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Research article
Ερευνητικό άρθρο

HER-2 positivity rate in dogs with mammary carcinoma: a systematic review and meta-analysis

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ABSTRACT: Human epidermal growth factor receptor 2 (HER-2) plays an essential role in cell growth and survival. HER-2 overexpression occurs in 20-30% of human breast tumors and has prognostic value as it is associated with disease progression. HER-2 overexpression is also associated with tumor progression and metastasis in malignant mammary tumors of the canine. However, in the literature, different positivity classifications/scoring were used in the evaluation of HER-2 status, and there is no consensus in terms of scoring of HER-2 expression in canine mammary tumors. In this study, it was aimed to estimate the HER-2 positivity rate by evaluating the results of the study using different positivity classifications by meta-analysis. In this context, by using ”HER-2 canine mammary tumor” keywords, Pubmed and Web of Science electronic databases were scanned until February 2019, and a total of 97 related studies were found. However, 20 of these studies were used for the analysis. Two different meta-analyses were performed to evaluate the HER-2 positivity status with “2+ and 3+” and “3+” scores. As a result, HER-2 positivity rates were determined at 25.87% and 25.99% for the studies using “2+ / 3+” scores and “3+” respectively for HER-2 positivity. Therefore, this result suggests that the rate of HER-2 positivity is similar between humans and dogs.

Keywords: HER-2, meta-analysis, canine, mammary tumor.

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INTRODUCTION

Changes in growth factors, growth factor receptors, and other regulators of cellular proliferation play a role in tumorigenesis and therapeutic response in both canine and human mammary carcinomas (Araújo et al., 2016). Human epidermal growth factor receptor 2 (HER-2), a member of the epidermal growth factor receptor (EGFR) family with tyrosine kinase activity, plays an important role in the regulation of cell growth, survival, and differentiation (Ressel et al., 2013). HER-2 overexpression is seen in 20-30% of human breast tumors and has a prognostic value, as it is associated with disease progression and shorter survival (Kim et al., 2011; Ressel et al., 2013). In addition to its prognostic value, analysis of HER-2 status in human medicine is important for the selection of the patient who will undergo treatment (Ressel et al., 2013). HER-2 overexpression is associated with tumor progression and metastasis in canine malignant mammary tumors as well. However, the relevance of HER-2 overexpression and tumor progression or prognostic factors has not been clearly determined so it is controversial in canine mammary tumors, mainly due to variations in methods that are used in the evaluation of HER-2 expression status (Kim et al., 2011). One of the most important reasons for this situation is the low level of accuracy obtained with the comparison of results from different scoring systems. In studies concerning the role of HER-2 in canine mammary tumor, there is no consensus in terms of scoring. Another important issue concerns the use of small sample sizes in studies making them of inadequate strength and consequently of limited validity and acceptability (Tas et al., 2018).

Meta-analysis is a method that can be used to solve such problems, and by combining similar study results, more general information about the population parameter can be obtained by increasing the sample size (Avci, 2018). The aim of this study was to estimate the HER-2 positivity rate by analyzing the results of the studies with different scoring systems used in the examination of HER-2 positivity by meta-analysis method.

MATERIALS AND METHODS

For researching the effects of different HER-2 expression scoring in immunohistochemical analysis of malignant canine mammary tumors, Pubmed and Web of Science electronic databases were scanned up to February 2019 using the keywords “HER-2 canine mammary tumor” and 97 studies were accessed. The referees were blinded to the author and institution of the studies under investigation in determining the studies to be included in this research. A total of 20 studies were found suitable for analyses (Fig. 1, Table 1).

