collection criteria

The medical record database of cats with vertebral fractures and dislocation admitted to Small Animal Teaching Hospital, Chiang Mai University (SATH, CMU), Thailand, from October 2016 to December 2019 was collected and reviewed retrospectively. Ethical approval was granted to this study by the Faculty of Veterinary Medicine's Institutional Animal Research Ethics Committee, Chiang Mai University, Thailand (FVM-ACUC Ref. No. S10/2563). The data included age groups (young animal (<1.5 years), mature (1.5–7 years), old (>7 years)), sex (male and female), breed, body weight (<3.5 kg and  $\geq$ 3.5 kg), clinical history, clinical signs on the first presenting day, duration of clinical signs (or time last observed as normal), and neurological examination results.

### Paretic score

The cats were graded the severity levels from 0 to 5 as the neurological signs by veterinarians were recorded in the patient's data, as previously described (Fossum et al., 2007; Owen, 2007). Briefly, the scoring criteria were as follows: 0–normal cats, 1–pain only, no motor weakness, 2–persistent pain, proprioceptive deficit, ambulatory paraparesis, 3–non-ambulatory paraparesis, 4–paraplegia with deep pain perception, and 5–paraplegia without deep pain perception.

## Fracture and dislocation type

Radiographic images diagnostically confirmed the vertebral fracture's cats. All radiographs have been proofed and interpreted by a veterinarian in our team who has 14 years of working experience in small animals' clinics. The damage locations were classified as their neural location within the spinal column; C1–C5, C6–T2, T3–L3, L4–L7, and S1–S3 (Garosi, 2013). Additionally, fracture and dislocation types were classified as per the classification system of spinal trauma modified by Bali et al. (2009) from the original publication by Shores (1992) (Shores, 1992; Bali et al., 2009). The lesions are composed of hyperflexion injuries, hyperextension injuries, luxation, subluxation, combined fracture and luxation, transverse fractures, and burst/compression fractures.

## Treatment options

The data on each patient's final diagnosis and treatment plan, such as conservative management, surgical treatment, the type of surgical technique, steroid application, use of a splint or bandage, and/or euthanasia, were recorded. Cats referred for surgery would be treated with appropriate surgical techniques based on financial constraints, veterinarian preference, and clinical severity. The surgical techniques included spinal stabilization techniques (such as pins, screws with Polymethyl methacrylate, and locking plate), spinal decompression techniques (such as laminectomy and hemilaminectomy), and a combination of stabilization and decompression techniques.

## Outcome investigation

The outcomes were investigated in patients who received conservative management and surgical treatment, as recorded in their medical records, via telephone interviews, and/or observation and neurological examination. The outcomes were determined three times, including 1, 3, and 6 months after treatment. The outcomes were categorized into two groups (modified from previous studies) (Olby et al., 2003; Bali et al., 2009), which were “better than before treatment” (Better group) and “fair or worse than before treatment” (FW group). Additionally, the patients who were euthanized or who had died were categorized into the FW group.

## Statistical analysis

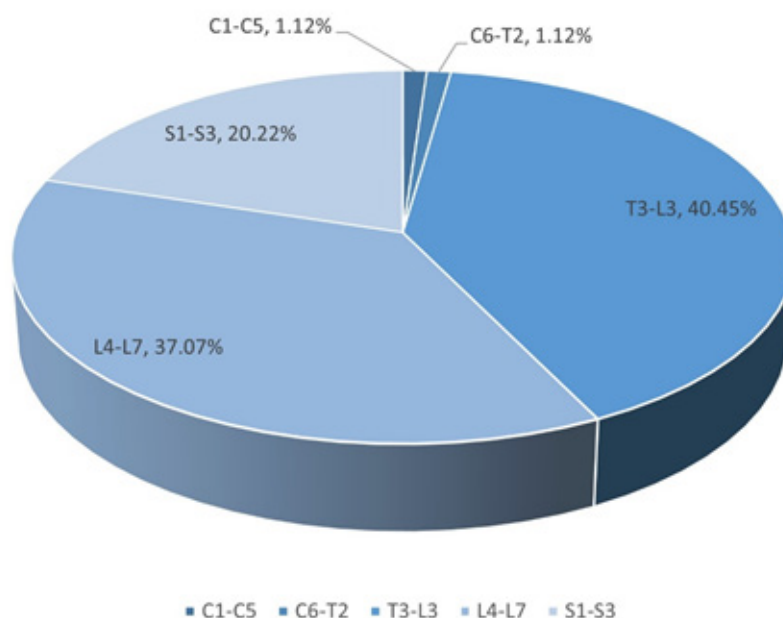
Data retrieved from the medical records, including body weight, age, locations of spinal damage, damage patterns, and the outcomes, were descriptively analyzed. The proportions of weight groups, age groups, damage locations, damage patterns, and the outcomes were presented as percentages. Factors, including gender, age, weight, lesion areas, damage patterns, parietic grading, and rehabilitation, affecting the outcomes 6 months after conservative treatment were evaluated using Fisher's Exact test and Wilcoxon ranked sum test.

