Prognostic Factors Associated with Recovery of Ambulation and Urinary Continence in Dogs with Acute Lumbosacral Spinal Cord Injury


Background: Limited information is available about prognostic factors for recovery after spinal cord injury (SCI) to the L4-S3 segments. Previous research suggests that L4-S3 SCI does not have a worse prognosis than T3-L3 SCI.

Hypothesis/Objectives: To elucidate prognostic factors for regaining urinary continence and ambulation in dogs with L4-S3 SCI and compare prognosis to T3-L3 SCI.

Animals/Methods: A retrospective study on 61 nonambulatory dogs with L4-S3 SCI, matched to dogs with T3-L3 SCI, compared 3 weeks after onset. Prognostic factors explored using logistic regression and used for matching: nonchondrodystrophic dogs >15 kg versus dogs that were chondrodystrophic or <15 kg; compressive versus noncompressive lesions; presence versus absence of conscious pain perception (CPP); and lower vs upper motor neuron (LMN/UMN) incontinence.

Results: Fewer L4-S3 dogs regained continence compared to T3-L3 dogs (64 vs 85%, \( P = .0033 \)), but no difference existed for regaining ambulation (66 vs 75%, \( P = .1306 \)). In L4-S3 SCI dogs, fewer dogs regained continence with loss of CPP (\( P < .001 \)), LMN incontinence (\( P = .004 \)), and noncompressive lesions (\( P = .006 \)). Negative prognostic factors for regaining ambulation included absent CPP (\( P < .001 \)) and large nonchondrodystrophic breed (\( P = .022 \)).

Conclusions and Clinical Importance: Dogs with L4-S3 SCI have a poorer short-term prognosis than do dogs with T3-L3 SCI. Dogs with L4-S3 SCI had a poor prognosis with loss of CPP, or noncompressive lesions combined with LMN incontinence. Small-breed or chondrodystrophic dogs with retained CPP, compressive lesions, and UMN incontinence had an excellent prognosis. These findings may help guide decision-making in L4-S3 SCI.

Key words: Disk extrusion; Disk herniation; Fibrocartilaginous embolism; Intervertebral disk disease.

Acute nonambulatory paraparesis or paraplegia resulting from spinal cord injury (SCI) is a common problem that may represent >2% of cases referred to veterinary teaching hospitals and is primarily caused by intervertebral disk herniation (either compressive intervertebral disk extrusion or acute noncompressive nucleus pulposus extrusion [ANNPE]), spinal fracture, luxation, and fibrocartilaginous embolism (FCE). Acute SCI of the lumbosacral intumescence (L4-S3 SCI) is distinct from thoracolumbar spinal cord injury (T3-L3 SCI) because the L4-S3 spinal cord contains the cell bodies of the lower motor neurons (LMN) that innervate the pelvic limb muscles, detrusor, and the urethral and anal sphincters. Both T3-L3 and L4-S3 SCI can result in paraparesis or paraplegia with urinary and fecal incontinence and loss of conscious pain perception (CPP) in the pelvic limbs. However, in L4-S3 SCI there also may be LMN dysfunction which results in loss of reflexes and muscular tone in the pelvic limbs and decreased anal and urethral sphincter tone associated with LMN incontinence. Lower motor neuron incontinence is characterized by a bladder that becomes flaccid, distended with urine, and easily expressed when a small amount of pressure is applied to the abdominal wall.

In dogs affected by L4-S3 SCI, the prognosis for regaining ambulation and continence is uncertain because limited data are currently available on factors that could help predict recovery. Previous studies have not found that caudal lumbar intervertebral disk herniation (from L3 vertebra caudally) is associated with a worse prognosis for recovery than is thoracolumbar disk herniation. In 3 studies in dogs with FCE affecting the lumbosacral intumescence, the prognosis for recovery was not different than for dogs with T3-L3 SCI.

