

Assessment of prognosis and survival rates in felines with lymphoma with and without retroviral infection**Avaliação do prognóstico e taxas de sobrevivência em felinos com linfoma com e sem infecção retroviral**Marta Carreira¹, Gonçalo Vicente¹, Solange Gil^{1,2*}¹ Hospital Escolar, Faculdade de Medicina Veterinária, Universidade de Lisboa, Portugal. ² CIISA – Centro de Investigação Interdisciplinar em Sanidade Animal, Faculdade de Medicina Veterinária, Universidade de Lisboa, Portugal.**Resumo**

As infeções por retrovírus podem contribuir para o desenvolvimento de linfoma em gatos e, apesar de estarem frequentemente associadas a uma menor sobrevida, os estudos mais recentes não valorizam a infecção retroviral como um fator de prognóstico. No entanto, estes estudos foram realizados em países onde a prevalência de infecção retroviral é consideravelmente inferior, comparativamente a Portugal. Este estudo visa a caracterização de uma amostra de felídeos com linfoma e a avaliação do efeito da infecção retroviral no prognóstico, em comparação com outros estudos. Foram incluídos 83 felídeos com linfoma e recolhidos os seus dados clínicos. O linfoma digestivo foi a forma anatómica mais comum (40%), surgindo maioritariamente em indivíduos com idades ≥ 13 anos e sem infecção retroviral, seguida do linfoma multicêntrico (28%) e do linfoma mediastínico (19%), este último sobretudo observado em felídeos com idades ≤ 4 anos e maioritariamente com infecção por FeLV. Dos 64 felídeos testados para retrovírus, 27 apresentavam infecção retroviral. Esta proporção revelou-se consideravelmente superior comparativamente a estudos anteriores. Os resultados obtidos demonstraram que a infecção por retrovírus afetou o prognóstico dos felídeos com linfoma, sendo que o tempo mediano de sobrevivência (TMS) dos indivíduos com infecção retroviral foi estatisticamente inferior ao TMS dos felídeos sem infecção retroviral (16 e 131 dias, respetivamente). Analisando os gatos com e sem infecção retroviral e tratados por quimioterapia, verificou-se igualmente que o TMS foi diferente e com significância estatística entre os dois grupos (122 e 984 dias, respetivamente). Este estudo permitiu também confirmar a resposta ao tratamento como um fator de prognóstico em felídeos com linfoma. Relativamente à análise de doenças concomitantes, os gatos com linfoma e infecção retroviral foram os mais predispostos a desenvolver doenças da cavidade oral, como estomatite e gengivite (44%), comparativamente aos indivíduos sem infecção retroviral (19%).

Palavras-chave: linfoma; retrovírus; tempo mediano de sobrevivência; prognóstico.

Summary

Retroviruses may contribute to the development of lymphoma in cats and although frequently associated to lower survival rates, the most recent studies do not pinpoint retroviral infection as a prognostic indicator. However, these studies are from countries where the prevalence of retroviral infection is considerably lower compared to Portugal. This study aims to characterize a sample of cats with lymphoma and to evaluate the effect of retroviral infection on the

prognosis of these individuals, in comparison to other studies. Eighty-three cats with a definitive diagnosis of lymphoma were included and data related to their clinical history were collected. Alimentary lymphoma was the most common anatomic location (40%), appearing mostly in individuals aged ≥ 13 years and without retroviral infection, followed by multicentric (28%) and mediastinal lymphoma (19%), this last one mainly seen in cats aged ≤ 4 years and positive for Feline Leukemia Virus (FeLV). Of the sixty-four cats tested for retroviruses, twenty-seven had retroviral infection. This proportion showed to be considerably higher when compared to other studies. Results showed that retroviral infection affected the prognosis of cats with lymphoma, as retroviral infected patients had a median survival time (MST) statistically lower in comparison to non-retroviral infected cats (16 and 131 days, respectively). Considering both retroviral and non-retroviral infected cats treated with chemotherapy, the MST was also statistically significant different when both groups were compared (122 and 984 days, respectively). This study also showed that the response to treatment is a prognostic indicator in cats with lymphoma. Regarding the analysis of concomitant diseases, cats with lymphoma and retroviral infection were more predisposed to develop oral diseases, such as stomatitis and gingivitis (44%), when compared to non-retroviral infected patients (19%).