## RESULTS

Eighty-nine cats that had traumatic spinal injuries were detected from the computer database. These were 47 females and 42 male cats. From those

populations, most cats (66/89, 74.16%) were in the mature age group (between 1.5 and 7 years). The second most (17/89, 19.10%) were young cats (<1.5 years old), and the least occurring age range was old cats (>7 years) (6/89, 6.74%). The cat's weight was classified into two groups: <3.5 kg (67/89, 75.28%) and >3.5 kg (22/89, 24.72%), with the maximum weight being 7.2 kg and the minimum weight being 0.4 kg.

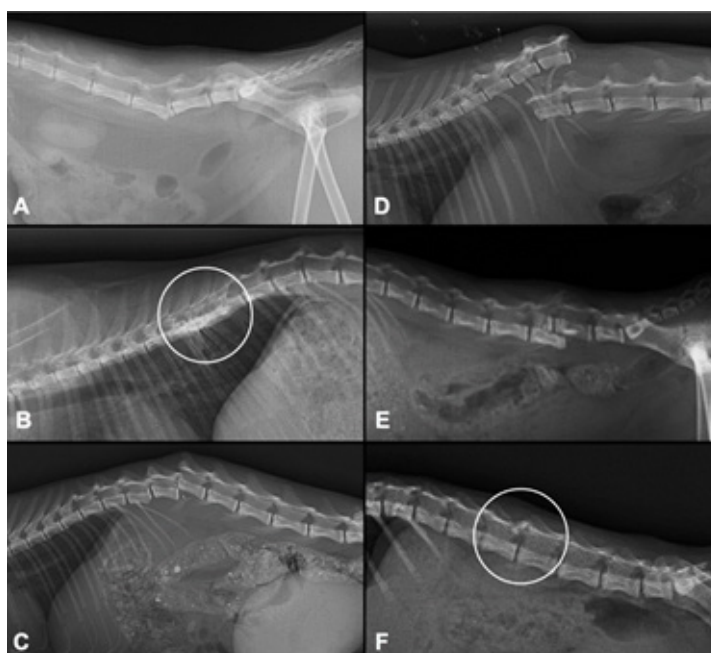
The most prevalent cause of vertebral damage was road traffic accidents (63/89, 70.79%), followed by a fall from height (16/89, 17.98%) and animal-animal fight (10/89, 11.23%). The most common spinal damaged location was T3–L3 (36/89, 40.45%), followed by L4–L7 (33/89, 37.07%), S1–S3 (18/89, 20.22%), C1–C5 (1/89, 1.12%), and C6–T2 (1/89, 1.12%) (Figure 1). The patterns of vertebral damage could be classified as burst/compression (24/89, 26.96%), subluxation (19/89, 21.35%), complete luxation (16/89, 17.97%), combined fracture, and luxation (19/89, 21.35%), transverse fracture (10/69, 11.23%), and hyperextension (1/89, 1.12%). No hyperflexion-damaged pattern was detected in 89 cats (Table 1) (Figure 2).



**Figure 1** The location of spinal damage in 89 cats, which were categorized as their neural location within the spinal column: C1–C5, C6–T2, T3–L3, L4–L7, S1–S3 (C is cervical vertebrae, T is thoracic vertebrae, L is lumbar vertebrae, and S is sacral vertebrae).