Abbreviations:

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ANNPE</td>
<td>acute noncompressive hydrated nucleus pulposus extrusion</td>
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<tr>
<td>CPP</td>
<td>conscious pain perception</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>FCE</td>
<td>fibrocartilaginous embolism</td>
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<tr>
<td>L4-S3</td>
<td>fourth lumbar spinal cord segment to third sacral spinal cord segment</td>
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<tr>
<td>LMN</td>
<td>lower motor neuron</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>SCI</td>
<td>spinal cord injury</td>
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<td>T3-L3</td>
<td>third thoracic spinal cord segment to third lumbar spinal cord segment</td>
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<td>UMN</td>
<td>upper motor neuron</td>
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In our study, the hypothesis was that dogs with L4-S3 SCI have a worse prognosis for functional recovery of ambulation and urinary continence than dogs with T3-L3 SCI. We further hypothesized that dogs with clinical signs of LMN incontinence would have a worse prognosis for recovery of continence than dogs with UMN incontinence and that dogs with loss of pelvic limb CPP have a worse prognosis for recovery of ambulatory function than dogs with preserved pelvic limb CPP.

Materials and Methods

Clinical records at 2 United Kingdom veterinary referral hospitals (Langford Veterinary Services, University of Bristol and Centre for Small Animal Studies, Animal Health Trust) were searched retrospectively for the period 2009 to 2015. Dogs were included in the L4-S3 SCI group if they (1) had an acute onset of paraparesis (presenting within 2 weeks of the onset of clinical signs); (2) were paraplegic or nonambulatory paraparetic; (3) had a decreased or absent withdrawal reflex in 1 or both pelvic limbs; (4) underwent spinal cord imaging with either magnetic resonance imaging (MRI), computed tomography (CT) or radiographic myelogram; (5) had a lesion affecting the spinal cord within 3 intervertebral disk spaces from the termination of the spinal cord (corresponding to the location of the L4-S3 spinal cord segments shown in Fig 1). In dogs diagnosed by MRI or radiographic myelogram, the termination of the spinal cord usually can be visualized. Dogs in which the termination of the spinal cord could not be visualized (e.g., plain CT scan) only were included if the lesion extended over the L4 or L5 vertebrae. This was to ensure that the lesion was at the level of the spinal cord (and not solely affecting the cauda equina nerves). It was based on previous research in dogs showing that the anatomical location of the lumbosacral spinal cord segments within the spinal canal is affected by body size and individual variation and can be within the L5, L6, or L7 vertebrae.

Dogs were excluded if they had compressive lesions that did not receive decompressive surgery, were diagnosed with a neoplastic, inflammatory or infectious disease, or were euthanized within 3 weeks of presentation (unless they developed clinical signs consistent with ascending myelomalacia, in which case they were retained in the analysis). Dogs with vertebral fracture or luxation also were excluded due to a high proportion of dogs with loss of CPP being euthanized shortly after neurological assessment.

A cohort of T3-L3 dogs also was found from the clinical records of 1 referral institution (Langford Veterinary Services, University of Bristol). These were matched for body weight, presence or absence of CPP in the pelvic limbs, compressive vs noncompressive disease affecting the spinal cord. These dogs were selected using identical inclusion and exclusion criteria, except that all had T3-L3 SCI with normal to increased pelvic limb reflexes and no signs of LMN incontinence.

Clinical records were reviewed to establish the neurological status of the dogs at presentation. Breed, age, body weight, presence or absence of CPP to the pelvic limbs, compressive or noncompressive lesions affecting the spinal cord, and evidence of any LMN incontinence (implying involvement of the S2-S3 spinal cord segments) defined as having 1 of the following signs: (1) decreased anal tone on rectal palpation; (2) decreased or absent perineal reflex; or (3) loss of urethral tone identified by manual bladder expression leading to urinary leakage were recorded. Where possible, clinical records were used to establish whether functional recovery occurred within 21 days of presentation. We chose 21 days based on previous studies showing that recovery of pain sensation in dogs with severe spinal cord injury occurred within 3 weeks in most dogs that later made a good recovery.

Functional recovery of ambulation was defined as being able to walk without assistance (as we judged that owners would easily be able to answer this question), and functional recovery for urinary continence was defined as having voluntary control of urination (pos- turing to urinate) without having incidents of accidental urination. A long-term successful outcome was defined as not being euthanized due to ascending myelomalacia or lack of improvement, and regaining both ambulation and urinary continence. Dogs that were lost to follow-up within 3 months were not included in the results regarding long-term outcome. Dogs that were discharged before regaining voluntary ambulation, urinary continence or both were followed up by requesting the clinical records of the referring veterinary surgeon. If necessary, owners were contacted by telephone for interview.

