

## RESEARCH ARTICLE

# Minimal clinically-important differences for the “Liverpool Osteoarthritis in Dogs” (LOAD) and the “Canine Orthopedic Index” (COI) in dogs with osteoarthritis

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**Data Availability Statement:** The data used in this study is the property of the Guarda Nacional Republicana, a governmental police force from Portugal, and is, by law, confidential. The authors obtained specific approval to use the data. Data requests may be sent to the Divisão de Medicina Veterinária ([cari.dsad.dmv.cvc@gnr.pt](mailto:cari.dsad.dmv.cvc@gnr.pt)). Other researchers, who meet the criteria for access to confidential data, can access data in the same manner as the authors. The authors had no special access privileges.

## Abstract

### Objective

Osteoarthritis is the most common joint disease in companion animals. Several client-report outcome measures (CROMs) have been developed and validated to monitor patients and their response to treatment. However, estimates for minimal clinically-important differences for these CROMs in the context of osteoarthritis have not been published.

### Patients and methods

Data from the Clínica Veterinária de Cães (Portuguese Gendarmerie Canine Clinic) clinical records were extracted. Baseline and 30-day post-treatment follow-up data from 296 dogs treated for hip osteoarthritis were categorized based on an anchor question, and estimates of minimal clinically-important differences (MCIDs) using distribution-based and anchor-based methods were performed.

### Results

For the LOAD, the anchor-based methods provided a MCID estimate range of -2.5 to -9.1 and the distribution-based methods from 1.6 to 4.2. For the COI, the anchor-based methods provided a MCID estimate range of -4.5 to -16.6 and the distribution-based methods from 2.3 to 2.4. For the dimensions of COI, values varied from -0.5 to -4.9 with the anchor-based methods and from 0.6 to 2.7 with the distribution-based methods. Receiver operator characteristic curves provided areas under the curve >0.7 for the COI, indicating an acceptable cut-off point, and >0.8 for the LOAD, indicating an excellent cut-off point.

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## Conclusion

Our estimates of MCIDs for dogs with OA were consistent with previously proposed values of -4 for the LOAD and -14 for the COI in a post-surgical intervention context. ROC curve data suggest that LOAD may more reliably differentiate between anchor groups. We also presented estimates from COI of -4 for Stiffness, Function, and Gait and -3 for quality of life. These estimates can be used for research and patient monitoring.

## Introduction

Osteoarthritis (OA) is a commonly diagnosed disease in veterinary medicine, affecting an expected growing number of animals worldwide [1, 2]. It has been associated with 80% of all lameness diagnoses in dogs [3]. For that reason, there is a need for proper evaluation tools to assess these patients. While objective modalities, such as gait analysis or weight-bearing evaluation, are accurate and reliable [4, 5], they are not widely available. Following a similar trend in human medicine, different client-reported outcome measures (CROM) have been developed and introduced in veterinary medicine over the last few decades [6, 7]. This patient-centered approach allows for a complete assessment of the multi-dimensional construct of OA and OA-related pain [8, 9].

While the patient reports on their experience in human medicine, in veterinary medicine, the client is the most common proxy. In addition to being able to identify changes and degrees of their pet's subjective status, owners can also interpret changes over an extended period of time [10, 11]. Several CROMs have been developed to assess canine joint disease, including the Liverpool Osteoarthritis in Dogs (LOAD) [12, 13] and the Canine Orthopaedic Index (COI) [14]. Both have been validated in original language and translated versions [15, 16]. They have also been recommended for use in dogs with OA in a recent COSMIN-based systemic review [17] and for chronic pain in WSAVA guidelines [18].

In addition to being validated, estimates of specific minimal clinically-important differences (MCID) should be determined for individual CROMs. Having this set threshold allows for the success of a given treatment in individual patients [19] and for study design and sample size estimates in research and clinical trials [20]. Anchor-based methods or distribution-based methods can be used to estimate MCID. The first compares changes in CROMs to an explicit metric of the proxy's opinion of the change. In contrast, the second relies on the statistical characteristics of a group's baseline scores to determine how much of a change would be clinically important [21]. The evaluation of MCID also has to be done under clinical contexts.

This study aimed to estimate MCIDs for LOAD and COI in dogs with osteoarthritis.

## Materials and methods

The study protocol was approved by the ethical review committee of the University of Évora (Órgão Responsável pelo Bem-estar dos Animais da Universidade de Évora, approval n° GD/37187/2021/P1) and complies with relevant institutional, national and ARRIVE guidelines for the care and use of animals. Written, informed consent was obtained from the Institution responsible for the animals (Republican National Guard, Portugal).