**Table 1** The patterns of spinal vertebrae damage that were evaluated from the radiographs of 89 cats.

Patterns of damage	Number, %
a) Hyperflexion	-
b) Hyperextension	1/89, 1.12%
c) Burst/compression	24/89, 26.96%
d) Subluxation	19/89, 21.35%
e) Complete luxation	16/89, 17.97%
f) Fracture and Luxation	19/89, 21.35%
g) Transverse fracture	10/69, 11.23%



**Figure 2** The various vertebral damage patterns from a few of the cats in this study. A; hyperextension pattern, B; burst/compression pattern, C; subluxation pattern, D; complete luxation pattern, E; combine fracture and luxation pattern, F; transverse fracture pattern.

The study outcome focused on cats who had injuries at the thoracic and lumbar vertebrae (T3–L3 and L4–L7); 69 cats had the damaged site at these areas. After the physical examination, the patients were assigned to one of several therapies based on their owners' decision. In total, 33 cats (47.83%) had conservative treatments, six cats (8.69%) had surgeries, nine cats (13.04%) were euthanized, and 21 cats (30.43%) refused to continue treatment at SATH, CMU. Additionally, the outcomes were studied of 27 cats with complete follow-up data 6 months after the initial treatments: 23 conservative cats and 4 surgical cats (Table 2).

**Table 2** The outcomes in 34 cats with thoracolumbar vertebral damage at 1, 3, 6 months after initial injuries. Thirty cats were in the conservative group and four in the surgical group. The outcome was divided into two groups: the Better group and the Fair/Worse (FW) group.

Treatment	Time	Outcome	
		Better Group	FW group
30 cats (Conservative)	1 month	40% (12/30)	60% (18/30)
	3 months	60% (18/30)	40% (12/30)
	6 months	60% (18/30)	40% (12/30)
4 cats (Surgery)	1 month	50% (2/4)	50% (2/4)
	3 months	75% (3/4)	25% (1/4)
	6 months	100% (4/4)	0% (0/4)

In the conservative group, the initial paretic grade was grade 3 (11/30), followed by grade 2 (8/30), grade 5 (7/30), grade 1 (2/30), and grade 4 (2/30). Interestingly, from 21 cats with conservative treatment graded as paretic grade 1, 2, and 3 at the initial event, 16 recovered to grade 0 (normal) within 6 months (16/21; 76.19%). Six months after treatment, two cats (one with grade 3 and another with grade 4) recovered to grade 2 (Table 3). The average duration of conservative treatment until the improvement of the paretic grade observed in better outcome cats was 74.89 days, with a minimum of 7 days and a maximum of 180 days. Seven cats (7/30; 23.33%) died in the conservative group (three cats had cystitis and renal failure, one cat had a severely infected wound from bedsores, and three cats had been recorded in the database without cause of death). With conservative treatment, the paretic grade of four cats (two with grade 3 and two with grade 5) remained unchanged (Table 4).

**Table 3** The data of 18 spinal injury cats who received conservative treatment had the clinical signs and neurological grade at 6 months better than the initial treatment.

Case No.	Gender	Weight	Age	Location	Pattern	Paretic grade				6 m. outcomes	Length of treatment until improvement was seen (day)	Rehabilitation
						Initial	1 m	3 m	6 m			
Cc1	m	<3.5 kg	age2	T3L3	burst/compression	1	0	0	0	b	30	no
Cc2	m	<3.5 kg	age1	T3L3	burst/compression	2	0	0	0	b	14	no
Cc3	m	>3.5 kg	age2	T3L3	burst/compression	2	0	0	0	b	20	yes
Cc4	m	>3.5 kg	age2	T3L3	burst/compression	3	2	0	0	b	70	no
Cc5	f	>3.5 kg	age3	L4L7	transverse frac.	1	0	0	0	b	7	no
Cc6	f	<3.5 kg	age3	T3L3	transverse frac.	2	2	0	0	b	60	yes
Cc7	f	<3.5 kg	age2	L4L7	transverse frac.	2	2	0	0	b	90	yes
Cc8	f	<3.5 kg	age2	L4L7	transverse frac.	2	2	0	0	b	60	no
Cc9	f	<3.5 kg	age2	L4L7	transverse frac.	3	2	2	0	b	150	yes
Cc10	f	<3.5 kg	age1	L4L7	Subluxation (10%dislocation)	2	2	0	0	b	60	no
Cc11	m	>3.5 kg	age2	L4L7	Subluxation (10%dislocation)	2	0	0	0	b	30	no
Cc12	m	<3.5 kg	age2	L4L7	Subluxation (10%dislocation)	2	0	0	0	b	7	no
Cc13	f	<3.5 kg	age2	L4L7	Subluxation (15%dislocation)	3	2	0	0	b	90	no
Cc14	f	<3.5 kg	age2	T3L3	fracture and luxation	3	3	2	0	b	180	yes
Cc15	f	>3.5 kg	age2	L4L7	burst/compression	3	2	0	0	b	90	no
Cc16	f	<3.5 kg	age1	L4L7	burst/compression	3	2	0	0	b	30	yes
Cc17	m	>3.5 kg	age2	L4L7	burst/compression	3	3	2	2	b	180	yes
Cc18	m	<3.5 kg	age2	L4L7	burst/compression	4	3	2	2	b	180	yes