Statistical analysis for comparison of matched L4-S3 SCI and T3-L3 SCI dogs was performed by McNemar’s test. Prognostic factors in the L4-S3 SCI group were analyzed using logistic regression with block entry method. The following factors were explored: presence versus absence of CPP (this was the only factor in the first block because it was considered the single most important factor based on previous medical data in dogs with SCI), presence versus absence of LMN incontinence, nonchondrodystrophic dogs >15 kg versus dogs that were chondrodystrophic or <15 kg (these criteria previously were used to define a population of large breed dogs in a study on thoracolumbar disk herniations), and compressive vs noncompressive lesions. The second block was a hierarchical entry of the other factors in order of
Results

Demographics and Overall Prognosis for Recovery in L4-S3 SCI Dogs

Sixty-one L4-S3 SCI dogs met the inclusion criteria. The center of the lesion on imaging ranged between the L2/L3 intervertebral disk space to the L6 vertebral body. The cranial extent of the lesion ranged between the T12 vertebra and the L5 vertebra. The caudal extent of the lesion ranged between the L4 and S1 vertebra. Twenty-three dogs were >15 kg and belonged to non-chondrodystrophic breeds and therefore were grouped to be analyzed against the 38 remaining dogs. Eight dogs had FCE, 4 dogs had ANNPPE, and 1 dog had a compressive epidural hematoma (with no identified etiology), all of which were scanned with 1.5 Tesla MRI. The remaining 48 dogs had compressive intervertebral disk extrusion and received decompressive surgery. Of these, 44 dogs had MRI scans performed, 2 had radiographic myelography, and 2 had plain CT scans. Thirteen dogs had loss of CPP, and 19 dogs had evidence of LMNI incontinence. Four dogs were euthanized due to suspected ascending myelomalacia (all within 3 days of presentation), and 3 of these had loss of CPP on presentation. This information is summarized in Table 1.

Of the L4-S3 SCI dogs, 40/61 (66%) regained ambulation and 39/61 (64%) regained urinary continence within 3 weeks. Thirty-seven of 61 (61%) dogs regained both ambulation and urinary continence, 3 dogs regained ambulation but did not regain urinary continence, and 2 dogs regained continence but did not regain ambulation. Forty-eight dogs were assessed for ambulatory function and continence by the referral clinician in charge of the case, 1 by the referring veterinary surgeon, and 12 by their owner. Of the 21 dogs that did not regain ambulation within 3 weeks, 4 were euthanized due to suspected ascending myelomalacia within 3 days of presentation and 4 were euthanized at 3 weeks because of lack of improvement. Two dogs were lost to follow-up within the first 3 months, leaving 11 dogs that had long-term follow-up. Eight dogs subsequently regained ambulatory function: 3 dogs within 3–8 weeks, and 5 dogs within 8–30 weeks. No dog regained ambulation after 30 weeks. Three dogs remained unable to walk with follow-up times of 5, 14, and 18 months. Overall, this meant that 48/59 (81%) of dogs successfully regained ambulatory function long term.

Of the 22 dogs that did not regain urinary continence within 3 weeks, 4 were euthanized due to suspected ascending myelomalacia within 3 days of presentation and 5 were euthanized at 3 weeks for nonimprovement. Four dogs were lost to follow-up within the first 3 months, leaving 10 dogs that had long-term follow-up. Five dogs subsequently regained urinary continence: 3 dogs within 3–8 weeks, and 2 dogs within 8–30 weeks. No dog regained urinary continence after 30 weeks. Five dogs remained urinary incontinent with follow-up times of 5, 18, 19, and 34 months. Overall, this meant that 44/57 (77%) of dogs successfully regained urinary continence long term.

Table 1. Number of individuals by each prognostic factor and by diagnosis.

