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Case Series

Survival Outcomes of Dogs with Appendicular Osteosarcoma Treated with Traditional Chinese Veterinary Medicine: Retrospective Analysis of 7 Cases

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ABSTRACT

Canine appendicular osteosarcoma (OSA) is an aggressive, malignant bone tumor of the limbs with high metastatic potential. Even with surgery and chemotherapy, average survival is approximately 52 weeks (1 year) and with surgery only, survival shortens to 26 weeks (6 months). This retrospective case series reports the post-amputation survival outcomes of 8 dogs with appendicular OSA. Four dogs (4/8) were treated with a combination of conventional therapeutics (chemotherapy, nonsteroidal anti-inflammatory drugs/NSAIDS) and traditional Chinese veterinary medicine (TCVM). The TCVM therapy was composed of various combinations of acupuncture, Chinese herbal medicine, food therapy and *Tui-na*. Three dogs (3/8) were treated with post-surgical TCVM without conventional therapy. One dog (1/8) received post-surgical chemotherapy (1 round) and NSAIDS. Among the 7 dogs receiving TCVM treatments, the median survival time was 114.4 weeks (ranging from 36.0 to 346.1 weeks). Patients who received conventional treatment and TCVM had greater median survival time (120 weeks) compared to those receiving TCVM treatment only (53 weeks). There were 6 (85.7%) TCVM-treated dogs that survived more than 1 year and 4 (57.1%) that lived more than 2 years after amputation. Based on Wilcoxon signed rank test, the median survival time of TCVM-treated subjects was significantly longer than the expected average survival of 52 weeks/1 year (p = 0.023). The NSAID/chemotherapy (1 round) treated dog survived 11 weeks. The study, while with limited cases, concluded that TCVM treatments might be beneficial to prolong the survival time in OSA dogs after amputation. Randomized controlled trials are warranted to confirm these observations.

Keywords: canines, osteosarcoma, post-amputation survival time, TCVM

ABBREVIATIONS: 5-FU: fluorouracil; ABC: ATP-binding cassette; AKT: protein kinase B; AP: acupuncture; CHM: Chinese herbal medicine; EMT: epithelial-to-mesenchymal transition; IL: interleukin; Icam-1: intercellular adhesion molecule-1; MMP: metalloproteinases; NF-κB: nuclear factor kappa B; NSAID: nonsteroidal anti-inflammatory drugs; OSA: osteosarcoma; p-38: multi-tasking kinase; p-ERK: phosphorylated-extracellular signal-regulated kinase; p-PI3K: phosphoinositide 3-kinases; PTEN: phosphatase and tensin homologue; QOL: quality of life; TCM: traditional Chinese medicine; TCVM: traditional Chinese veterinary medicine; TNF-α: tumor necrosis factor alpha; VEGFR2: vascular endothelial growth factor receptor 2; Wnt/β-catenin: wingless/integrated beta-catenin

Canine osteosarcoma (OSA) is highly malignant tumor with more than 90% of dogs having micrometastasis and 15% of dogs having detectable metastasis at the time of diagnosis. OSA can affect any breed of dog, but it is more commonly found in the larger breeds such as Rottweiler, German Shepherd, Boxer, Doberman Pinscher and Irish Setter.[1-4] The location of OSA includes the appendicular skeleton (64%), the axial skeleton (28.5%), or extraskeletal sites (7.5%).[2,5] This retrospective analysis focuses on appendicular skeleton OSA.

In conventional medicine, treatment that combines surgery (limb amputation or limb sparing) with single agent chemotherapy and radiotherapy is considered the most effective method of OSA treatment.[4] The most used cytostatic drugs are cisplatin, carboplatin and doxorubicin. Unfortunately, prognosis for these patients is usually poor even when treated with the most effective current treatments. The average survival in dogs with OSA treated with surgery and chemotherapy is approximately 52 weeks (1 year). For patients younger than 7 years of age with large proximal humerus tumors, the prognosis is even poorer.[1-4] Recently, a median survival time of 30 weeks (7 months) was

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reported for OSA dogs receiving radiation therapy along with chemotherapy; whereas, a combination of surgery and chemotherapy showed more encouraging median survival of 34 to 52 weeks with up to 28% surviving two years after diagnosis. Death of OSA dogs often occurs within 6 months of diagnosis in 96% of canine OSA patients.[4] Dogs between 7 and 10 years of age have greater survival rates than younger and older dogs.[1-4]

Cancer treatments with traditional Chinese medicine (TCM) have a history of more than 2,000 years. These treatments are described in classical TCM books such as *The Yellow Emperor's Inner Canon* and *the Classic of Medical Problems*.[6] TCM describes cancer as an inability of the body to maintain its balance from both internal and external causes, not as a single caused event. This can be complementary to Western (i.e. conventional) medicine in many ways. For example, from a conventional aspect, there are causes from genetics and environmental toxins, which all contribute and predispose an individual to cancer. Traditional Chinese medicine has similar considerations with the following creating body imbalance leading to development of cancer: Kidney *Jing* Deficiency (i.e. genetics), External Pathogens, Internal Pathogens, imbalanced *Yin* and *Yang* (particularly *Zang-fu* organ deficiencies).[6]

Osteosarcoma is considered as developing from a Deficiency of *Qi*, which can lead to Stagnation of *Qi* followed by a Deficiency of Blood and the development of Damp, Phlegm and Toxic-Heat. Eventually Stagnation of *Qi*, Blood, Damp-Phlegm and Toxic-Heat (exogenous or endogenous) occur, leading to Blood Stasis with tumor formation (OSA).[6] These elements are present in variable degrees depending on the individual. Due to these complex patterns of cancer development, TCM uses a multimodal therapy for optimal disease treatment.

Traditional Chinese veterinary medicine (TCVM) takes a similar multimodal approach combining acupuncture (AP), food therapy, Chinese herbal medicine (CHM) and *Tui-na* as an optimal cancer treatment strategy to put the body back into balance. The objective of this retrospective case series was to evaluate the effectiveness of using TCVM therapy to promote post-surgical survival of canine OSA patients undergoing limb amputation with or without conventional cancer therapy.

MATERIALS AND METHODS

Inclusion Criteria

The subject population for this study consisted of companion pet dogs diagnosed with OSA and treated with limb amputation. The subjects in this retrospective study were cases collected from KK's Holistic Veterinary Service, Queensland, Australia and collaborating TCVM clinics. There were no inclusion restrictions on age, breed, and sex, with all cases starting their post-amputation treatments between 2009 and 2018.