Keywords: lymphoma; retrovirus; median survival time; prognosis.

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1. Introduction

Lymphoma represents up to 90% of hematopoietic neoplasms in cats (Horta *et al.* 2020) and 30% of all the tumours in this species (Gustafson *et al.*, 2014). Infections by Feline Leukemia Virus (FeLV) and Feline Immunodeficiency Virus (FIV) are widely recognized as important predisposition factors for the development of lymphoma (Paulin *et al.*, 2018; Mandara *et al.*, 2016).

In the past, several studies reported an enhanced proportion of cats with lymphoma that were infected with FeLV and showed a poorly prognosis (Vail *et al.*, 1998). The beginning of FeLV vaccination in the 1980s in countries such as the United Kingdom (UK) (Taylor *et al.*, 2009; Fabrizio *et al.*, 2014) and the United States of America (USA) (Moore *et al.*, 2012; Collette

et al., 2015) resulted in a significant decrease of the proportion of cats with FeLV infection. Consequently, it was reported a decrease of the population at risk of developing lymphoma associated with this infection (Beatty, 2014), in particular the mediastinal form. In opposition, an increased prevalence of the alimentary lymphoma was observed (Louwerens *et al.*, 2005).

Recent studies have evaluated the effect of FeLV and FIV infections on the prognosis of cats with lymphoma and the vast majority did not show any correlation (Teske *et al.*, 2002; Hadden *et al.*, 2008; Waite *et al.*, 2013; Fabrizio *et al.*, 2014; Collette *et al.*, 2015). However, these studies were assessed in countries where the prevalence of feline retroviral infections is considerably lower in comparison to Portugal (Maruyama *et al.*, 2003; Duarte *et al.*, 2010; Chhetri *et al.*, 2013; Burling *et al.*, 2017; Studer *et al.*, 2019).

Regarding differences in retroviral prevalence between Portugal and other countries, the present study aims to characterize a sample of cats with lymphoma and to evaluate the effects of retroviral infection on the prognosis of these patients.

2. Material and methods

2.1. Patients and clinical data

Medical records of feline patients with a cytological or histologic definitive diagnosis of lymphoma at the Hospital Escolar, in Lisbon, were assessed between January 2013 and May 2020. Cats were excluded if clinical data were not available, as well as animals whose age was unknown. A descriptive analysis regarding the anatomic locations of lymphoma was performed in eighty-three lymphoma reported cases. Statistical and survival analysis were then analyzed in the sixty-four cats that had a reported diagnosis test for retroviral infections. Finally, survival rates were assessed in the twenty-three patients with retroviral known status and that undergone chemotherapy. The study design is represented in Figure 1.

Retroviral infection status was defined based on the results of enzyme-linked immunosorbent assay (ELISA), immuno-chromatographic assay and/or polymerase chain reaction (PCR).

Clinical data such as date of birth, sex, breed, fertility status, treatment adopted, concomitant diseases, lifestyle, vaccination, clinical history and date of death, if applicable, were collected. In some cases, tutors were contacted in order to obtain the follow-up and the date and cause of death, if applicable.

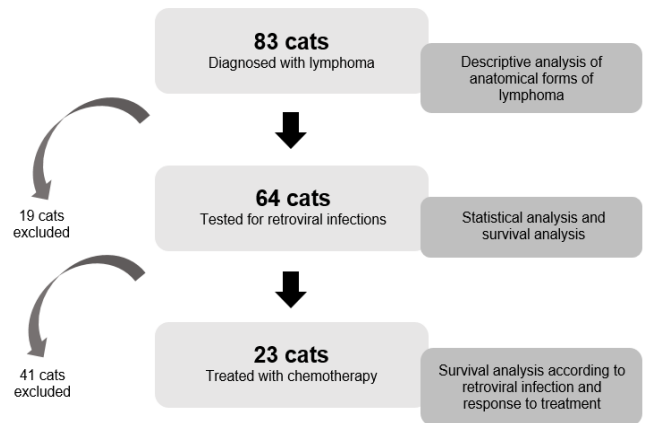


Figure 1 - Study design.