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
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<tr>
<td>FCE</td>
<td></td>
<td></td>
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<tr>
<td>CPP + ANNPE</td>
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<tr>
<td>L4-S3 SCI</td>
<td></td>
<td></td>
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<tr>
<td>Chondrodystrophic or &lt;15 kg</td>
<td>CPP +</td>
<td>1</td>
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<tr>
<td></td>
<td>LMNI</td>
<td>1</td>
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<tr>
<td></td>
<td>UMNI</td>
<td>1</td>
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<tr>
<td>Nonchondrodystrophic and &gt;15 kg</td>
<td>CPP +</td>
<td>4</td>
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<tr>
<td></td>
<td>UMNI</td>
<td>1</td>
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<tr>
<td></td>
<td>UMNI</td>
<td>1</td>
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<tr>
<td>T3-L3 SCI</td>
<td></td>
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<tr>
<td>Chondrodystrophic or &lt;15 kg</td>
<td>CPP +</td>
<td>2</td>
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<td></td>
<td>CPP –</td>
<td>1</td>
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<tr>
<td>Nonchondrodystrophic and &gt;15 kg</td>
<td>CPP +</td>
<td>7</td>
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<tr>
<td></td>
<td>CPP –</td>
<td>0</td>
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NC, noncompressive; C, compressive; CPP +, retained conscious pain perception; CPP –, loss of conscious pain perception; LMNI, lower motor neuron incontinence; UMNI, upper motor neuron incontinence; FCE, fibrocartilaginous embolism; ANNPPE, acute noncompressive nucleus pulposus extrusion; IVDE, intervertebral disk extrusion (compressive); EH, epidural hematoma.

*One T3-L3 dog could not be found to match an L4-S3 dog—this was excluded from the cohort analysis.
and dogs that were chondrodystrophic or <15 kg were not found to be significantly different (P = .257; OR, 3.922 [0.370–41.63]). Interaction terms were tested, but none were found to be significant.

**Prognosis for Recovery According to Specific Combinations of Prognostic Factors in L4-S3 Dogs**

The variation in prognosis according to different combinations of factors is given in Table 4.

**Combinations of Factors Indicating an Excellent Prognosis**

Of the combinations of risk factors explored, the highest recovery rate for ambulatory function was in small-breed or chondrodystrophic dogs with preserved CPP, which appear to have an excellent prognosis for regaining ambulation (26/28 [93%] had done so within 3 weeks, and the 2 remaining dogs had regained ambulation and urinary continence by 32 and 40 days). Likewise, dogs with preserved CPP, compressive lesions, and UMN incontinence had an excellent prognosis for regaining urinary continence (30/31 [97%] had recovered within 3 weeks and the remaining dog had recovered continence by 4 weeks). With regard to a complete functional recovery (i.e., both ambulatory function and urinary continence), small-breed or chondrodystrophic dogs with retained CPP, compressive lesions, and UMN incontinence appeared to have an excellent prognosis because 22/23 (96%) had regained these functions within 3 weeks and the remaining dog had done so by 40 days. This category of dogs represented almost half of dogs with preserved CPP (48 dogs in total).

**Combinations of Factors Indicating a Fair Prognosis**

Of the large, nonchondrodystrophic dogs with retained CPP, 11/20 (55%) regained both urinary continence and ambulatory function within 3 weeks. Of the remaining 9 dogs, 1 was euthanized within 3 days because it developed ascending myelomalacia, and 3 were euthanized at 3 weeks for lack of improvement. One was continent within 5 days but remained nonambulatory at a 14-month follow-up. Two dogs regained both urinary continence and ambulatory function after 3 weeks (1 at 9 weeks and another at 15 weeks). One dog was lost to follow-up within 3 months. Overall, this meant that 13/19 (68%) of dogs had a long-term successful outcome.

Of the dogs with retained CPP, LMN incontinence, and compressive lesions, 4/6 (67%) regained both urinary continence and ambulatory function within 3 weeks. Of the remaining 2 dogs, 1 was euthanized at 3 weeks for lack of improvement. One dog regained both urinary continence and ambulatory function between 3 and 4 weeks. Overall, this meant that 5/6 (83%) of dogs had a long-term successful outcome.

Of the dogs with retained CPP, UMN incontinence, and noncompressive lesions, 3/6 (50%) regained both urinary continence and ambulatory function within
3 weeks. Of the remaining 3 dogs, 1 was euthanized within 3 days because it developed suspected ascending myelomalacia and 1 was continent within 5 days but remained nonambulatory at a 14-month follow-up. One dog regained both urinary continence and ambulatory function at 9 weeks. Overall, this meant that 4/6 (67%) of dogs had a long-term successful outcome.