Data Retrieved

With owner consent, data collected from each subject included: breed, age (at the time of amputation), method of OSA diagnosis, affected anatomic site, information about conventional treatment (chemotherapy, radiation, NSAIDs), TCVM treatments (AP, food therapy, CHM, *Tui-na*), TCVM treatment starting date, and survival time (time between amputation and death).

Statistical Analysis

For descriptive analysis, numerical data (age, survival time) were summarized with mean±SD and median. Categorical data (e.g. breed, type of treatment) were reported individually. In addition, Kaplan-Meier survival curve was used to present the survival curve among the TCVM treated subjects. Due to the small sample size and non-normally distributed survival data, nonparametric Wilcoxon test was applied to compare the median survival time to published median survival from non-TCVM treated subjects. All data graphic presentations and statistical analysis were performed using commercial statistical software[a].

RESULTS

Subject Signalment and Demographic Information

The study compiled data from a total of 8 OSA dogs undergoing limb amputation. Geographic locations included 7 dogs in Australia and 1 dog in Japan. The data collected were recorded between 2012 (time of amputation) and 2020 (time of death), except for one subject who was still alive when the study was concluded (Table 1).

Among the 7 TCVM-treated OSA dogs (subjects 1-7), the mean age at limb amputation was 8.9±2.2 years old, ranging from 5.5 to 13 years old. The age of the conventional treatment only subject (Dog 8) was 1.5 years old. Among the TCVM-treated dogs, breeds represented were 3 Greyhounds, 2 Boxers, 1 Rottweiler and 1 Golden Retriever. The conventional treatment only was a German Shorthaired Pointer.

Study Findings

TCVM: Out of the 7 TCVM-treated subjects, 2 dogs started TCVM treatments before amputation (range 8-30 days), 3 subjects started close to the time of amputation (range 2-60 days following surgery), and 2 dogs had a delayed start (range 207-365 days), with a median treatment starting time 6.4 weeks (ranging from -4.3 to 52.1 weeks) from the amputation (Table 1). The remaining 1 dog (Dog 8) did not receive TCVM treatment.

Chemotherapy, NSAIDs: All 5 dogs in the study that underwent chemotherapy received carboplatin every 3-4 weeks in a saline IV drip for a full 5-cycle course, with the exception of Dog 8, who only received 1 cycle (Table 2). All dogs in the study consistently received post-surgical NSAIDs (Previcox®[b], firocoxib[b], or meloxicam[c]), with only occasional use after that. Dog 8 was the exception, as he received daily meloxicam[c] (3.0 mg).

TCVM Patterns Recorded: Patterns diagnosed in these patients included *Yin* Deficiency, *Qi* Deficiency, Blood Stasis, *Yang* Deficiency, Liver *Qi* Stagnation with Heat, *Qi*-Blood Stagnation, Damp and Phlegm. Each TCVM Pattern exhibited different clinical signs, tongue, and pulse diagnoses (Table 3).

Table 1: Summary of subject information, limb location of osteosarcoma (OSA), commencement of TCVM and chemotherapy treatments relative to limb amputation

Case Number and Location	Breed (Sex)	OSA Location	Diagnostic Test (s)	Age* (years)	TCVM Commenced Relative to Amputation	Chemotherapy Commenced Relative to Amputation (days)	Life Span (weeks)
1 Noosa AU	Rottwr (NF)	RHL (distal tibia)	Radiographs + biopsy	8	2 days	14	114.4
2 Noosa AU	Greyhd (NM)	RFL (distal ulnar)	Radiographs + biopsy	9	60 days	30	220.6
3 Noosa AU	Greyhd (NM)	LFL (distal radius)	Radiographs + biopsy	9	~365 days	9	76.7
4 Noosa AU	Greyhd (NF)	RFL (distal radius)	Clinical findings + radiographs^	9	30 days BEFORE	Data not available	125.4
5 Noosa AU	Boxer (NF)	RFL (proximal to carpus, not defined further)	Clinical findings + radiographs^	5.5	45 days	NA	346.1
6 Noosa AU	Boxer (NF)	LFL (proximal humerus)	Clinical findings + radiographs^	9	8 days BEFORE	NA	36
7 Vet Clinic, Japan	Golden Retriever (NF)	LFL (data not available)	Radiographs + biopsy	13	207 days	NA	52.8
8 Vet Clinic, Brisbane AU	German Short-haired Pointer (NM)	LHL (proximal tibia)	Radiographs + biopsy	1.5	No TCVM	17	11

AU=Australia, Rottwr=Rottweiler, Greyhd=Greyhound; NF=neutered female, NM=neutered male; * = Age at amputation of OSA limb; NA=not applicable
^ = OSA diagnosis based on characteristic clinical and radiographic findings, histopathologic diagnosis not available

Table 2: Summary for both conventional and TCVM treatments

Study Dog	NSAID*	Chemotherapy	Acupuncture	Chinese Herbal Medicine	Food Therapy	*Tui-na*^
#1	Previcox Tramadol Gabapentin	Carboplatin 324mg via IV saline drip – Every 3-4 weeks apart (5 cycles)	Dry needle – Every 4-6 weeks	Started 2 days after surgery – Dosed entire time	Yes Entire time	Once/day Several days/wk
#2	Metacam Only post op	Carboplatin 258mg via IV saline drip – Every 3-4 weeks apart (5 cycles)	Dry needle – Every 4-8 weeks	Started 2 days after surgery – Stopped after 3 years (dog lived 1 more year)	Yes Entire time	Once/day Several days/wk
#3	Firocoxib	Carboplatin 300mg IV drip – Every 3-4 weeks apart (5 cycles)	Dry Needle – Every 4-6 weeks	Started 365 days after surgery – Dosed rest of life span	Yes Entire time	Once/day Several days/wk
#4	Meloxicam	Carboplatin (6 cycles) – Dosing data unavailable	Dry Needle – Every 4-5 weeks	Started 30 days BEFORE surgery – Dosed entire time	Yes Entire time	Once/day Several days/wk
#5	Metacam	None	Dry Needle – Every 4-6 weeks	Started 45 days after surgery – Dosed entire time	Yes Entire time	Once/day Several days/wk
#6	Metacam	None	Dry Needle – Every 4-6 weeks	Started 8 days BEFORE surgery – Dosed entire time	Yes Entire time	Daily
#7	Metacam	None	None – due to distance	Started 207 days after surgery – Dosed entire time	Yes Entire time	Daily
#8	Meloxicam 3.0mg daily	Carboplatin (1^{st} cycle only) – Dose not recorded	None	No TCVM	No	No