Data were obtained from the clinical information of dogs presented for treatment for bilateral hip OA at the Clínica Veterinária de Cães (Portuguese Gendarmerie Canine Clinic). To be included in the study, dogs had to be diagnosed with bilateral hip OA, have available radiographic results consistent with the disease, and have confirmed absence of any other disease.

As a standard approach the Clínica Veterinária de Cães Before treatment and at set intervals, the canine handlers complete an online version of the LOAD, the COI, and an anchor question. The Portuguese versions of the LOAD and COI have been previously validated [15, 16, 22]. Only patients with a single treatment modality were considered (e.g., a nonsteroidal anti-inflammatory drug or an intra-articular platelet-rich plasma administration). The anchor question was “How do you describe your dog’s overall quality of life”. The possible responses were “Poor”, “Fair”, “Good”, “Very Good”, and “Excellent”. Only the pre-treatment (T0) and the 30 days post-treatment (+30d) data were used in this study. Only patients with T0, +30d, and anchor question answers were included.

Relevant clinical data were exported to an Excel (Microsoft, Seattle, USA) spreadsheet. Statistical analyses were performed with commercially available software (IBM SPSS Statistics version 20). For the subsequent analysis, two groups were set: a “the same” and a “somewhat better” groups, based on the canine handler’s responses to the anchor question at +30d. The “the same” group comprised the animals with the same response at the T0 and +30d evaluations. The “somewhat better” group included the animals where a one-level better response was obtained at the +30d evaluation compared to the T0 evaluation. Baseline characteristics of the two groups were compared with the Mann-Whitney U test, while categorical data were compared with Fischer’s exact test. The Wilcoxon signed-rank test was used to compare changes in scores from T0 to +30d. The Mann-Whitney U test was used to compare differences in the CROMs and the mean change in the CROMs between the groups. Significance was set at  $p < 0.05$ .

We used four anchor-based methods to calculate the MCID. First, the “average change” (AC) was determined, corresponding to the mean change in the score of the ‘somewhat better’ group. A “change difference” was also determined, defined as the difference in the average change in score between the “somewhat better” and “the same” groups. The third method consisted in calculating the “minimum detectable change” (MDC). The MDC is the smallest change that can be considered beyond the measurement error at a 95% confidence level. Since an improvement with the LOAD and COI consisted of a reduction in total score, the MCID was equal to the lower value of the 95% confidence interval for the average change in the “the same” group’s score. Finally, a receiver operating characteristic (ROC) curve was used to define the point that best discriminated between the two groups. This optimal cut-off point was estimated using the point that maximized specificity and sensitivity. The area under the ROC curve (AUC) was also calculated to assess reliability. Based on previous reports, AUC values between 0.7 and 0.8 were considered acceptable, and 0.8 and 0.9 were considered excellent.

In addition to the anchor-based methods, two distribution methods were used to estimate the MCID. One was based on the effect size, calculated as the difference in mean score from T0 to +30d (in the present example) divided by the standard deviation (SD) of the T0 scores. Since an effect size of 0.2 is considered small, MCID with the following formula:  $(SD_{T0} * 0.2)$  [21]. The second method was based on the “standard error of measurement” (SEM) of CROM scores since SEM is an intrinsic property of the CROM and, therefore, independent of the patient cohort considered [21]. SEM with the following formula:  $SEM = SD * \sqrt{1-r}$ . In this case, “r” is the reliability of the instrument. For LOAD, a previously published value was used [23]. For the COI and its dimensions, previously calculated “r” values were used [16].

## Results

Data from 296 animals fulfilled the inclusion criteria. The breeds represented were German Shepherd Dogs (n = 160), Labrador Retriever (n = 56), Belgian Malinois Shepherd Dogs (n = 45), Dutch Shepherd Dog (n = 23), Rottweiler (n = 3), and others (n = 9). One hundred

**Table 1. Mean and standard deviation (SD) pre-treatment and 30 after-treatment scores for Liverpool Osteoarthritis in Dogs (LOAD) and Canine Orthopedic Index (COI).**

CROM		n	T0		+30d		p value
			mean	SD	mean	SD	
LOAD (0–52)		296	21	10	15	12	<0.01*
COI	Stiffness (0–16)	296	6	3	4	4	0.04*
	Function (0–16)		6	4	4	4	0.03*
	Gait (0–20)		9	5	6	5	0.04*
	QOL (0–12)		6	3	4	3	0.01*
	Overall (0–64)		28	14	19	4	<0.01*

QOL—Quality of Life.

\* indicates significance.