Table 1. Studies and frequency distribution of score values for meta-analysis

Study	Frequency of score value (Score value:n)	Sample Size
Nguyen et al., 2017	**0**: 262; **1**$^+$: 71; **2**$^+$:17; **3**$^+$:0	*350*
Damasceno et al., 2016	**0**: 1; **1**$^+$**:**14; **2**$^+$:22; **3**$^+$:6	*43*
Campos et al., 2015	**0**: 9; **1**$^+$:10; **2**$^+$:9; **3**$^+$:0	*28*
Silva et al., 2014	**0**: 2; **1**$^+$: 1; **2**$^+$:4; **3**$^+$:8	*15*
Dutra et al., 2004	**0**: 12; **1**$^+$:19; **2**$^+$:11, **3**$^+$:6	*48*
Ressel et al., 2013	**0, 1**$^+$: 25; **2**$^+$**,3**$^+$: 10	*35*
Im et al., 2012	**0, 1**$^+$: 103; **2**$^+$**,3**$^+$:36	*139*
Oh et al., 2012	**0, 1**$^+$: 56; **2**$^+$**,3**$^+$: 6	*62*
Kim et al., 2011	**0, 1**$^+$: 34; **2**$^+$**,3**$^+$:18	*52*
Kurilj et al., 2011	**0, 1**$^+$: 46; **2**$^+$**,3**$^+$: 5	*51*
Millanta et al., 2010	**0, 1**$^+$: 36; **2**$^+$**,3**$^+$: 10	*46*
Hsu et al., 2009	**0, 1**$^+$: 64; **2**$^+$**, 3**$^+$: 27	*91*
Gama et al., 2008	**0, 1**$^+$: 79; **2**$^+$**,3**$^+$: 21	*100*
Martín de las Mulas et al., 2003	**0, 1**$^+$: 14; **2**$^+$**, 3**$^+$: 3	*17*
Abadie et al., 2018	**0, 1**$^+$**, 2**$^+$: 350; **3**$^+$: 0	350
Araujo et al., 2016	**0, 1**$^+$**, 2**$^+$: 67; **3**$^+$: 6	73
Shin et al.,2015	**0, 1**$^+$**, 2**$^+$: 53; **3**$^+$: 34	*87*
Burrai et al., 2015	**0, 1**$^+$**, 2**$^+$: 7; **3**$^+$**:** 2	*9*
Muhammednejad et al., 2012	**0, 1**$^+$**, 2**$^+$: 23; **3**$^+$:12	*35*
Bertagnolli et al., 2011	**0, 1**$^+$**, 2**$^+$**:**61**; 3**$^+$**:**10	*71*