* NSAIDS consistently used post-op with only occasional use after that; except Case 8 who received daily dose;
^*Tui-na* massage techniques taught to owners (first session) with instructions to perform daily or at least several times each week

Table 3: TCVM Patterns diagnosed in study dogs with associated clinical signs, tongue and pulse characteristics

Pattern	Clinical Signs	Tongue	Pulse
Yin Deficiency	Heat signs such as constantly panting, prefers cool place, unsettled at night, warm/hot extremities	Red, little coating, small size, crack(s)/lines	Weaker on left, thin and rapid
Qi Deficiency	Poor appetite, weakness, loose stools, fatigue, sleeping more, tiredness, weak voice/reluctance to bark	Wet, white coating, large size	Weaker on right, empty, weak, thin, slippery
Blood Stasis	Cancer mass or previously diagnosed with malignant cancer	Purple	Wiry, choppy
Yang Deficiency	Cold extremities, urinary incontinence, weak	Wet, white coating	Weaker on right
Liver *Qi* Stagnation with Heat	Hypochondriac pain, poor appetite or polyphagia, diarrhea or constipation, anger +/ skin conditions	Purple, red, yellow coating	Wiry, forceful/fast/deep
Qi and Blood Stagnation	Back pain, lameness, pain	Dark or red-purple	Deep
Damp	Heaviness of the head/body, dizziness, poor appetite, chest congestion, excessive mucus, poor health	Sticky coating	Slippery, slow
Phlegm	Poor general health, heaviness, lumps, masses	Pale purple, white coating	Slippery and choppy

Acupuncture: Acupuncture points used for each patient varied depending on the TCVM Pattern observed during the clinical examination. The following acupoints were primarily used for all patients: GV-14, GV-20, LI-4, LIV-3, BL-11, BL-17, BL-18, BL-20, BL-21, BL-23, BL-40, KID-3, BL-60, ST-36 and *Bai-hui* (Table 4). The 4 acupoints used most frequently included: GV-14, LIV-3, LI-4 and BL-18. The use of GV-14 was to regulate the immune system, with the intent to strengthen *Qi* around the chest area to prevent lung metastasis. Acupoints LIV-3 and LI-4, known as "The Four Gates", were used to move *Qi* and Blood through the body. The acupoint BL-18 was used to relieve emotional stress, as well as to nourish muscle/tendon, to support an animal that functions with a three-legged body. Dry needle technique was used for each subject with calming music in the background in both the clinic environment as well as the house calls. The AP treatments usually lasted for 15-20 minutes. Most subjects were treated monthly to every few months throughout their lives.

Chinese Herbal Medicine: The patients were treated with commercially available and compounded herbal formulas with selection based on the TCVM Pattern of a subject determined during clinical exams. The top 3 Chinese herbal medicine formulas used in study subjects (5/7 animal incidence) were Stasis Breaker[d], Immune Booster (compounded based on *Wei Qi* Booster[d]) and *Zhi Bai Ba Wei Wan*. This was followed by *Shu Jin Huo Xue Tang*, and Happy Liver (compounded based on Liver Happy[d]), in 4 of the 7 dogs. Three of 7 dogs were dosed with *Wei Qi* Booster[d], *Liu Wei Di Huang Wan* and *Xue Fu Zhu Yu Tang*. The following Chinese herbal medicines were used in 1 or 2 dogs out of the 7 TCVM-treated study dogs: *Si Jun Zi Wan*, *Ba Zhen San*, Max's formula[d], Bone Stasis[d], *Di Gu Pi*[d], Body Sore[d], *Shen Tong Zhu Yu Tang*, *Fu Gui Ba Wei Wan*, Head Stasis/Stasis in Mansion of Mind[d], *Sheng Mai San*, *Ding Chuan Wan*, *Bu Zhong Yi Qi Wan*, *Ling Zhi* (single herb), and Mind Calm (based on *Shen* Calmer[d]). Most subjects received 2 to 3 formulas based on the TCVM Pattern diagnosed (Table 5). General dosage of the CHM formulas was 0.25g/5kg twice daily for powder formulas or 1 teapill/5 kg twice daily for teapill formulas. The TCVM-treated subjects were dosed with CHM throughout their lives except for Dog 2, whose herbal medicine treatment was discontinued after 3 years.

Food Therapy: Foods were prescribed at each TCVM appointment according to the TCVM Pattern diagnosed, based on clinical signs, tongue and pulse diagnoses (Table 6). Usually 2-3 food items were chosen by a practitioner according to the pattern of an individual's health condition and seasonal change.

Table 4: Acupuncture points and common indications for use in study dogs

Acupoint	Indications
*GV-14	Immune regulation, clears Heat, fever, cough, asthma, false Heat, cervical stiffness
GV-20	Opening permission point, headache, cervical stiffness
*LI- 4	*Yuan*-source point, Master point for face and mouth; immune regulation, clears Heat
*LIV-3	*Shu*-stream point, *Yuan*-source point, Liver *Qi* Stagnation
BL-11	Influential point for Bone; fever, shoulder pain, cervical stiffness, DJD, disc disease, back pain
BL-17	Influential point for Blood, Blood Deficiency, *Yin* Deficiency, vomiting, regurgitation, cough, dyspnea
*BL-18	Back-s*hu* point for Liver; muscle and tendon problems
BL-20	Back-s*hu* point for Spleen; Damp, abdominal fullness, vomiting, diarrhea, edema
BL-21	Back-s*hu* point for Stomach; abdominal fullness or pain, constipation, gastric ulcer, diarrhea
BL-23	Back-s*hu* point for Kidney; Kidney *Qi*/*Yin* Deficiency, sore/weak back, urinary incontinence
BL-40	Master point for caudal back/hip; sore/weak back, gastrointestinal issues, fever
KID-3	Source and *Shu*-stream point; strengthens the caudal back
BL-60	Fire and *Jing*-river point; expels Wind, Clears Heat, relaxes tendons, strengthens the caudal back/hock
ST-36	*He*-sea (Earth) point; *Qi* tonification, Master point for the GI tract/abdomen; nausea, vomiting, gastric pain, food stasis
Bai-hui	Opening permission point, distal point along the GV, *Yang* Deficiency, IVDD, hind limb