**Combinations of Factors Indicating a Poor Prognosis**

Loss of CPP occurred in 13 dogs with L4-S3 SCI, 12 of which had intervertebral disk extrusions and 1 of which had FCE. Three were nonchondrodystrophic dogs >15 kg, and 8 had LMN incontinence. Only 1/13 dogs (7.7%) regained ambulation or urinary continence within 3 weeks. Of the remaining 12 dogs, 3 were euthanized within 3 days because it had suspected ascending myelomalacia, and 1 was euthanized at 3 weeks because it had not regained CPP. Two dogs remained nonambulatory and incontinent at 5- and 18-month follow-ups. Two dogs had regained ambulatory function at 4 and 12 weeks, but remained incontinent at a 34- and 19-month follow-ups, respectively. One was continent within 5 days but remained nonambulatory at a 14-month follow-up. Two dogs regained both urinary continence and ambulatory function at 14 and 30 weeks. Two dogs were lost to follow-up within 3 months. Overall, this meant that 3/11 (27%) of dogs had a long-term successful outcome. None of the nonchondrodystrophic dogs >15 kg with loss of CPP recovered and all 3 dogs remained incontinent at 5-, 19-, and 34-month follow-ups, with the former dog remaining nonambulatory.

Of the dogs with retained CPP, noncompressive lesions, and associated LMN incontinence, 0/5 (0%) regained urinary continence and 3/5 (60%) regained ambulatory function within 3 weeks. Of the remaining 5 dogs, 3 were euthanized at 3 weeks for lack of improvement. Two were able to walk within 3 weeks but were lost to follow-up within 3 months. Overall, this meant that 0/3 (0%) of dogs had a long-term successful outcome.

**Discussion**

Our results show that dogs with L4-S3 SCI had a significantly lower rate of regaining urinary continence when compared to T3-L3 SCI dogs, which supports the hypothesis that the short-term prognosis in dogs with L4-S3 SCI is worse than in dogs with T3-L3 SCI. Our data support the consensus from previous studies indicating that presence or absence of CPP is the most important prognostic factor for functional recovery from SCI. Indeed, we found that loss of CPP seems to be an indicator for poor recovery in dogs with L4-S3 SCI (1/13 dogs recovered within 3 weeks, and 3/11 had a long-term successful outcome). Excluding individuals with noncompressive lesions and associated LMN incontinence, which have a poor prognosis for recovery of urinary continence (0/5 dogs recovered within 3 weeks and 0/4 dogs recovered long term), dogs with L4-S3 SCI and preserved pain sensation have a fair to excellent prognosis (Table 4).

Our results show that dogs with loss of CPP have a low rate of recovery compared to 3 previous studies regarding dogs with T3-L3 SCI and intervertebral disk herniation (58%, 62%, and 58%). In our study, of 13 dogs with loss of CPP and a L4-S3 SCI lesion, only 1 dog had a complete functional recovery within 3 weeks (i.e., only 7.7% regained ambulation and continence) and only 3/11 (27%) dogs had a successful long-term outcome.

Chondrodystrophic or small-breed dogs with L4-S3 SCI in our study generally had a good prognosis for regaining ambulation and continence if their CPP was preserved. For instance, 22/23 (96%) of L4-S3 SCI small-breed or chondrodystrophic dogs with compressive lesions and LMN incontinence recovered within 3 weeks, and the remaining dog had recovered by 40 days. This result is not surprising, because these dogs are analogous to small-breed, chondrodystrophic dogs with T3-L3 SCI and preserved CPP caused by intervertebral disk extrusions, and a consensus exists that these dogs have an excellent prognosis (86%-96% recovery rate) after decompressive surgery.
Some dogs had preserved CPP, but other negative prognostic factors appeared to worsen their prognosis. Larger, nonchondrodystrophic dogs with preserved CPP did not regain ambulation as well as their small-breed or chondrodystrophic counterparts. Within 3 weeks, only 65% regained ambulation, and 55% regained both ambulation and continence. Large dogs previously have been reported as having a slightly lower recovery rate (78%) after decompressive surgery for thoracolumbar disk herniation. This result may be affected by the 3-week cutoff we used, because large dogs with intervertebral disk herniation previously have been shown to regain ambulation later than small dogs (a median of 4 weeks in 1 study). Two dogs had long-term follow-up with successful outcome, and once these were included, our results showed a 65% successful long-term outcome.