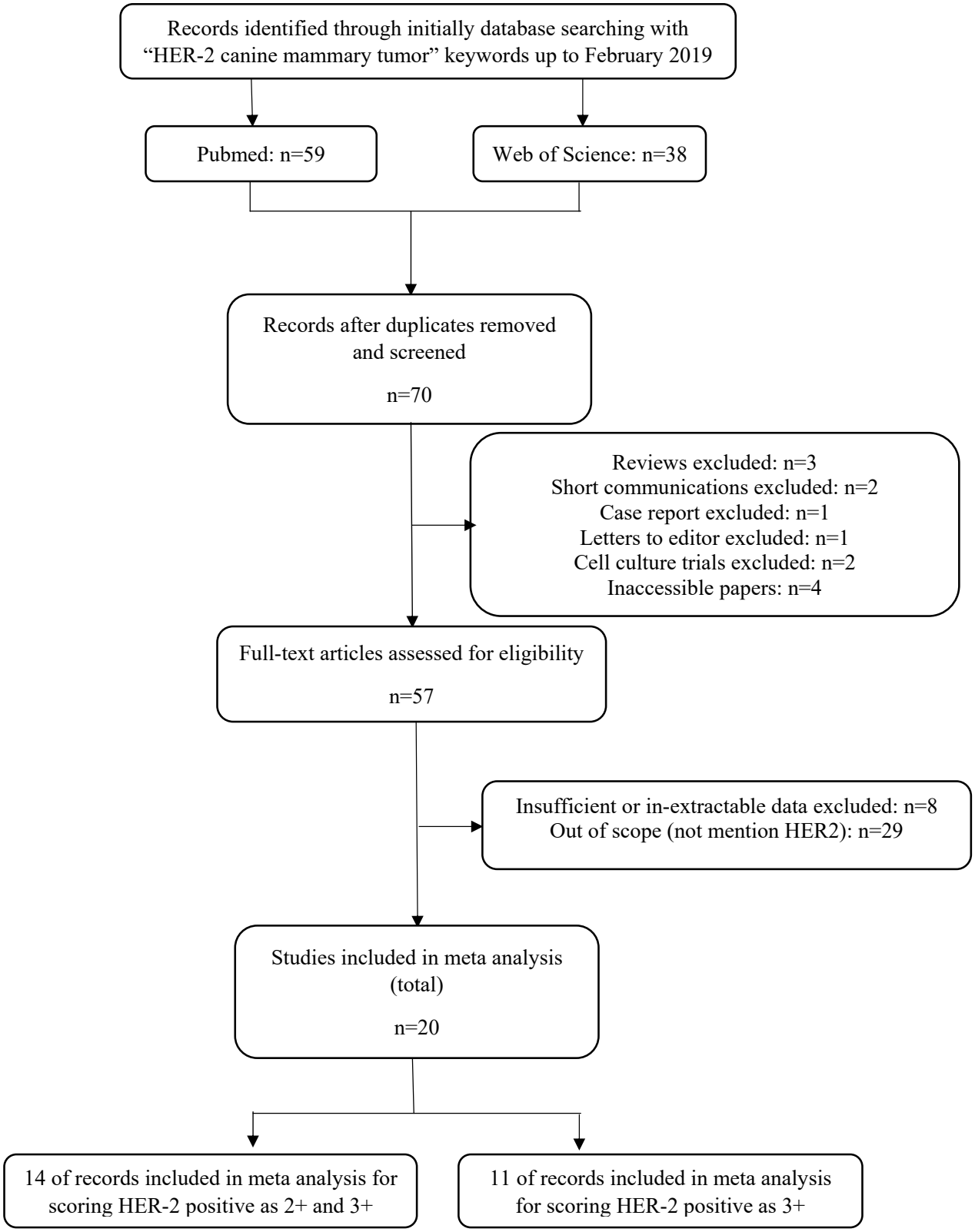

Figure 1. Flow chart showing the selection of studies for meta-analysis

Studies in which HER-2 expression status was indicated separately as a score (0, 1+, 2+, 3+) or was classified with scores clearly as "positive" and "negative" were included in the meta-analysis. Number of HER-2 positive and total number of cases were extracted from studies and used to calculate proportions (number of HER-2 positive/total number of cases) in the analysis. Different scoring systems were used in the studies evaluating HER-2 positivity. Studies that use three types of scoring systems were considered in this research. In the first type of studies, frequencies of scores were reported for 0, 1+, 2+ and 3+ scores separately (n=5). Furthermore, in the second type of studies, results were classified as negative for scores 0 and 1+ and as positive for scores 2+ and 3+ (n=9). Finally in the third type of studies, only 3+ score was used to determine HER-2 positivity, whereas 0, 1+ and 2+ scores indicate HER-2 negativity (n=6). In order to increase the number of publications included in analyses and thus, to obtain as much detailed information as possible, two different meta-analyses were performed considering particularly two different scoring systems. These meta-analyses were performed for second type of studies, indicating HER-2 positivity with 2+ and 3+ scores (n=14), and third type of studies indicating HER-2 positivity with 3+ score (n=11). Studies that use "0, 1+, 2+, 3+" scoring system (first type of studies) were used in both meta-analyses.

Statistical Analysis

The publication bias of the studies was examined before the meta-analysis with Begg's and Egger tests. Even if one of these tests is significant, it indicates that there is a publication bias; in this case, the trim and fill method was applied. The heterogeneity of the studies was evaluated with the Cochran Q test. In the evaluation of homogeneity and publication bias, α=0.10 was taken (Erdoğan and Kanık, 2011). Since heterogeneity was determined with the Cochran Q test, then DerSimonian Laird method was performed using the random effects model. For statistical analysis, "metafor" and "meta" packages were used in R version 3.5.3 software (R Development Core Team, 2014).

RESULTS

Evaluation of the studies that use 2+ and 3+ scores for HER-2 positivity

In dogs with mammary tumors, 14 studies classify HER-2 positivity based on immunohistochemical staining value of "2+ and 3+". There was no publication bias according to the Egger test (p = 0.630) and Begg's test (p = 0.956). Cochran Q test showed heterogeneity among studies ($p<0.001$; $I^2=89.4\%$). The meta-analysis results of the studies in which HER-2 positivity is scored as 2+ and 3+ were given in Table 2, and the related forest plot was shown in Fig. 2.