*=4 most frequently used acupoints, DJD=degenerative joint disease

Table 5: Herbal formulas used for different TCVM patterns and conditions

TCVM Pattern	Herbal Formula
Yin Deficiency	*Zhi Bai Ba Wei Wan, Liu Wei Di Huang Wan, Di Gu Pi, Sheng Mai San* – *Sheng Mai San*, *Ding Chuan Wan* (included when condition **a** is present) – *Di Gu Pi* (included when condition **c** is present) – *Zhi Bai Ba Wei Wan* (included when condition **g** is present) – *Liu Wei Di Huang Wan* (included when condition **h** is present)
Blood Stasis	Stasis Breaker, *Xue Fu Zhu Yu Tang*, Bone Stasis – Bone Stasis (included when condition **i** is present) – Stasis Breaker or *Xue Fu Zhu Yu Tang* (included when condition **e** is present) – Max's Formula or *Nei Xiao Luo Li Wan* (included when condition **f** is present)
Qi Deficiency	*Wei Qi* Booster, *Xiang Sha Liu Jun Zi Wan, Si Jun Zi Wan, Ba Zhen San, Ling Zhi* – *Wei Qi* Booster or *Xiang Sha Liu Jun Zi Wan* or *Si Jun Zi* or *Ba Zhen San, Bu Zhong Yi Qi Wan* (included when condition **b** is present) – *Jin Suo Gu Jing Wan* or *Fu Gui Ba Wei Wan* (included when condition **d** is present) – *Wei Qi* Booster (included when condition **e** is present) – *Xiang Sha Liu Jun Zi Wan* (included when conditions **f** and **j** are present)
Liver *Qi* Stagnation with Heat	Liver Happy
Qi and Blood Stagnation	*Shu Jin Huo Xue Tang*, *Du Huo Ji Sheng Wan* (Cold Damp), Body Sore, *Shen Tong Zhu Yu Tang* – *Shu Jin Huo Xue Tang* and/or *Du Huo Ji Sheng Wan* (Cold Damp) and/or Body Sore (included when condition **c** is present)
Damp	*Ba Zheng San, Du Huo Ji Sheng Wan, Xiang Sha Liu Jun Zi Wan* – *Du Huo Ji Sheng Wan* (included when condition **c** is present) – *Ba Zheng San* (included when condition **d** is present) – *Xiang Sha Liu Jun Zi Wan* (included when condition **f** and/or **j** is present)
Phlegm	Max's Formula, *Nei Xiao Luo Li Wan*, Stasis Breaker, Stasis in Mansion of Mind – Stasis Breaker and or *Nei Xiao Luo Li Wan* (included when condition **e** is present) – Max's Formula and or *Nei Xiao Luo Li Wan* (included when condition **f** is present)

a. Lung (metastasis or cough); b. Spleen (immune system, appetite, loose bowel, pre/post/during chemotherapy, incontinence); c. Kidney (arthritis/muscular pain); d. Bladder (UTI, bladder incontinence); e. Good appetite; f. Decreased appetite; g. Strong Heat signs (panting/red tongue, drinking a lot, seeking cool place or during chemotherapy with good GI system); h. Weak Heat signs; i. Bone cancer (metastasis); j. Diarrhea

Table 6: Food items prescribed for each TCVM Pattern

Pattern	Food Item
Qi Tonic	Chicken, beef, herring mackerel, kangaroo, rabbit, mutton, trout, oats, millet, brown rice, squash, sweet potato, yam, figs, dates, lychee, molasses, shiitake mushroom, coconut, tofu, ginseng, lentil, licorice, royal jelly, bay, eel, *Yi Yi Ren*, longan, microalgae, potato, rutabaga
Drain Damp	Mackerel, radish, turnip, alfalfa, rye, azuki beans, kidney beans, barley, celery, corn, garlic, *Yi Yi Ren*, marjoram, mustard
Transform Phlegm	Clam, pear, orange, garlic, seaweed, apple, radish, marjoram, mustard
Resolve Stagnation	Mutton, venison, crab, shrimp, garlic, peach, clove, coriander, dill seed, radish, mustard, turmeric, Hawthorn berry, chestnut
Blood Tonic	Azuki/black beans, beef, kangaroo, pork, oyster, salmon beetroot, bone marrow, apricot, carrot, green leafy vegetable, date, egg, heart (organic), kelp, kidney beans, liver (organic), logan, lychee, molasses, parsley, pollen, sardine, avocado, barley, black sesame, dandelion, *Dang Gui*, egg yolk, fig, *Yi Yi Ren*, microalgae, mulberry nettle, oats, rice, soy milk, spinach, watercress, berries (blueberries, raspberries)
Yin Tonic	Duck, rabbit, crab, oyster, clam, egg (chicken and duck), pork (lean), tofu, kelp, kidney beans, string beans, honey, black sesame seeds, asparagus, alfalfa sprout, barley, spinach, peas, apple, apricot, mango, pear, pumpkin, avocado, banana, coconut milk, malt, coconut water, mung bean sprout, nettle, nori/seaweed, plantain, sweet potato, water chestnut, watermelon, coconut water
Yang Tonic	Cherry, chicken, kidney, lamb, oats, shrimp/prawn, lobster, cinnamon bark, clove, nutmeg, dried and fresh ginger

***Tui-na*:** The clients were instructed by the investigator on how to perform *An-fa* (pressing) technique in their initial consultation. The technique used firm pressure applied to distinct points on the body surface. The clients were asked to use *An-fa* technique on acupoints GV-14, BL-23, BL-60, KID-3, BL-20, BL-21, *An-shen* and GV-26 at home. The *Tui-na* technique was applied for one minute per acupoint, once daily (total time 8-10 minutes) or at least a few times per week.

Case Outcomes

Subject #1 had chemotherapy (5 cycles) and started prescribed TCVM treatments soon after the amputation (2 days). Food therapy used foods to address *Qi*/*Yin*/Damp/Stagnation TCVM Patterns presented at each session and dry food was discontinued. Chinese herbal medicines used to address the various TCVM Patterns included: *Liu Wei Di Huang Wan*, *Zhi Bai Ba Wei Wan*, *Si Jun Zi*, *Wei Qi* Booster, Stasis Breaker, *Xue Fu Zhu Yu*

Tang. The dog had a good survival outcome of 114 weeks and was euthanized due to an unrelated illness (fall from stairs-fractured vertebrae) with still no evidence of metastasis on computerized tomography (CT) imaging.