In our study, significantly fewer L4-S3 SCI dogs regained urinary continence when compared to their matched T3-L3 SCI counterparts. This finding can be explained by 6 of the negative prognostic factors that we found to be significantly associated with recovery in the dogs with L4-S3 SCI. Firstly, LMN incontinence resulting from S2-S3 spinal cord segment dysfunction is not a feature of incontinence in T3-L3 dogs. Secondly, noncompressive lesions that cause ischemia and laceration may cause selective and irreversible S2-S3 gray matter damage in L4-S3 dogs. This finding contradicts previous research that has found an association between low lumbar SCI and the probability of functional recovery or regaining ambulation. However, these studies have deficiencies rendering their power low. The first problem is that these studies classified SCI according to the level of the lesion relative to the vertebral bodies rather than in relation to the spinal cord, or according to neurological signs. Because of the variability of the location of the conus medullaris, some of the dogs in these studies potentially could have had (1) a L3-L4 disk extrusion causing a SCI at the L3 spinal cord segment; or (2) a compression of the cauda equina nerves resulting from an L5-L6 disk extrusion in a dog in which the spinal cord terminates at L5. These cases would differ clinically from the population we tried to test in our study. In 1 study, the subset of L4-S3 SCI dogs with LMN signs that was selected for comparison with T3-L3 SCI dogs also may have had spinal shock. In our study, we attempted to minimize this problem by only including dogs if the lesion was within 3 intervertebral spaces of the termination of the spinal cord. However, no diagnostic test or clinical data can differentiate spinal shock (which is shown to resolve within 60 days in dogs) from LMN signs that resolve with resolution of the SCI, and our study was affected by the pathophysiological consequences might be different (for instance between ANNPE and FCE). This finding contradicts previous research that has found an association between low lumbar SCI and the probability of functional recovery or regaining ambulation. However, these studies have deficiencies rendering their power low. The first problem is that these studies classified SCI according to the level of the lesion relative to the vertebral bodies rather than in relation to the spinal cord, or according to neurological signs. Because of the variability of the location of the conus medullaris, some of the dogs in these studies potentially could have had (1) a L3-L4 disk extrusion causing a SCI at the L3 spinal cord segment; or (2) a compression of the cauda equina nerves resulting from an L5-L6 disk extrusion in a dog in which the spinal cord terminates at L5. These cases would differ clinically from the population we tried to test in our study. In 1 study, the subset of L4-S3 SCI dogs with LMN signs that was selected for comparison with T3-L3 SCI dogs also may have had spinal shock. In our study, we attempted to minimize this problem by only including dogs if the lesion was within 3 intervertebral spaces of the termination of the spinal cord. However, no diagnostic test or clinical data can differentiate spinal shock (which is shown to resolve within 60 days in dogs) from LMN signs that resolve with resolution of the SCI, and our study was affected by the pathophysiological consequences.
S3 SCI. Not only do our results support the hypothesis that L4-S3 SCI in dogs has a worse short-term prognosis than T3-L3 SCI, but also show that with certain combinations of negative prognostic factors, a successful outcome is unlikely. This information may guide decision-making because euthanasia may be expedited if an owner is not satisfied with the likelihood of a long-term successful outcome in his or her dog, or used to set appropriate expectations regarding the projected time frame for recovery. For instance, if a decision is made at the outset to commit to long-term management of a dog that has a low probability of recovery at 3 weeks, the owner can be given advanced warning that he or she is likely to need to make special arrangements for the pet’s care.

In conclusion, nonambulatory paraparetic and paraplegic dogs with SCI to the L4-S3 spinal cord segments appear to have a decreased rate of regaining urinary continence at 3 weeks when compared to T3-L3 SCI dogs, but no significant difference exists for regaining ambulation. In dogs with L4-S3 SCI, individuals with loss of CPP and those with noncompressive lesions and associated LMN incontinence appear to have a low likelihood of a successful long-term outcome. Small-breed or chondrodystrophic dogs with retained CPP, compressive lesions, and UMN incontinence appear to have an excellent prognosis and represent approximately one-third of dogs with L4-S3 SCI.

Acknowledgments

Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References