Table 2. Results of meta-analysis for studies in which HER-2 positivity is expressed with 2+ and 3+ scores

Study	Positive	Total	Positivity Percent of HER-2 (%)	95% C.I.	Weight (%) REM
Damasceno et al., 2016	28	43	65.12	49.07-78.99	7.4
Campos et al., 2015	9	28	32.14	15.88-52.35	7.0
Ressel et al., 2013	10	35	28.57	14.64-46.30	7.2
Im et al., 2013	36	139	25.90	18.85-34.01	8.0
Oh et al., 2014	6	62	9.68	3.63-19.88	6.8
Kim et al.,2011	18	52	34.62	21.97-49.09	7.6
Millanta et al., 2010	10	46	21.74	10.95-36.36	7.2
Nguyen et al., 2018	17	350	4.86	2.85-7.66	7.8
Gama et al., 2008	21	100	21.00	13.49-30.29	7.8
Dutra et al., 2004	17	48	35.42	22.16-50.54	7.5
Silva et al., 2014	12	15	80.00	51.91-95.67	5.6
Kurilj et al., 2011	5	51	9.80	3.26-21.41	6.6
Hsu et al.,2009	27	91	29.67	20.55-40.16	7.9
Martín de las Mulas et al.,2003	3	17	17.65	3.80-43.43	5.6
Random Effects	219	1077	**25.87**	17.24-36.88	100

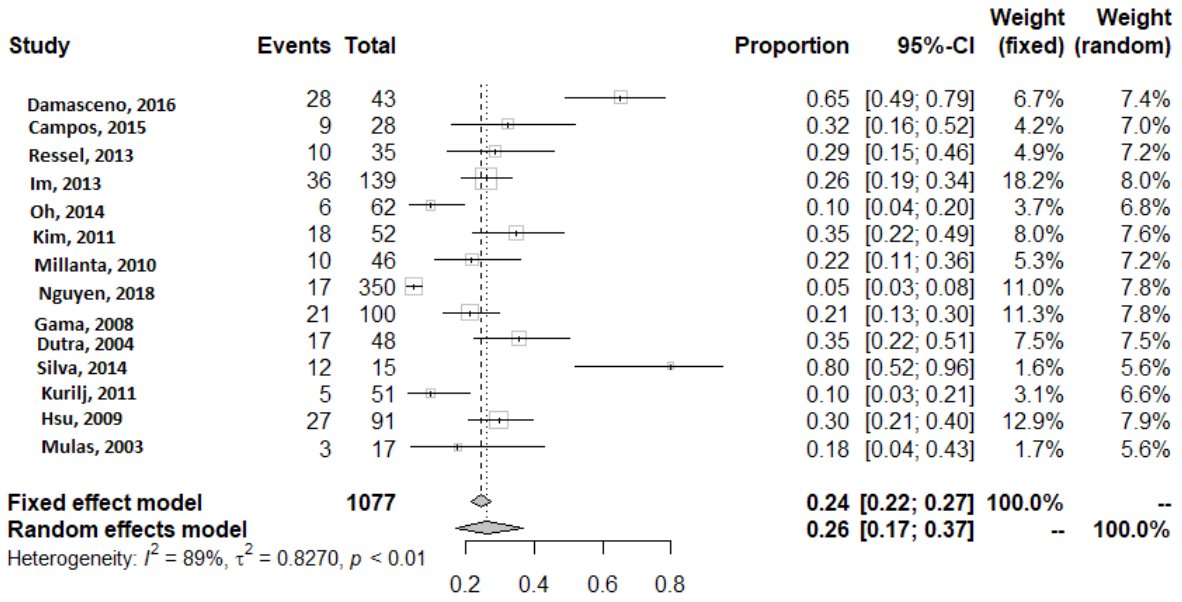

Figure 2. Forest plot for studies in which HER-2 positivity is expressed with 2+ and 3+ scores

Evaluation of the studies that use 3+ score for HER-2 positivity

In dogs with mammary tumors, 11 studies classify HER-2 positivity based on immunohistochemical staining value of "3+". Unlike studies that use "2+ and 3+", there was publication bias in studies that use 3+ score for HER-2 positivity according to the Egger test (p = 0.014) and Begg's test (p = 0.158). Because of the observed publication bias, trim and fill method was applied. However, the Cochran Q test demonstrated heterogeneity among studies (p<0.001; I^2=88.4%). The meta-analysis results of the studies in which HER-2 positivity is scored as 3+ were given in Table 3 and the related forest plot was given in Fig. 3.