Subject #2 was a 9-year-old rescue at the time of the amputation. The TCVM treatments were initiated 2 months after the amputation. Food therapy primarily used the addition of anticancer foods such as reishi/ shiitake mushrooms and cruciferous vegetables (e.g. broccoli, cauliflower, cabbage) along with discontinuing dry food. Chinese herbal medicines used to address the various TCVM Patterns included *Wei Qi* Booster, Bone Stasis, Stasis Breaker, *Zhi Bai Ba Wei Wan*, *Shu Jin Huo Xue Tang*. The owner stopped treating the dog at 3 years after amputation thinking the dog was cured. The dog lived for another year (4-year survival post-amputation) and was euthanized due to an unrelated retrobulbar tumor that resulted in poor quality of life (QOL).

Subject #3 had a delay of 1 year after amputation before starting TCVM treatments. Food therapy used foods to address *Qi*/*Yin*/Damp/Stagnation TCVM Patterns variously presented at clinic sessions and dry food was discontinued. Chinese herbal medicines used to address the TCVM Patterns included *Zhi Bai Ba Wei Wan*, Stasis Breaker, *Wei Qi* Booster and Liver Happy. It is fair to suspect that this dog had OSA metastasis by the time TCVM treatments started, since the subject was euthanized due to diagnosis of OSA in the other front limb (humerus). Subject #3 had the shortest life span (76.7 weeks) compared to the other TCVM-treated subjects.

Subject #4 was still alive (at study termination) without signs of metastasis at 125.4 weeks after amputation. The subject began TCVM treatments 30 days prior to amputation. Food therapy was initially a keto diet which was then adjusted to food items that addressed *Yin*/Blood/ Damp/Phlegm TCVM Patterns. Dry food was discontinued. Chinese herbal medicines used to address the various TCVM Patterns included: *Zhi Bai Ba Wei Wan*, Immune Booster, Happy Liver, *Sheng Mai San*, *Shu Jin Huo Xue Tang*, *Ba Zheng San*, Mind Calm, *Si Wu Tang*, *Liu Wei Di Huang Wan* and *Ling Zhi*. The dog has continued TCVM treatments and receives both AP and CHM prescribed according to the TCVM Pattern presented on the day of the re-check/AP treatment. This patient suggests that post-amputation life expectancy of OSA dogs can be significantly extended in some individuals.

Subject #5 did not receive chemotherapy and the TCVM treatments were started shortly after amputation (45 days). This subject had the longest life span of all study dogs at 346.1 weeks. The patient had regularly scheduled AP treatment every 4-6 weeks, and food therapy included foods to address *Qi*/*Yin*/Damp/Phlegm/ Stagnation changing TCVM Patterns. Chinese herbal medicines were prescribed and adjusted according to the TCVM Pattern(s) presented on the day of re-check/AP treatments. These included: *Zhi Bai Ba Wei Wan*, Immune Booster, Happy Liver, *Sheng Mai San*, *Shu Jin Huo Xue Tang*, *Ba Zheng San*, Mind Calm, *Si Wu Tang*, *Liu Wei Di Huang Wan* and *Du Huo Ji Sheng Wan*. Radiographic evidence of pulmonary OSA metastasis had been found 76 weeks prior to the euthanasia but the owner decided to continue TCVM treatment due to the dog's excellent QOL at that time. The subject was later euthanized due to progressive osteoarthritis creating QOL decline.

Subject #6 had TCVM treatments initiated one week before the amputation. The dog also presented with lung metastasis on radiographs at the time of amputation. The usual recommendation for subjects presenting with radiographic evidence of pulmonary OSA metastasis at the time of presentation to their regular veterinarian is euthanasia. The owner, however, elected to amputate and continue TCVM treatments to improve the dog's quality of life. Food therapy instituted for this dog included items to address *Qi*/Damp/Phlegm/Stagnation TCVM Patterns. Chinese herbal medicines prescribed included: Immune Booster, Stasis Breaker, *Xue Fu Zhu Yu Tang*, *Shu Jin Huo Xue Tang* and Bone Stasis. The subject lived for another 36 weeks after amputation, despite presentation with metastatic disease at the time of surgery.

Subject #7 was the only subject that did not receive AP treatment, as the dog lived in a different country, and local AP treatment was unavailable. The owner was given food therapy guidance and advised on selection of foods to address changing *Qi*/*Yin*/Damp/Phlegm/Stagnation/ *Yang* TCVM Patterns along with discontinuation of dry food. The Chinese herbal medications were prescribed according to telecommunication with the dog's owner and included: Immune Booster, Stasis Breaker, *Xue Fu Zhu Yu Tang*, *Shu Jin Huo Xue Tang* and Happy Liver. The TCVM treatments were commenced almost 6 months after the amputation. This subject lived for over a year after the amputation.

Subject #8 received conventional treatment only. The dog was dosed with daily meloxicam (3.0 mg) and received one cycle of carboplatin. The dog was euthanized at 11 weeks post-amputation.

Group Survival Outcome Data

Each of the OSA subjects receiving TCVM treatments (dogs 1-7), either with conventional (1-4) or without (5, 6, and 7) conventional treatments, had a longer survival time than Dog 8, who received only conventional treatment (chemotherapy, NSAIDs) after the amputation (Figure 1). Among the 7 dogs receiving TCVM treatments, the median survival time was 114.4 weeks (ranging from 36.0 to 346.1 weeks). Patients who also received conventional treatments had greater median survival time (120 weeks) compared to those receiving only TCVM treatments (median = 53 weeks). Six subjects (6/7 = 85.7%) survived more than 1 year and 4 subjects (4/7=57.1%) lived more than 2 years after amputation (Figure 2). Based on Wilcoxon signed rank test, the median survival time of the TCVM-treated subjects was significantly longer than 12 months ($p = 0.023$). Based on the box-plot analysis, Dog 5's survival time was considered an outlier to the rest of the group. Dog 8 (no TCVM treatment) had a survival time of 11 weeks.