Gender; m = male, f = female, Age group; 1 = young animal (<1.5 years), 2 = mature (1.5–7 years), 3 = old (>7years), Location; T3L3 = 3<sup>rd</sup> thoracic vertebrae–3<sup>rd</sup> lumbar vertebrae, L4L7 = 4<sup>th</sup> lumbar vertebrae–7<sup>th</sup> lumbar vertebrae

**Table 4** The data of 12 spinal injury cats who received conservative treatment had the clinical signs and neurological grade at 6 months equal to or worse than the initial treatment.

Case No.	Gender	Weight	Age	Location	Pattern	Paretic grade				6 m. outcomes	Cause of death	Rehabilitation
						Initial	1 m	3 m	6 m			
Cc1	f	<3.5 kg	age1	L4L7	Subluxation (10%dislocation)	3	3	3	3	fw		no
Cc2	m	<3.5 kg	age3	L4L7	Subluxation (10%dislocation)	3	3	3	3	fw		yes
Cc3	f	<3.5 kg	age2	T3L3	Subluxation (10%dislocation)	4	4	D	D	fw	no information	yes
Cc4	m	<3.5 kg	age2	L4L7	fracture and luxation	3	3	3	D	fw	no information	no
Cc5	m	>3.5 kg	age2	L4L7	complete luxation	5	5	5	5	fw		yes
Cc6	m	<3.5 kg	age2	L4L7	complete luxation	5	5	5	D	fw	cystitis, renal failure	yes
Cc7	f	<3.5 kg	age2	T3L3	complete luxation	5	5	D	D	fw	cystitis, renal failure	yes
Cc8	m	<3.5 kg	age2	T3L3	burst/compression	3	3	D	D	fw	no data record	no
Cc9	m	>3.5 kg	age2	T3L3	burst/compression	5	5	5	D	fw	cystitis, renal failure	yes
Cc10	f	>3.5 kg	age2	L4L7	burst/compression	5	5	D	D	fw	infected wound, bed sores	no
Cc11	f	<3.5 kg	age2	L4L7	burst/compression	5	5	5	5	fw		yes
Cc12	m	<3.5 kg	age2	L4L7	burst/compression	5	5	5	5	fw	infected wound, bed sores	yes

Gender; m = male, f = female, Age group; 1 = young animal (<1.5 years), 2 = mature (1.5–7 years), 3 = old (>7years), Location; T3L3=3<sup>rd</sup> thoracic vertebrae–3<sup>rd</sup> lumbar vertebrae, L4L7 = 4<sup>th</sup> lumbar vertebrae–7<sup>th</sup> lumbar vertebrae, D = Death

There were six cats in the surgery group; however, two cats had parvovirus infection and died, only four were studied for their surgical outcomes (Table 5). One month after surgery, two cats had a better outcome, while another two cats had a fair outcome. One cat recovered to a normal gait 6 months after surgery, but three other cats still had some defects. Therefore, long-term outcomes in those three surgical cats were continuously investigated. Two cats improved their paretic grade from ambulatory paraparesis to normal gait and movement (one cat had 17 months and another had 12 months after surgery); however, one cat had no change.