Table 3. Results of meta-analysis for studies in which HER-2 positivity is expressed with 3+ scores

Study	Positive	Total	Positivity Percent of HER-2 (%)	95% C.I.	Weight (%) REM
Damasceno et al., 2016	6	43	13.95	5.30-27.93	10.8
Araujo et al., 2016	6	73	8.22	3.08-17.04	10.9
Campos et al., 2015	0	28	0.00	0.00-12.34	4.7
Bertagnolli et al., 2011	10	71	14.08	6.97-24.38	11.4
Burrai et al., 2015	2	9	22.22	2.81-60.01	8.3
Muhammednejad et al.,2012	12	35	34.29	19.13-52.21	11.3
Shin et al., 2015	34	87	39.08	28.79-50.13	12.0
Nguyen et al., 2018	0	350	0.00	0.00-1.05	4.7
Dutra et al., 2004	6	48	12.50	4.73-25.25	10.8
Abadie et al., 2018	0	350	0.00	0.00-1.05	4.7
Silva et al., 2014	8	15	53.33	26.59-78.73	10.4
Random Effects	84	1109	12.96	6.47-24.27	100
Random Effects (Trim fill was applied)	84	1109	**25.99**	13.49-44.16	100

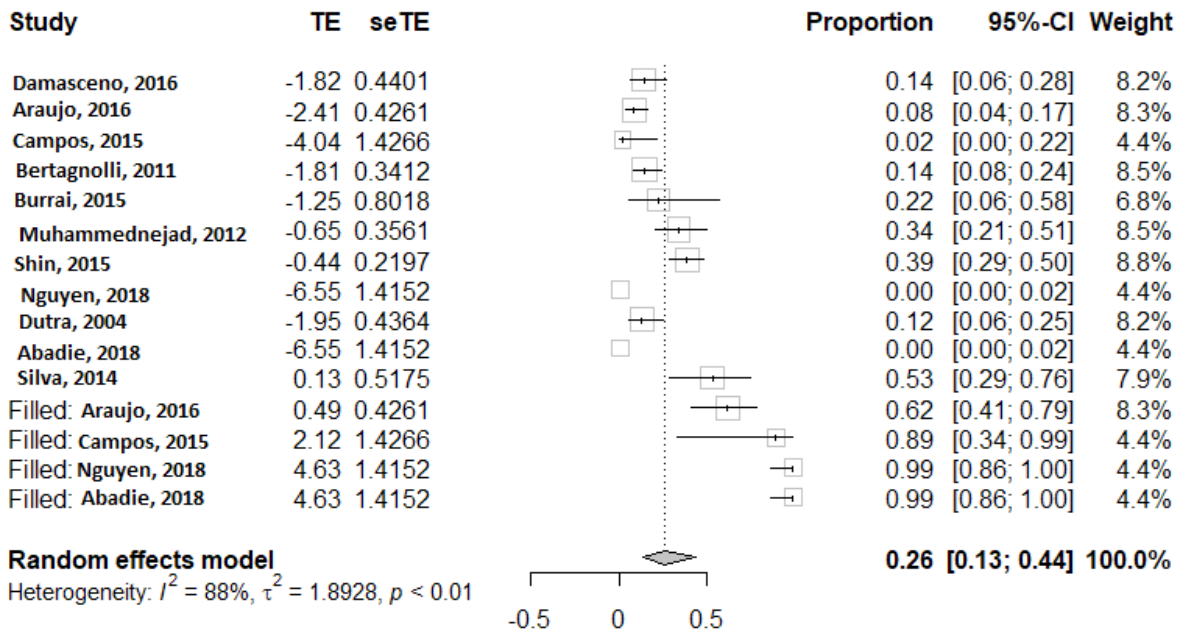

Figure 3. Forest plot for studies in which HER-2 positivity is expressed with 3+ score

DISCUSSION

There are many restrictions on research planning and implementation. The most effective of these constraints are cost and time. Cost and time constraints may prompt studies that use a relatively small number of cases. In addition to a large number of studies with a small number of cases, there also exist a few studies that use a large number of cases. Both of these situations may lead to conclusions with inadequate strength about population. To eliminate this concern and to ensure generalization in science, meta-analysis studies are used.