2.2. Evaluation of response to therapy

Response to therapy was assessed for each treatment by combining physical examination findings with the clinical history and the imaging complementary exams (Taylor *et al.*, 2009). Complete Response (CR) was defined as the regression of all measurable parameters of disease, such as clinical signs and mass size. Partial Response (PR) was defined as a > 50% but < 100% reduction of these parameters. No Response (NR) was defined as any change in the measurable parameters, a decrease of 50% or even an increase in the mass size (Fabrizio *et al.*, 2014; Gustafson *et al.*, 2014). The response rate was correlated with the percentage of individuals that revealed CR or PR (Teske *et al.*, 2002). For patients with a palpable gastrointestinal tract mass and thoracic effusion, CR was defined as the resolution of the thoracic effusion and the reduction in the mass size that was no longer possible to feel. PR was defined as a reduction of mass size although it was still palpable (Milner *et al.*, 2005).

2.3. Survival time

Survival time relates to the period of time between the date of diagnosis till the date of death. Cats lost to follow-up or alive at the end of the study period were censored and patients that died were considered as events (death).

2.4. Statistical tests

Statistical analysis was performed using Microsoft Excel 16.0 and IBM SPSS Statistics 25 software. Pearson's chi-square test and Fisher's exact test were used for comparative analysis between retroviral infection and variables like chemotherapy treatment, response to treatment and concomitant diseases. Kaplan-Meier method was performed for survival analysis and the Log Rank test was used to evaluate the effect of sex, breed, fertility status, response to treatment and retroviral infection on survival time. A P-value < 0.05 was considered significant.

3. Results

3.1. Patients characterization

Eighty-three cats met the inclusion criteria, of which 42 were male and 41 were female. The majority of cats were Domestic shorthair (75 cats) and sterilized (68 cats). Lymphoma was classified according to its anatomical form as alimentary/gastrointestinal (n = 33), mediastinal (n = 16), multicentric (n = 23), renal (n = 4), nasal (n = 3), laryngeal/pharyngeal/tracheal (n = 2) and Central Nervous System (CNS) (n = 1). One lymphoma was classified as indeterminate, as it was not possible to know the origin of the neoplasm.

According to its behavior, 13 alimentary lymphomas were low-grade, the others were classified as high-grade.

Cats whose retroviral status was unknown were excluded from the remaining statistical analysis. Regarding the sixty-four patients with known retroviral status, nineteen cats (30%) were FeLV-positive, 4 (6%) were FIV-positive and 4 cats (6%) tested positive for both FeLV and FIV infections. Considering patient's lifestyle, 55% (n = 35) were strictly indoor, 23% (n = 15) were classified as outdoor and 22% (n = 14) had unknown lifestyle. The origin of all cats was unknown. Only two retroviral infected patients had vaccines, one was correctly vaccinated for RCP (Feline Viral Rhinotracheitis, Feline Calicivirus and Feline Panleukopenia) and the other was vaccinated for FeLV. Four non-retroviral infected patients were correctly vaccinated for RCP and 2 were vaccinated against FeLV.

The median age at diagnosis was 8,5 years. Results showed a bimodal age distribution with one peak at 1-3 years and another peak at 13-15 years. Information regarding age and retroviral status related to different types of lymphoma are summarized in Table 1.

The median age of cats diagnosed with alimentary lymphoma was 13 years, for mediastinal lymphoma was 1 year, for multicentric lymphoma was 7 years, for renal lymphoma was 6 years and for nasal lymphoma was 8,5 years. Patients diagnosed with laryngeal/pharyngeal/tracheal lymphoma and CNS were diagnosed at 4 and 12 years, respectively.

Table 1 - Data related to anatomic forms of lymphoma, age and retroviral status of the 64 cats.