**Table 5** Data of six cats who had a spinal injury between T3 and L7 in the surgical group.

Case no.	location	Inj to Sx	Pattern	Surgical techniques		Con-current injury	Paretic grade				Rehabilitation	Outcome at 6 m. after surgery	Cause of death
				Stab.	Decom		Initial	1 m.	3 m.	6 m.			
Csx1	T9–10	>72hrs.	burst/compression	-	Lami		3	2	2	0	No	b	Alive
Csx2	T11–13	<72 hrs.	subluxation (10% dislocation)	-	Hemi		3	3	3	2	No	b	Alive
Csx3	L3	<72 hrs.	transverse frac.	-	Lami		4	3	3	2	Yes	b	Alive
Csx4	L5–6	>72hrs.	hyperextension	Locking plate	Lami		4	4	3	3	Yes	b	Alive
Csx5	L2–3	<72 hrs.	subluxation (10% dislocation)	Locking plate	Hemi		4	D	D	D	No	fw	PV
Csx6	L7–S1	<72 hrs.	complete luxation	PMMA	Lami	Abd. hernia	3	D	D	D	No	fw	PV

Location; T = thoracic vertebrae, L = lumbar vertebrae, outcome; b = the clinical signs and neurological grade better than the initial treatment, fw (fair/worse) = the clinical signs and neurological grade equal or worse than the initial treatment, Inj. to Sx = Time from injuries to surgery, PMMA = Polymethyl Methacrylate, PV = Parvovirus infection, D = Death, Stab. = stabilization, Decom = decompression, Lami = laminectomy, Hemi = heminectomy, Abd. Hernia = Abdominal hernia

To summarize, four cats were alive >6 months after surgery, and their outcomes gradually improved. There was no significant association between the factors (gender, age, weight, lesion location, patterns of damage, and rehabilitation) and the outcomes 6 months after treatment (Table 6). However, at the beginning, cats with complete luxation pattern had severe neurological damage (high paretic grade) (p = 0.01), and cats with transverse fracture patterns had less severe neurological damage (low paretic grade) (p = 0.02).



**Table 6** The relation between the factors and outcomes (Better and Fair/Worse) at 6 months after conservative treatment in 30 cats were evaluated using Fisher's Exact test and Wilcoxon ranked sum test. The outcomes were divided into the Better group and the Fair/Worse (FW) group.

Factors	The outcomes at 6 months		Odds Ratio	P-value
	Better group (n)	FW group (n)		
<b>Gender</b>			1.717328	0.7104
: Male	8	7		
: Female	10	5		
<b>Age</b>				0.8299
: <1.5 years	3	1		
: 1.5–7 years	13	10		
: > 7 years	2	1		
<b>Weight</b>			1.86897	0.6942
: <3.5 kgs	11	9		
: >3.51 kgs	7	3		
<b>Lesion location</b>			1	1
: T3–L3	6	4		
: L4–L7	12	8		
<b>Patterns of damage</b>				0.07562
: Hyperflexion	0	0		
: Hyperextension	0	0		
: Burst/compression	8	5		
: Subluxation	4	3		
: Complete luxation	0	3		
: Combined fracture and luxation	1	1		
: Transverse fracture	5	0		
<b>Rehabilitation</b>			2.423135	0.2839
: Yes	8	8		
: No	10	4		

## DISCUSSIONS

In this study, the most prevalent cause of vertebral damage in cats was motor vehicle accidents. Falling from a height was the second most prevalent cause, similar to previous studies that reported the most common causes of vertebral trauma in cats, including road traffic accidents and falls. (Lewis et al., 1989; McKee, 1990; Grasmueck and Steffen, 2004; Bruce et al., 2008; Bali et al., 2009). The other causes were animal-animal interaction and animal abuse. So then, to prevent this type of injury, keep the cat in a closed system and safe environment.

Regarding the damage location, most cats had vertebral damage at the T3–L3 area (36/89, 40.45%), which is consistent with previous studies (Bali et al. 2009, Bruce et al. 2008). The most detected damage pattern in this study was the burst/compression. However, a previous study (Bali et al., 2009) in 2009 reported that the combined fracture and luxation patterns were the most detected patterns of damage in cats. In this study, a subluxation was found secondly, followed by completed luxation. None of the cats had a hyperflexion pattern, and only one cat had a hyperextension pattern. The reason was

associated with the direct force of the causes; patients who were hit by a car mostly had perpendicular and sometimes rotation forces, causing the most common type of injury being luxation or burst/compression (Shores, 1992).