In this study, 20 out of 97 publications retrieved from Pubmed and Web of Science were found suitable for meta-analysis. Fourteen out of 20 studies employed 2+ and 3+ scores whereas 11 out of 20 employed 3+ score for HER-2 positivity. Five studies used "0, 1+, 2+ and 3+" scoring system for HER-2 expression status; therefore, these studies were included in both groups. Because two different scores were used for HER-2 positivity in the studies, two meta-analyses were performed to evaluate HER-2 positivity in both situations.

Since the 2+ and 3+ scores were considered as HER-2 positive, the pooled proportion was 25.87%, and when the 3+ score was considered as HER-2 positive, the pooled proportion was 25.99%. These two ratios can be considered as lower and upper limits in estimating the population parameter. However, HER-2 positivity proportions of studies with 2+ and 3+ scores ranged between 4.86% to 80.00%, and for 3+ score ranged from 0.00% to 53.33%. This result indicates that HER-2 positivity rate varies considerably in individual studies using different scoring systems. Therefore, the need for a meta-analysis of HER-2 positivity was justified. Moreover, given the relatively fewer number of studies (20 studies) that give detailed information about HER-2 positivity, a meta-analysis was needed to evaluate HER-2 positivity across studies better.

Canine malignant mammary neoplasms are common tumors, and the prevalence varies from 26% to 73% in female dogs and, in terms of morphology and biological behavior, represent a remarkably heterogeneous group of cancers (Burrai et al., 2015; Campos et al., 2015). Identification of diagnostic, prognostic, and therapeutic biomarkers is an urgent need to evaluate and manage this disease more effectively (Burrai et al., 2015). In addition to the estrogen and progesterone receptors, HER-2 is an essential biomarker for human breast cancer prognosis (Charpin et al., 1997; Ross and Fletcher, 1998). HER-2 overexpression is observed in 20–30% of human breast cancers (Slamon et al., 1989; Almasri and Al Hamad et al., 2005) but characterization of HER-2 expression and its association with histologic type and tumor grading is controversial in canine mammary tumors (Kim et al.,

2011; Kurilj et al., 2011).

HER-2 protein overexpression is observed in different percentages in canine malignant mammary tumors (19 to 74%) and this is related to a number of factors, including number of cases, different immunohistochemical methods, the sensitivity of the detection method, antibody used, the level of gene expression or the stages of tumor samples (Martín de las Mulas et al., 2003; Gouvea et al., 2006; Hsu et al., 2009; Kurilj et al., 2011; Oh et al., 2012). The most frequently used scoring system for HER-2 expression status is based on Hercept Test, but this system gives a significant number of false positives (Bertagnolli et al., 2011). Other methods (ASCO and CAP) established cut-off points for defining HER-2 status. A threshold was adopted to avoid false positives, which is at least 30% of tumors (rather than the originally specified 10%). This ratio (%30) concerns the degree of membrane staining. If more than 30% of the total number of the neoplasmatic cells have their membrane uniform and intense stained immunohistochemically with the HER-2, then this neoplasm will be considered as positive for HER-2 (Bertagnolli et al., 2011). Moreover, Ressel et al. (2013) reported that they could not compare their result, which was observed by another researcher due to the different scoring system. The prognostic significance and clinical importance of HER-2 status remain unclear in canine mammary tumors (Bertagnolli et al., 2011). No relationship was identified between HER-2 overexpression and tumor progression or prognostic factors (Martín de las Mulas et al., 2003; Hsu et al., 2009; Kim et al., 2011; Ressel et al., 2013; Burrai et al., 2015). Moreover, Peña et al. (2014) reviewed that implication of HER-2 expression in canine mammary carcinogenesis was controversial and inconclusive. Thus, a standardized method is needed to obtain objective results for HER-2 overexpression status (Oh et al., 2012). Alternatively, the meta-analysis method may be used as a more suitable technique to evaluate the results of different studies that use different scoring systems for HER-2 positivity.

CONCLUSIONS

In conclusion, according to the results obtained by the meta-analysis of studies that use two different scorings for HER-2 positivity, HER-2 positivity rate in dogs with mammary tumors ranges from 25.87% to 25.99%. Therefore, this result suggests that the rate of HER-2 positivity is similar between humans and dogs.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

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