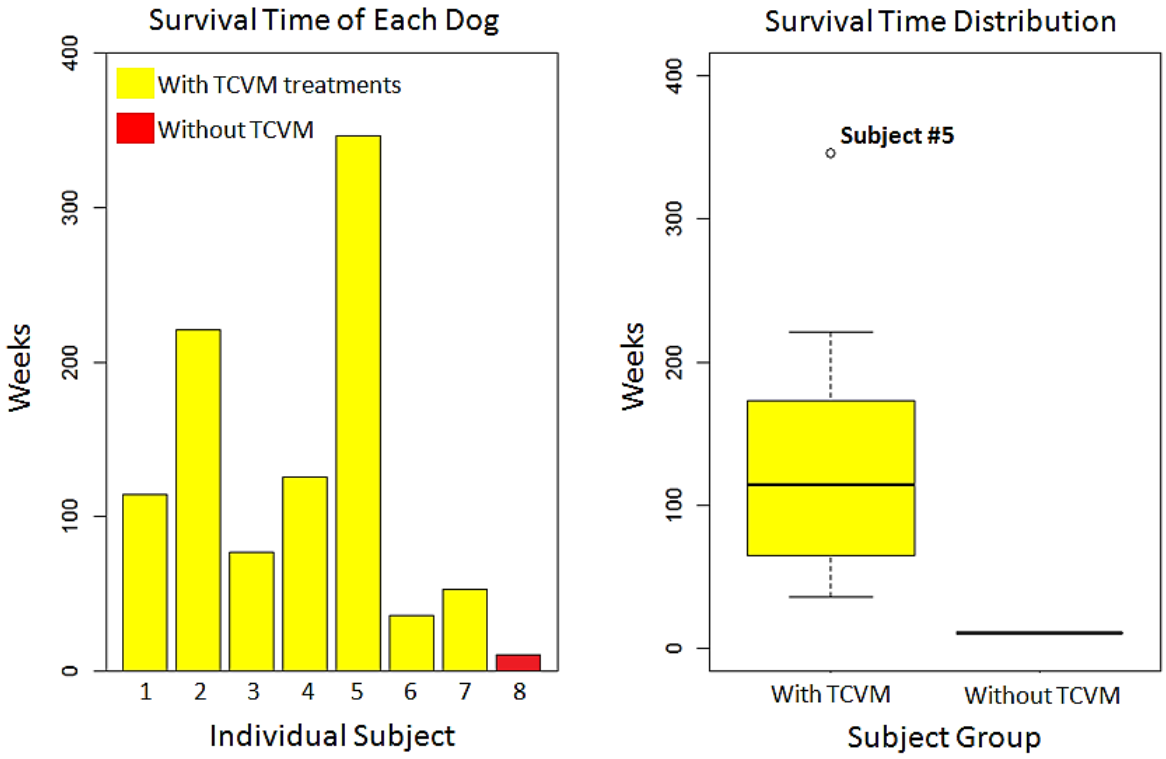

Figure 1: Survival time after amputation of each individual dog (left) and their distribution (right). Dogs (1-7) received TCVM treatment; dogs (1-4) additionally received chemotherapy, while dogs (5-7) were treated with TCVM only. Dog 8 received a daily NSAID and 1 cycle of chemotherapy post-amputation.

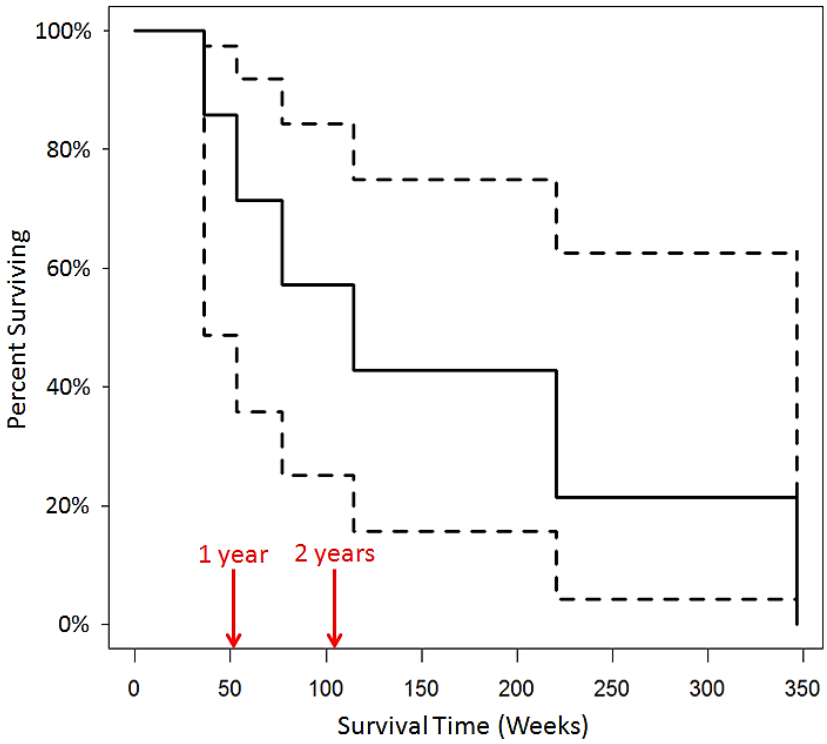

Figure 2: Kaplan–Meier plot of cumulative survival probability curve (with 95% confidence interval; the dashed lines for lower and upper bounds, respectively) at different survival times for subjects treated with TCVM (n = 7). The curve (solid line) shows the percentage of subjects (y-axis) that survived up to each time point on the x-axis. For example, there were 6 (out of 7) TCVM-treated subjects who survived longer than 50 weeks after the amputation, and therefore, the percentage of subjects surviving at Week 50 was 6/7 = 86%.