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eighty were intact males and 116 were intact females, with a mean age of  $7.8 \pm 2.1$  years and a body weight of  $30.3 \pm 6.2$  kg. Forty two had mild hip OA (14.2%), 162 had moderate hip OA (54.7%), and 92 had severe hip OA (31.1%) according to the Orthopedic Foundation for Animals hip grading scheme. Different treatments were identified: nonsteroidal anti-inflammatory drugs (meloxicam  $n = 8$  and carprofen  $n = 8$ ), intra-articular treatments (hyaluronan  $n = 35$ , triamcinolone  $n = 36$ , and hyaluronan+triamcinolone  $n = 33$ ), photobiomodulation ( $n = 23$ ), mesotherapy ( $n = 62$ ) and biologicals (platelet rich plasma  $n = 53$  and blood cell secretome,  $n = 38$ ).

The mean T0 and +30d scores for LOAD and COI are presented in [Table 1](#). Both CROMs demonstrated a significant difference between pre-treatment and post-treatment scores.

Considering the anchor question, there were 152 (51.4%) dogs in the “somewhat better” and 144 (48.6%) in the “the same” group. Scores at T0 and +30d for these two groups are presented in [Table 2](#).

The MCID estimates with the four anchor-based methods and the two distribution-based methods are shown in [Table 3](#).

The four anchor-based methods provided a range of MCIDs for each CROM (2.5 to 9.1 for LOAD and -4.5 to 16.1 for COI). Different ranges were also provided for the dimensions of COI. In the two different distribution-based methods, the MCID for LOAD ranged from 1.6 (effect size) to 4.2 (SEM), while the MCID for COI ranged from 2.3 (SEM) to 2.4 (effect size), showing a variation depending on the method applied. All AUCs calculated by the ROC curve were greater than 0.7, indicating an acceptable cut-off point. The greater AUC was found with LOAD (0.867) and the smallest with the quality of life dimension of the COI (0.770).

## Discussion

In the presented study, we estimated MCIDs for the LOAD and the COI, both validated for use in dogs with OA. We used data available from a population of police working dogs submitted to various treatments. The +30d follow-up moment was selected based on the expectation that it would be enough to obtain different responses to treatment, spreading answers to the anchor question and allowing us to estimate the MCID. However, this should not be considered a recommendation for evaluation post-treatment outcome in dogs with OA, as most treatments are expected to produce an earlier effect. Since the LOAD and the COI are a part of the routine follow-up for this population of dogs, and all fields are mandatory in the follow-up, we obtained results for both CROMs in all patients. The baseline values for the LOAD and COI were similar to the ones previously published for police working dogs with OA [24–31].

Table 2. Scores in the “the same” and “somewhat better” groups at T0 and +30d.

CROM		"The same" group		"Somewhat better" group		P value
		mean	SD	mean	SD	
<b>LOAD</b>						
	n	152		144		
	T0	18.05	0.96	19.85	10.07	0.054
	30d	20.33	0.9	11.26	9.87	0.005*
	mean change	2.28		-8.59		0.027*
<b>COI</b>						
<b>Stiffness</b>						
	n	152		144		
	T0	5.09	0.91	6.08	3.37	0.061
	30d	6.19	1.07	2.04	3.43	0.011*
	mean change	1.1		-4.04		0.029*
<b>Function</b>						
	n	152		144		
	T0	5.17	1.1	6.25	4.13	0.731
	30d	6.36	1.11	2.11	3.93	0.006*
	mean change	1.19		-4.14		0.078*
<b>Gait</b>						
	n	152		144		
	T0	7.58	1.11	9.25	4.72	0.147
	30d	9.38	1.07	4.51	4.89	0.009*
	mean change	1.8		-4.74		0.014*
<b>QOL</b>						
	n	152		144		
	T0	5.04	5.04	6.21	2.76	0.147
	30d	6.29	0.18	3.00	2.68	0.017*
	mean change	1.25		-3.21		0.002*
<b>Overall</b>						
	n	152		144		
	T0	22.88	1.34	27.79	14.07	0.271
	30d	28.21	0.93	11.66	14.14	0.011*
	mean change	5.33		-16.13		0.037*

COI—Canine Orthopedic Index; LOAD—Liverpool Osteoarthritis in Dogs; QOL—Quality of Life.

\* indicates significance.

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It is well established that the estimates of MCIDs can be affected by extrinsic and intrinsic factors [32]. While the present study provided results in an important clinical context, as is OA, it is important to remember that the patients included comprise a very homogenous sample, as the animals represent a set number of breeds and experience similar housing, feeding, and exercise conditions. Future studies will be needed to evaluate if this context influences the results. Still, the obtained results are very similar to a previous report, estimating MCIDs for the same CROMs in dogs surgically treated for cruciate ligament disease [20].