Anatomic form	n	Mean age (years)	Median age (years)	Retroviral status	
Alimentary	19	12,53	13,00	Negative	90% (n = 17)
				FeLV	5% (n = 1)
				FIV	5% (n = 1)
Mediastinal	15	2,93	1,00	Negative	33% (n = 5)
				FeLV	60% (n = 9)
				FIV and FeLV	7% (n = 1)
Multicentric	21	8,10	7,00	Negative	48% (n = 10)
				FeLV	33% (n = 7)
				FIV	14% (n = 3)
Renal	4	7,50	6,00	Negative	50% (n = 2)
				FeLV	25% (n = 1)
				FIV and FeLV	25% (n = 1)
Nasal	2	8,50	8,50	Negative	50% (n = 1)
				FIV and FeLV	50% (n = 1)

The 64 cats were divided into three groups based on age at presentation (≤ 4 years, 5-12 years and ≥ 13 years). The majority of the younger cats (≤ 4 years) (n = 20) tested positive for retroviral infection (70%, n = 14) and had mediastinal lymphoma (55%, n = 11). Differently, the majority of older cats (≥ 13 years, n = 19) were non-retroviral infected (79%, n = 15) and had alimentary lymphoma (58%, n = 11).

3.2. Therapeutic approach

Considering the treatment options adopted, cats were also divided into four groups: patients treated with CHOP-based protocol, patients treated with chlorambucil and prednisolone, patients treated with prednisolone and cats that did not received any treatment. The decision regarding the treatment instituted was related to the type and behavior of lymphoma and the associated expected prognosis, as well as the owner's compliance.

Twelve patients (44%) from the twenty-seven retroviral-infected cats did not receive any form of treatment and only seven (26%) were submitted to chemotherapy. In contrast, seventeen (46%) of the thirty-seven non-retroviral infected cats were treated with chemotherapy and nine patients (24%) did not receive any treatment (Figure 2). Pearson's chi-square test was performed in order to evaluate the association between retroviral infection and treatment (either by the CHOP-based protocol or by chlorambucil and prednisolone). Results did not show any significant statistical correlation ($p = 0,102$).

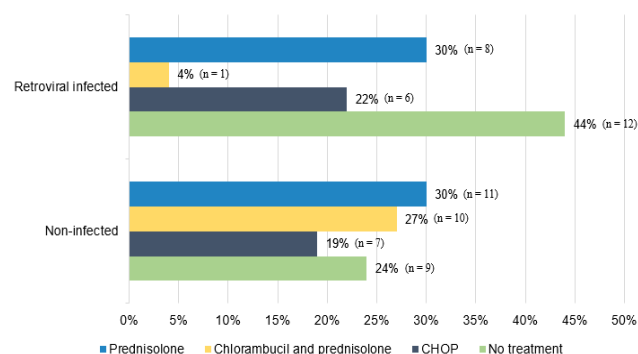


Figure 2 - Treatment options adopted for the 64 cats.

Regarding patients treated with chemotherapy (n=23), cats diagnosed with high-grade types of lymphoma (mediastinal, multicentric, renal, nasal, laryngeal/ pharyngeal/ tracheal and CNS), as well as patients diagnosed with high-grade alimentary lymphoma, were treated with a CHOP-based protocol (CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone). Patients diagnosed with low-grade alimentary lymphoma (LGAL) were treated with chlorambucil and prednisolone. Regarding patients treated with chemotherapy, 2 cats were diagnosed with stage 3 lymphoma and 3 cats were diagnosed with stage 4, all multicentric forms, being the stage of the other patient's unknown. The decision to pursue

with chemotherapy was due to the prognosis presented by the veterinarians and/or the owners compliance.

3.3. Survival analysis

The reported median survival time (MST) for the 64 cats was 33 days. According to anatomic forms of lymphoma, cats diagnosed with the alimentary type had the longest MST (410 days). Patients diagnosed with mediastinal, multicentric, renal and nasal forms of lymphoma had lower values of MST (9, 13, 10 and 140 days, respectively). The patient diagnosed with CNS lymphoma received only treatment with prednisolone and had a survival time of 34 days.