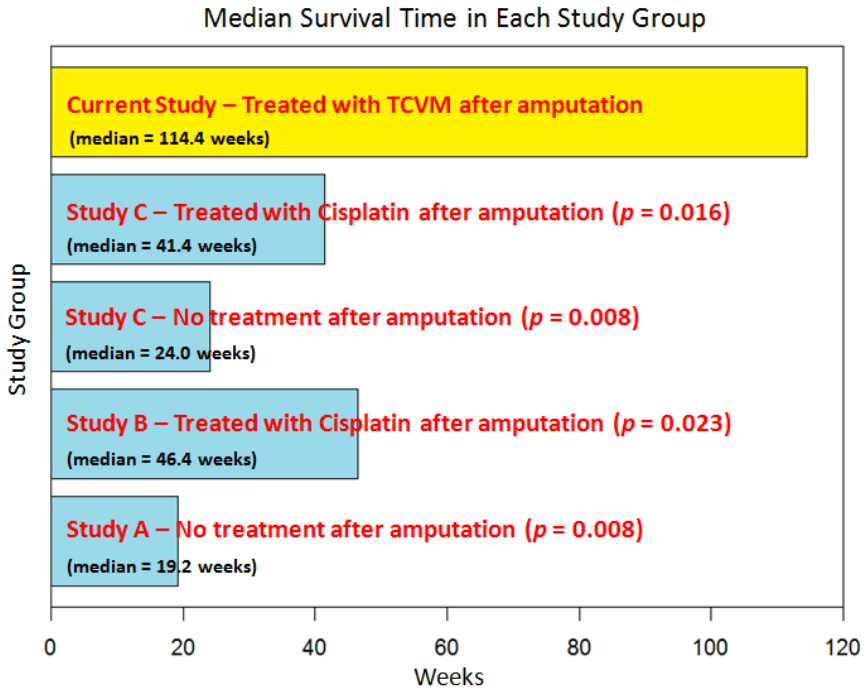

Figure 3: The median survival time of TCVM-treated study dogs in the current study was compared with each OSA group in 3 published studies. The median survival time in the TCVM-treated group was significantly longer than each of the published OSA groups. The *p*-value for each comparison of current to published study is shown.

DISCUSSION

Canine appendicular osteosarcoma is a highly malignant tumor with poor mean survival times for affected individuals. Even with surgery and chemotherapy, the prognosis is poor with a median survival of 34 to 52 weeks (1 year). The objective of this retrospective case series was to evaluate the effectiveness of TCVM therapy to improve mean survival time of canine OSA patients. Based on Wilcoxon signed rank test, the median survival time of the TCVM-treated subjects (114.4 weeks) was significantly longer than 52 weeks (p = 0.023), which is average expected survival associated with combination surgery and chemotherapy treatment. The findings from this small-sample study, suggest the potential of TCVM treatments to prolong life expectancy of OSA dogs after undergoing amputation.

As there was only one dog in the current study that did not receive TCVM treatment; to investigate the efficacy of TCVM, the study compared the "control" data in clinical studies found from a literature search. Published studies were identified through PubMed, Library & Information Resources Network (LIRN) and Google Scholar using the following keywords: osteosarcoma, canine (and/or dog), TCM (and/or TCVM, and/or acupuncture, and/or herb), and cancer. Three studies were identified. Study A had 162 OSA dogs that received no treatment after amputation. The median survival time was estimated to be 19.2 weeks. The 52-week (1 year) and 104-week (2-year) survival rates were estimated to be 11.5 and 2.0% respectively.[7] Study B had 22 OSA dogs that were treated with cisplatin after amputation, with median survival time estimated to be 46.4 weeks. The 52-week (1 year) and 104-week (2-year) survival rates were estimated to be 45.5 and 20.9%, respectively.[7] Study C had 30 OSA dogs divided into 15 receiving no treatment after amputation, and the other 15 receiving cisplatin after amputation. The median survival time for the no-treatment group was 24.0 weeks. There were 3 dogs (20%) that survived more than 48 weeks (1 year). The median survival of the cisplatin-treated group was 41.4 weeks after amputation, with 5 dogs (33.3%) surviving more than 52 weeks (1 year).[8]

The median survival time among the TCVM-treatment dogs (114.4 weeks) in the current study was compared with each of the above OSA dog groups in the literature (Figure 3; Study C had 2 groups). The median survival time in the TCVM-treated group was significantly longer than each of the compared OSA groups (Study A without chemo=19.2 weeks, Study C without chemo=24 weeks), and with chemotherapy (Study B=46.4 weeks, Study C=41.4 weeks). Specifically, the TCVM-treated group in this study had significantly longer median survival time than both no-treatment groups reported in the literature (Studies A and C, p = 0.008 for both), and also had significantly longer median survival time than both cisplatin treated groups (Studies B and C, p = 0.023 and 0.016, respectively).

A canine OSA case series study, using TCVM treatment similar to the present case series, was reported by Bartholomew and Xie.[9] Five dogs diagnosed with neoplastic bone disease (OSA or nasal chondrosarcoma) and treated with TCVM (AP + CHM), either as the sole or part of an integrative treatment were included in this

report. All cases had poor prognoses for QOL and chance of survival. The TCVM treatments resulted in good outcomes (QOL, increased survival) in all 5 cases. One case lived pain-free for 91 weeks (almost 2 years); 1 case lived for over 165 weeks (a little over 3 years) in good health; and the other 3 cases lived beyond anticipated survival time for 65 weeks (15 months) to 156 weeks (3 years). This case series report, similar to the current study, demonstrated the potential to use TCVM as an alternative or integrative approach to improve QOL with prolonged survival time for canine OSA patients.[9]

When evaluating different TCVM modalities for use in cancer therapy, increasing numbers of studies have documented the benefit of using traditional CHM.[10] It has demonstrated low adverse reactions, particularly when compared to other cancer therapies.[10] It is based on multiple components which can target a number of signaling pathways, providing synergistic therapeutic effects.[11] Chinese herbal medicines frequently used in this case series include a number of herbal constituents with bioactive anticancer compounds. For example, in the Chinese herbal medicines targeting Blood Stasis; Oldenlandia (*Bai Hua She She Cao*), which is present in 1 of the 3 most frequently used herbal formulas in this study, has been used extensively and with proven efficacy in metastatic breast cancer and gastric cancer patients.[12,13] Extracts of Oldenlandia (*Hedyotis diffusa*) possessed cytotoxicity towards highly invasive breast cancer cells, but not towards normal cells of different origins. It inhibits the expression of metalloproteinases (MMPs) and caveolin1; as well as p-ERK, p-38, NF-κB, MMP-9, and Icam-1.[11] Additionally, it was shown to attenuate the secretion of pro-inflammatory interleukins IL-1β, IL-6, and TNF-α while inducing anti-inflammatory IL-4 and IL-10.[12] In colorectal cancer, oleanolic acid, another bioactive component of this herb, may suppress angiogenesis by blocking VEGFR2 signaling.[11]