We followed a variety of methods to generate MCIDs. It has been argued that anchor-based estimates are more clinically-relevant, but distribution methods are based on larger data set [33]. With distribution methods, the SEM is preferred, as it is an intrinsic property of the CROM [21]. The four anchor-based methods we used have been previously used in human [34] and animal patients [20]. Similar to those studies, we observed that the different methods

Table 3. MCIDs for Liverpool Osteoarthritis in Dogs and Canine Orthopedic Index.

CROM		Anchor-based				Distribution-based	
		AC	CD	MDC	ROC Curve (AUC)	Effect size	SEM
	LOAD	-8.6	-9.1	-4.4	-2.5 (0.872)	±1.6	±4.2
COI	Stiffness	-4.0	-4.2	-1.2	-1.0 (0.777)	±0.7	±1.1
	Function	-4.1	-4.3	-1.4	-0.5 (0.774)	±0.8	±1.6
	Gait	-4.7	-4.9	-2.0	-1.5 (0.770)	±1.1	±2.7
	QOL	-3.2	-3.3	-1.4	-0.5 (0.768)	±0.6	±1.8
	Overall	-16.1	-16.6	-14.5	-4.5 (0.778)	±2.4	±2.3

AC—Average Change; AUC—Area under the curve; CD—Change difference; MDC—Minimum detectable change; ROC—Receiver operating characteristic; SEM—standard error of measurement.

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generated different MCID estimates. The largest estimate for the LOAD was for “change difference” at -9.1, as for the COI, at -16.6. For the various dimensions of the COI, the largest estimates were also obtained with “change difference”, ranging from -3.3 (for quality of life) to -4.9 (with gait). On the opposite end, the ROC curve generated the lowest estimates. The AUC of the ROC curve showed an acceptable ability of the COI and its dimensions to discriminate between the two groups of dogs, while the LOAD showed an excellent ability to do so. Although we included a relatively large sample, a broader sample would be preferred for future studies. Considering these results, the previously proposed working MCID of -4 for LOAD [20] seems appropriate for dogs with OA. This value is supported by the ROC (-2.5) anchor-based method and both distribution-based methods (ES ±1.6 and SEM ±4.2). Support for the previously proposed working MCID of -14 for the COI [20] is also reasonable, based on MDC (-14.5), ROC (-4.5), ES (±2.4), and SEM (±2.3) methods. For the different dimensions of the COI, a working MCID of -4 for Stiffness, Function, and Gait can be proposed, and of -3 for the quality of life, based on the different methods. These results reinforce the previously proposed estimates for use in sample size calculation and as a reference for researchers and regulators.

As with different evaluation modalities, and as a proxy completes the CROMs, the risk for a caregiver placebo effect exists. This effect has been attributed to the wish for the dog to get better, but also, in the case of OA, to the fact that some animals may exhibit some level of improvement due to the disease’s natural evolution and a regression to the mean effect [35–38]. The LOAD has not shown a major placebo effect in previous reports. This finding has been attributed to the emphasis of the questions on activity “activity/exercise” and “stiffness/lameness [13]. This rationale has been supported by a placebo effect not being found at the animal level, as the ability to perform daily activities will likely reflect a lower level of pain and disease impairment [39, 40]. Similar to the LOAD, much of the emphasis of the COI’s question is placed on the animal’s ability to perform daily activities. Criterion validity versus objective assessment of load-bearing has been observed for the LOAD and the COI [16]. Still, the scores observed in the “the same” group had a very small variation, in contrast to what was observed in the “somewhat better” group, consistent with the anchor question. With that in mind, while a certain level of caregiver placebo effect could be present in the present data, particularly since some treatments were more invasive in nature [41], it should not have influenced the results significantly. Future should include an objective measure, that allows the comparison of objective data with the results of the CROM.

This study had some limitations. The data were obtained from a specific population of dogs, and future studies should focus on a broader sample. Only patients with hip OA were



included, and OA from other joints should also be considered. Different post treatment follow-up moments should also be considered, to determine if this factor influences the MCID. Future studies should also look at determining what would constitute a client-acceptable clinical state, a threshold where a client is likely to define the outcome as “satisfactory”, and the substantial clinical benefit level, defined as the clinical value that the client considers as “substantial improvement” [20].

## Conclusions

We presented estimates of MCIDs for LOAD and COI in dogs with OA, consistent with previously proposed values of -4 and -14, respectively. For the first time, we also presented estimates for the dimensions of the COI, of -4 for Stiffness, Function, and Gait can be proposed, and of -3 for quality of life. These estimates can be used for research and patient monitoring. Future studies should include OA from other joints and animals from a broader clinical context.

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## Author Contributions

**Conceptualization:** John F. Innes.

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**Methodology:** J. C. Alves, John F. Innes.

**Project administration:** J. C. Alves.

**Writing – original draft:** J. C. Alves.

**Writing – review & editing:** John F. Innes.

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