The Kaplan-Meier product limit was used to analyse the effect of sex, breed and fertility status on survival and the results showed no significant difference for any of these variables ($p = 0.958$, $p = 0,640$ and $p = 0.369$, respectively).

The survival time of the 64 cats is illustrated in Figure 3. The Log Rank test allowed to compare the survival time between retroviral infected and non-retroviral infected cats. A p-value of 0,005 indicated that the MST of cats diagnosed with lymphoma and retroviral infected (16 days) was significantly lower when compared to cats with lymphoma but non-retroviral infected (131 days).

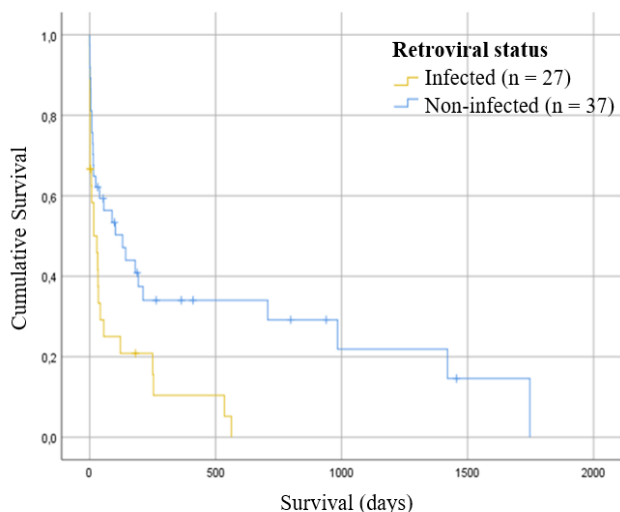


Figure 3 - Kaplan-Meier survival time stratified by retroviral status for the 64 cats.

In order to increase the reliability of the results, a second survival analysis was performed regarding the group of cats treated with chemotherapy ($n = 23$). The survival time of these patients is illustrated in Figure 4 and the resulting p-value for the Log Rank test was 0,006. These results showed that considering patients with lymphoma that undergone chemotherapy, the MST of cats with retrovirus was significantly lower (122 days) when compared to non-retroviral infected cats (984 days).

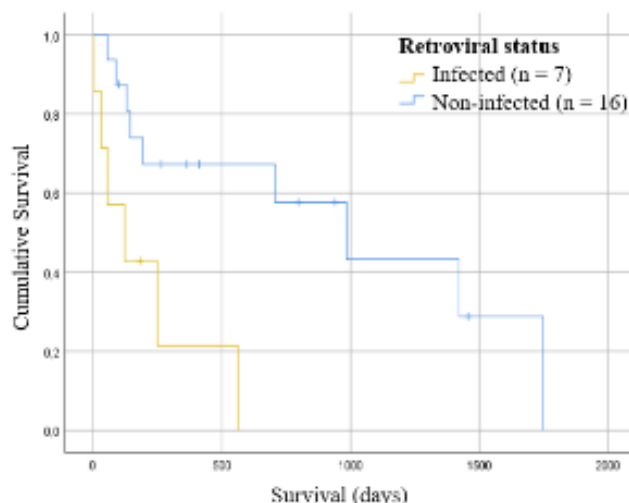


Figure 4 - Kaplan-Meier survival time stratified by retroviral status for the 23 cats.

Cats treated with chemotherapy ($n = 23$) had a MST of 250 days and a response rate of 87% ($n = 20$). Of these, patients diagnosed with alimentary lymphoma ($n = 13$) had a MST of 707 days and most of these cats (92%, $n = 12$) had LGAL. In relation to mediastinal, multicentric and nasal lymphomas, the MST was 186, 44 and 140 days, respectively. The survival of these patients, according to their responses to treatment, is shown in Figure 5.