Oldenlandia is frequently paired with another bioactive herb used in the present study, Scutellaria (*Ban Zhi Lian)*, to enhance synergy of anticancer properties.[14] Among the chemical compounds identified are flavonoids, diterpenoids and volatile oils.[15] The flavonoids (scutellarein, scutellarin, carthamidin) are thought to be primarily responsible for the anticancer properties. An oral aqueous extract of the herb evaluated for treatment of metastatic breast cancer was associated with cell cycle arrest, apoptosis and inhibition of glycolysis.[16,17] Scutellarein reduced tumor growth and metastasis while another flavonoid compound, scutellarin, mitigated colitis-derived colorectal cancer by inhibiting the Wnt/β-catenin signaling pathway.[11] In gastric cancer cells, this compound was able to up-regulate PTEN (attenuates p-PI3K and EMT). It also appeared to attenuate the PI3K/AKT pathway, inhibit ABC transporters, and restore susceptibility to 5-FU.[18] The combination of Oldenlandia and Scutellaria display antineoplastic capacity involving multiple mechanisms acting synergistically. It has been noted that the study of a combination of extracts or individual compounds of these plants is a promising area of anticancer research.[11]

In addition to the herbal formulas targeting Blood Stasis, the formulas tonifying Spleen *Qi* in this study, also contained constituent herbs with anticancer activity. Zhang et al. showed that Citrus Aurantium called "*Chen Pi*" (or *Qing Pi*) can inhibit OSA progression and local recurrence.[19,20] Ginseng, characterized by the presence of ginsenosides (main bioactive compounds), have demonstrated anticancer activity. Of interest in the present study is the report by Mao et al. demonstrating that Ginsenoide (Rg3) can inhibit the proliferation of OSA cells and diminish metastasis via Wnt/β-Catenin and EMT Signaling Pathways.[21] When considering TCM theory, the benefit of this group of formulas stem from their ability to tonify *Qi* and produce Blood (both deficient in cancer), by strengthening the Spleen and Stomach. Additional benefits provided include nourishing the Liver and Kidney, removing Heat from Blood and Heat-toxins from the body. The use of these herbs and herbal formulas have been reported by multiple groups to improve the clinical efficacy of conventional treatments, as demonstrated in the present study.[22-41]

The use of AP in multimodal treatment of human cancer patients is increasing with recent advances in clinical research demonstrating reduction of radiation and chemotherapy related adverse side-effects, as well as improved QOL.[42,43] Additionally, AP analgesia and its multiple targeted areas of pain relief have been documented in the laboratory and clinic for decades.[42] Its use, as in the present study, assists pain relief, which is a long-standing unresolved issue in patients with bone cancers.[42] Other cancer-related clinical challenges in humans that AP therapy improves include fatigue, neuropathies, depression and anxiety, which can also manifest in dogs undergoing cancer therapies. A recently published human clinical trial reported massage combined with AP in post-operative cancer patients improved depressive mood in patients (p=0.003). Persistent fatigue associated with cytotoxic cancer therapy was improved in 31.3% of the patients following AP therapy.[42] The evidence currently available has suggested that AP is a safe and effective therapy to manage the adverse effects associated with cancer and conventional cancer treatments.[42,43]

Limitations for this study are typical of those for a retrospective case series: missing data (documented in the tables), selection and recall bias. A particular challenge was the establishment of a control group. The author's clinic offers TCVM treatment, therefore, data for only 1 patient receiving conventional treatment without TCVM therapy was available for inclusion in this study. Although not ideal, this was addressed by using a literature search to identify studies with median survival of conventionally treated OSA dogs for comparison to the present study. Other limitations included obtaining true survival times of study dogs. Limited owner finances and the decision to euthanize by owners may have affected calculation of survival time. For example, one subject (#1) was euthanized due to unrelated illnesses without metastasis, which was confirmed by regular CT scans. Another subject (#2), had reduced frequency of TCVM

treatments due to finances and was treated for only the first three years post-amputation. The owner stopped treatment due to continued financial constraint and owner's belief the dog was cured. The dog survived another year without therapy (greater than 4 year survival) and was euthanized due to sudden onset of a large retrobulbar mass. Therefore, it is reasonable to assume that these subjects' true post-amputation survival times from OSA would be longer than observed. Subject #4 was still alive and receiving TCVM treatment at study termination (125.4 weeks post-amputation). Hence, it is reasonable to suggest that several survival times analyzed in this study were underestimated.

The survival effect associated with CHM was also difficult to determine. All subjects were given at least two formulas: one to tonify Spleen *Qi* (root cause of cancer)/*Wei Qi* (boost immune response) and a second formula to treat Blood Stasis associated with tumor formation. The variety and number of herbal formulas used, therefore, complicated summary assessment of the exact contribution of each CHM to mean survival. Finally, not all study subjects were able to go through CT scan or radiographs; hence, the presence of metastasis at the beginning of TCVM therapy was unknown. This information might be an important factor to determine efficacy of TCVM treatments as well as investigation of treatment effects.

Similar to humans, there continues to be increasing numbers of cancer patients presented for treatment in the veterinary field. It has been reported that TCM in combination with chemotherapy can promote efficacy and diminish some of the limitations induced by chemotherapy.[10,11,43] The present study suggests a synergism of TCVM with chemotherapy which resulted in prolonged life spans for OSA canine patients treated with both. These results are encouraging and suggest TCVM studies in this subject population may create more positive treatment approaches to animals affected by this aggressive malignancy.

In summary, it was found that 7 dogs receiving TCVM treatment post-amputation for OSA had a median survival time of 114.4 weeks. One dog (control) which received daily NSAID treatment and 1 cycle of chemotherapy following surgery had a survival time of 11 weeks. Patients who received conventional treatments (chemotherapy, NSAIDs) in addition to TCVM treatments had greater median survival time (120 weeks) compared to those receiving only TCVM treatments (53 weeks) which is similar to the average chemotherapy treatment survival of 52 weeks. Four of the TCVM treated subjects (57.1%) had extended survival of more than 2 years after amputation. This study, while with limited case numbers, suggests that TCVM treatments may be beneficial to prolong the survival time in OSA dogs after amputation. In the future, randomized controlled trials with sufficient sample size for meaningful statistical inference are needed to compare TCVM treatment with and without various conventional therapies (e.g. surgery, chemotherapy) to determine optimum treatment.

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FOOTNOTES

[a] R version 3.5.2. The R Foundation for Statistical Computing, Vienna Austria; http://www.R-project.org

[b] Previcox (Firocoxib), Boehringer Ingelheim Pharmaceuticals, Ingelheim, Germany

[c] Meloxicam (brand name Metacam®) – generic, multiple manufacturers

[d] Dr Xie's Jing Tang Herbal, Inc., Ocala, Florida, USA

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