Several treatment methods were presented, but the selected options depended on the owners' decision. Most cats in the study had conservative treatment, while some owners refused to undergo any treatments after the vertebral injury was diagnosed. This study did not show a significant impact of rehabilitation on the outcome. However, several studies revealed that rehabilitation is a crucial factor in improving better outcomes of spinal injuries (Gallucci et al., 2020; Gallucci et al., 2021). Therefore, the rehabilitation method, duration, and frequency of rehabilitation should be studied more specifically in future studies. In this study, cats with a severity grade from 1–3 have a high chance of recovering their clinical signs to that of a normal cat, while cats with paretic grade 5 had no improvement. This information is useful in prognosis and treatment plans for feline vertebral fracture and dislocation in veterinary practice.

In the surgical group, focusing on timing before surgery, there were many previous studies in humans (Kishan et al., 2005; Fehlings and Wilson, 2010; Dvorak et al., 2015; El Tecle et al., 2016; Glennie et al., 2017), as well as in dogs and cats, that revealed that performing the operation as fast as possible, typically <72 h, results in outstanding outcomes. However, most studies have focused on the context of SCI caused by intervertebral disc herniation (Tarlov and Klinger, 1954; Carlson et al., 1997; Davis and Brown, 2002; Rabinowitz et al., 2008). In this study, two cats (50%, 2/4) had surgery longer than 72 h after being injured, and their outcomes were better than before surgery. However, further studies with greater sample size should be conducted because this study had a small sample size in the surgical group (four cats). Although there were only a few surgical cats in this study, the findings of this study are critical for veterinarians in advising owners on surgical outcomes and positively influencing animal owners to select a surgical approach. Two cats had parvovirus infection after surgery, one of which died within a week, and the other died within a month. The patients were weak from their illness and concurrent injuries, such as abdominal hernia. Traumatic injuries, long-time anesthesia, and surgical procedures can put a lot of stress on the patient, and improper vaccination programs and the virus's ease of dissemination make such cats more susceptible to infections. Besides, the causes of death in spinal injuries cats could be from several factors, such as shock, pain, blood loss, and some concurrent injuries, including diaphragmatic hernia, abdominal hernia, etc.

Furthermore, chronic complications, such as cystitis, chronic renal insufficiency, and bedsores, are common in spinal injury cats. Thus, proper urinary excretion management and long-term care must be considered and explained to owners. Even though the goal of the surgical treatment is to improve the patients' outcomes to be better than the initial injuries and have excellent clinical signs (i.e., regained deep pain perception, ability to walk without support and without falling, and controllable urine excretion), three cats still had some neurologic dysfunction 6 months after surgery. Despite improving their paretic grade, they still walked with a neurologic disorder. According to the database, the cats could walk almost normally, but they showed ataxia and knuckle foot in some steps. Therefore, long-term follow-up

should gradually be performed with surgical cats to improve the clinical signs and paretic grade. In this study, the longest duration in which neurological alterations could still be observed was 17 months.

## CONCLUSION

Although no factor (gender, age, weight, lesion location, patterns of damage, and rehabilitation) statistically influenced the outcomes at 6 months after treatment, clinical signs and severity scores in the patients with paretic grades 1–4 improved to be better than the initial injuries after 6 months and more. Then, either conservative treatment or surgery was suggested to those patients. Cats with paretic grades 1–3 had a high chance of recovering their clinical signs to that of a normal cat; however, cats with paretic grades 5 had no improvement. The secondary viral infection can occur due to suffering from pain and concurrent injuries, resulting in death. Further studies are necessary to evaluate the factors associated with the outcome to potentially and professionally plan on treatments to predict or make prognosis more precisely.

## ACKNOWLEDGEMENTS

The authors would like to thank you the Small Animal Teaching Hospital, Chiang Mai university, Thailand that allows the use of data for study and research purposes.

## AUTHOR CONTRIBUTIONS

**A-Dul Saengthong** : Analysis and interpretation, Drafting manuscript, Data collection, Final manuscript approval.

**Areerath Akatvipat** : Conception and design, Analysis and interpretation, Drafting manuscript, Critical revisions, Final manuscript approval.

**Sukolrat Boonyayatra** : Conception and design, Analysis and interpretation, Critical revisions, Final manuscript approval.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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**How to cite this article;**

A-Dul Saengthong, Areerath Akatvipat and Sukolrat Boonyayatra. Vertebral fracture and dislocation patterns, location of injuries, and 6-month clinical outcomes in cats: A retrospective study. *Veterinary Integrative Sciences*. 2022; 20(2): 405-417.

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