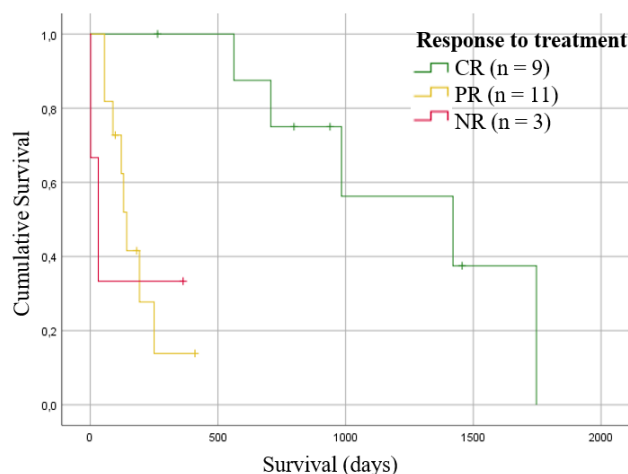


Figure 5 - Kaplan-Meier survival time stratified by response to treatment for the 23 cats.

The Log Rank test was used in order to compare the survival times between cats with different responses to chemotherapy. The MST for cats with CR to treatment (1420 days) was significantly higher compared to those with PR (143 days) (p -value = 0,000).

Regarding the seven retroviral infected cats, one had CR, four PR and two NR; while of the sixteen non-retroviral infected, eight had CR, seven PR and one NR. Using Fisher's exact test, the association between retroviral infection and the response to chemotherapy was evaluated but no correlation was found ($p = 0.209$). Considering the retroviral infected cats that responded to treatment ($n = 5$), two were FIV-positive

(one had CR and the other one had PR to treatment, both treated with recombinant feline interferon omega (rFeIFN- ω)), two were FeLV-positive (both had PR to treatment, one was treated with rFeIFN- ω) and one was positive for both retroviral infections and had PR to treatment. The only retroviral infected cat (FIV-positive) with a CR to treatment (diagnosed with LGAL) was submitted to antiviral therapy with rFeIFN- ω and had a survival time of 563 days.

3.4. Concomitant diseases

Data on infectious and non-infectious concomitant diseases have also been analyzed. This classification was based on Paulo (2019) and it is presented in Table 2. Retroviral infected cats were more affected by concomitant infectious diseases compared to non-retroviral infected, namely by Feline Respiratory Disease Complex (FRDC) (30%, $n = 8$ versus 19%, $n = 7$) and Feline Infectious Peritonitis (FIP) (7%, $n = 2$ versus 3%, $n = 1$).

Table 2 - Concomitant diseases according to retroviral infection.

Concomitant diseases	Retroviral infected (n=27)		Non-infected (n=37)		p-value
	n	%	n	%	
Abscesses/wounds	0	0	2	5,4	0,504
Other tumours	1	3,7	5	13,5	0,388
Urinary diseases	8	29,6	12	32,4	0,811
Hepatobiliary/pancreatic diseases	0	0	6	16,2	0,035
Gastrointestinal diseases	0	0	3	8,1	0,255
Ophthalmic diseases	3	11,1	3	8,1	0,691
Dermatological diseases	2	7,4	2	5,4	1,000
Cardiovascular diseases	1	3,7	3	8,1	0,632
Neurological diseases	3	11,1	3	8,1	0,691
Otitis	0	0	2	5,4	0,504
Oral cavity diseases	12	44,4	7	18,9	0,027
Anaemia	8	29,6	6	16,2	0,200
Flea infection	2	7,4	2	5,4	1,000
Other parasites	1	3,7	0	0	0,422
Toxoplasmosis	1	3,7	0	0	0,422
Mycoplasmosis	2	7,4	1	2,7	0,568
Other respiratory diseases	1	3,7	2	5,4	1,000
FRDC	8	29,6	7	18,9	0,503
FIP	2	7,4	1	2,7	0,568

Anaemia was also more frequent in retroviral infected cats in comparison to non-retroviral infected cats (30%, $n = 8$ versus 16%, $n = 6$). Oral diseases were the only variable that showed statistical significance, with a value of $p = 0.027$ in Pearson's chi-square test, meaning that the proportion of oral diseases was enhanced in retroviral infected cats (44%, $n = 12$) when compared to non-retroviral infected cats (19%, $n = 7$). Oral diseases included cats with gingivitis, stomatitis, gingivostomatitis and/or feline odontoclastic resorptive lesions were included.

Hepatobiliary/pancreatic diseases were more frequent in non-retroviral infected cats (16%, $n = 6$), in comparison to the retroviral infected ($n = 0$), with a p-value of 0.035.

4. Discussion

Most of the cats diagnosed with lymphoma were Domestic shorthair and sterilized. Alimentary lymphoma was the most common form (40%, $n = 33$), in accordance to the previous literature (Krick *et al.*, 2011; Waite *et al.*, 2013; Sato *et al.*, 2014; Collette *et al.*, 2015; Wolfesberger *et al.*, 2016). Mediastinal lymphoma, the third most observed form, was higher than reported in other studies (19%, $n = 16$) (Milner *et al.*, 2005; Hadden *et al.*, 2008; Krick *et al.*, 2011; Krick *et al.*, 2013; Collette *et al.*, 2015).

In the present study, the median age of the 64 cats was 8,5 years. A clear bimodal age distribution was observed, with a peak around 1-3 years and a second peak around 13-15 years. It was possible to distinguish the group of younger cats, aged less than 4 years, which were mostly retroviral infected (70%, $n = 14$) and diagnosed with mediastinal lymphoma (55%, $n = 11$) from the group of older cats, aged more than 13 years, in which few were infected (21%, $n = 4$) and mostly were diagnosed with alimentary lymphoma (58%, $n = 11$).

The proportion of retroviral infected cats receiving chemotherapy (26%, $n = 7$) was lower compared to those non-retroviral infected (46%, $n = 17$). In addition, the proportion of retroviral infected cats that did not receive any treatment (44%, $n = 12$) was higher when compared to cats non-retroviral infected (24%, $n = 9$). Although this differences were not statistically significant, results suggested a trend were cats with lymphoma and without retroviral infection are more likely to undergone chemotherapy.

Twenty-seven cats (42%) were found to be retroviral infected and this prevalence was higher when compared to other studies (Kristal *et al.*, 2001; Teske *et al.*, 2002; Patterson-Kane *et al.*, 2004; Milner *et al.*, 2005; Hadden *et al.*, 2008; Taylor *et al.*, 2009; Waite *et al.*, 2013; Sato *et al.*, 2014; Collette *et al.*, 2015). Probably, this higher proportion of retroviral infection is due to lower numbers of correctly vaccinated cats for FeLV (5%, $n = 3$).

Regarding the FeLV positive cats ($n = 23$), 43% ($n = 10$) were diagnosed with mediastinal lymphoma and 35% ($n = 8$) with multicentric lymphoma. These anatomic lymphoma forms were the most associated with FeLV (Weiss *et al.*, 2010).

Before the widespread of FeLV vaccination in the 1980s, more than 70% of cats with lymphoma were FeLV positive and the mediastinal lymphoma was a common anatomic presentation, accounting for 20-40% of cases in the USA and 10-50% of cases in the UK (Fabrizio *et al.*, 2014). The implementation of vaccination programs resulted in a significant decrease in the prevalence of FeLV infection and, consequently, in the proportion of cases that are associated, namely mediastinal lymphoma. In the present study, the proportion of retroviral infected cats that were diagnosed with mediastinal lymphoma was considerably higher in comparison to other studies (Louwerens *et al.*, 2005; Taylor *et al.*, 2009). This difference is probably due to the ineffectiveness of the

control and eradication of feline retroviral infections in Portugal, since studies by Studer and collaborators (2019) revealed a prevalence of FeLV infection in Portugal of 8.8% and a vaccination rate against this infection of 14.2%, comparing for example with the UK, which had a prevalence of infection of 0.7% and a vaccination rate of 81.5%. Probably, our results showing a higher proportion of mediastinal lymphoma may be related to the higher prevalence of FeLV-infection in Portugal, as this is an oncogenic retrovirus often associated with this anatomic form of lymphoma.

Comparing the results of our study with others suggest that the current situation in Portugal is more similar to the situation in the UK, Austria, the Netherlands, USA, Japan, among others, prior to the implementation of vaccination programs. A Brazilian study conducted in one hundred and twenty-five cats (Leite-Filho *et al.*, 2020) revealed an enhanced proportion of cats with mediastinal lymphoma (28%) and FeLV infection (52%). These results are closer to our results, which is probably due to the fact that Brazil also has an enhanced prevalence of cats with retroviral infection, reaching values of 10.1% for FeLV and 31% for FIV in some areas (Costa *et al.* 2017). This prevalence is probably associated with the ineffectiveness of the control and prophylaxis for feline retroviruses, through vaccination, diagnostic tests and control of infected cats.

Variables like sex, breed and fertility status revealed no relation to the survival.

Retroviral infection was shown to be a prognostic indicator, as cats diagnosed with lymphoma and retroviral infection (MST of 16 days) had a significantly lower median survival compared to those non-retroviral infected (MST of 131 days). The second survival analysis, performed only in cats that received chemotherapy (n = 23), confirmed these results, showing also a significant lower survival rate in retroviral infected cats (MST of 122 days) in comparison to patients without retrovirus (MST of 984 days). These results confirmed studies from other countries before FeLV eradication (Mooney *et al.*, 1989; Vail *et al.*, 1998), as well as the studies from countries where the retroviral prevalence is similar to Portugal, such as Brazil (Leite-Filho *et al.* 2020).

Cats that undergone chemotherapy (n = 23) had a higher response rate to treatment (87%, n = 20), with a MST of 250 days. Cats diagnosed with alimentary lymphoma, mostly with LGAL, had the highest median survival (MST of 707 days), followed by cats with nasal lymphoma, which had a MST of 140 days.

As in other studies (Vail *et al.*, 1998; Teske *et al.*, 2002; Milner *et al.*, 2005; Taylor *et al.*, 2009; Moore *et al.*, 2013; Waite *et al.*, 2013; Fabrizio *et al.*, 2014; Gustafson *et al.*, 2014; Finotello *et al.*, 2017), the response to treatment was confirmed as a prognostic indicator. Cats that achieved a CR to treatment had a longer survival time (MST of 1420 days) when compared to patients that achieve a PR (MST of 143 days).

Regarding the retroviral infected cats that undergone chemotherapy (n = 7), five responded (4

PR and 1 CR) to treatment and three of which were submitted to antiviral therapy, namely with rFeIFN- ω . The only retroviral infected cat with CR to treatment, diagnosed with LGAL, was submitted to antiviral therapy with rFeIFN- ω and had a survival time of 563 days. Despite the low number of patients, these results may suggest the benefits of chemotherapy in cats diagnosed with lymphoma and retroviral infection, although more studies are needed.

Regarding the analysis of concomitant diseases, this study demonstrated that cats diagnosed with lymphoma and retroviral infection are more likely to develop oral diseases, such as gingivitis, stomatitis, gingivostomatitis and/or feline odontoclastic resorptive lesions (44%, n = 12), in comparison to those without retroviral infection (19%, n = 7). This result is compatible with the literature, which presents this disease as one of the complications most often associated with FeLV and/or FIV infection (Sykes 2014; Studer *et al.*, 2019).

The limitations of our study were primarily attributed to its retrospective nature. It was not possible to access some clinical data, as well as the remaining follow-up of several individuals. In addition, the classification of feline lymphomas has changed over the years and some authors are not consistent with each other. Finally, one of the major limitations of this study was the low number of cases, particularly of some anatomic forms of lymphoma, like CNS lymphoma, and patients with FIV infection.

In conclusion, the present study demonstrated that the alimentary form of feline lymphoma is the most common form followed by the multicentric and mediastinal forms at Lisbon, Portugal. In opposition to what is observed in other countries, where effective control and prophylaxis of retroviral infections have been implemented in domestic cats, in Portugal the proportion of retroviral infected cats remains high. Retroviruses play an important role in the development of lymphoma in cats, particularly in the mediastinal form due to FeLV infection.

Beyond the response to treatment, retroviral infection is also a prognostic indicator for feline lymphoma. Retroviral infected cats have shorter survival times, possibly due to non-lymphomatous changes associated with retroviruses, such as oral diseases. Nevertheless, this study suggests that the option for chemotherapy treatment is also advantageous in retroviral infected cats.

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