# Evaluation of the modified Glasgow Prognostic Score to predict outcome in dogs with newly diagnosed lymphoma

**Abbreviated title: mGPS in canine lymphoma.**

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Key words:

**Biomarker, C-reactive protein, albumin, survival time, canine, lymphosarcoma**

## Abstract

The modified Glasgow Prognostic Score (mGPS) assigns a numerical value (0-2) from pre-treatment serum concentrations of C-reactive protein (CRP) and albumin to predict patient outcome. CRP and albumin were evaluated in 77 untreated dogs with lymphoma to determine the relationship of mGPS to clinicopathological parameters and whether it could predict progression-free (PFS) and overall survival (OS) in treated dogs. mGPS distribution was significantly associated with clinical stage, substage b, weight loss, gastro-intestinal disturbances and lethargy at presentation. On univariate analysis, mGPS was significantly associated with OS and PFS, with shorter median survival times for mGPS 2 compared to mGPS 0 and 1 combined. Hypoalbuminaemia significantly reduced OS and PFS, however increased CRP had no effect. Only clinical stage was significantly associated with OS and PFS on both univariate and multivariate analysis. mGPS has potential prognostic value for canine lymphoma , but further studies are needed.

## Introduction

Lymphoma is the most common haemopoietic tumour in dogs, accounting for 83% of all such malignancies in this species.[1] Classification of the disease by cell morphology, lineage and histological grade using the most recent human World Health Organisation (WHO) system defines similar B and T cell, low and high grade subtypes to those in humans.[2] Diffuse large B cell lymphoma (DLBCL) is the most common subtype in both species making the dog a useful comparative model for human non-Hodgkin lymphoma (NHL).[2, 3]

The prognosis for canine lymphoma depends on both histopathological and clinical features. High grade disease and T cell immunophenotype are often associated with poor prognosis although low grade T cell lymphomas also occur. [4-6] Expression of class II major histocompatibility complex and high Ki67 are also negative prognostic indicators along with clinical features such as higher WHO clinical stage, substage b, some anatomic locations and the presence of hypercalcaemia.[7-11] Different subtypes of lymphoma respond variably to combination chemotherapy protocols with widely ranging survival times and disease-free intervals, but a poor response to chemotherapy is considered to be a negative prognostic indicator.[8] Prior treatment with steroids also negatively affects prognosis.[12]

Pre-treatment blood parameters that have been explored as prognostic biomarkers in canine lymphoma include haematocrit [13], thymidine kinase [14], and serum lactate dehydrogenase.[15] Serum acute phase proteins (APPs) are widely used as biomarkers in the diagnosis and prognosis of human lymphoid neoplasia, particularly C-reactive protein (CRP), a positive APP that is increased by interleukin-6 (IL-6) and

elevated in human patients with NHL.[16, 17] CRP is increased in untreated dogs with lymphoma and has potential as a highly sensitive but non-specific serum biomarker.[18-20] Albumin is a negative APP that decreases in response to inflammation, injury and disease. Hypoalbuminaemia correlates strongly with the systemic inflammatory response and weight loss in human cancer patients and is associated with reduced complete remission (CR) rate and survival time in NHL.[21, 22] Hypoalbuminaemia is also reported in canine lymphoma and is associated with shorter remission and survival time.[12, 23]

In human medicine, combined use of several serum biomarkers is considered preferable to a single biomarker in isolation. In human solid cancers including lymphoma, scoring systems which combine serum biomarkers of systemic inflammation (for example the international prognostic index (IPI), prognostic nutritional index (PNI), neutrophil lymphocyte ratio (NLR), and the Glasgow Prognostic Score/modified Glasgow Prognostic Score (GPS/mGPS)) are used to predict prognosis, guide treatment decisions and improve patient outcomes.[24-30] In contrast, no veterinary prognostic scoring systems are currently in routine use for canine lymphoma, Although one study evaluated NLR in 77 dogs with multicentric lymphoma, it was not found to be of prognostic value.[31]

Of the above prognostic scores, GPS and mGPS (based on CRP and albumin concentrations), are reliable independent prognostic factors in human lymphoid neoplasia [26-29, 32] and we hypothesised that they may also be useful for canine lymphoma patients. Both scoring systems assign a score of 0 (when both parameters are within normal range), or 2 (both outside normal range). In the GPS, a

score of 1 can be given for either low albumin or high CRP, however, with mGPS a score of 1 is only assigned for high CRP (normal albumin) and a patient with hypoalbuminaemia but normal CRP is given a score of 0 to reflect the observation that hypoalbuminaemia without elevated CRP is rare and is not necessarily associated with poor survival.[32, 33] mGPS rather than GPS may therefore be of more relevance for some tumour types. [33]

The aims of this study were to assign an mGPS to an untreated cohort of dogs with lymphoma, investigate how these related to patient clinicopathological characteristics and determine whether mGPS provided prognostic information in dogs that were treated with chemotherapy.

## Materials and Methods

This prospective study was performed with full ethical approval from the department of Ethics and Welfare, University of Glasgow with owner consent obtained for retention of spare serum for CRP analysis. Albumin was assayed in the biochemical screen for diagnostic purposes.

### *Dogs*

One-hundred and seventy-five dogs with lymphoma that were presented to the University of Glasgow's Small Animal Hospital between 2004 and 2010 were eligible for recruitment onto the study. Inclusion criteria included dogs with a cytological or histopathological diagnosis of lymphoma with excess serum obtained prior to treatment, no concurrent infectious or active inflammatory disease, no previous treatment of lymphoma with surgery or chemotherapy and no steroid treatment in the last 7 days prior to referral. Diagnosis was confirmed by cytology, histopathology, or

both, and where possible immunophenotyping was performed using antibodies against CD3 (T cell) and CD79a (B cell) on cytology or histology slides. Where possible for the final cohort of dogs, histology and cytology slides were obtained for retrospective review using the WHO classification [2] and the Updated Kiel classification respectively.[34] Clinical staging was performed on all dogs including complete blood count, biochemistry analysis, abdominal ultrasonography and thoracic radiography. Computed tomography (CT) was performed when clinically appropriate. Splenic and hepatic cytology, bone marrow evaluation, and urinalysis (including urine protein and creatinine ratio) were performed when deemed clinically important and when client finances permitted. Chemotherapy treatment with a 25 week CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) multidrug protocol [35] was offered as the first line treatment to most dogs with high grade lymphoma. Some dogs received a modified version of this standard CHOP protocol (eg no L-asparaginase, substitution for doxorubicin if heart disease present), a different chemotherapy protocol or just prednisolone depending on lymphoma grade, owner finances and other patient/owner factors.

***Samples***

**CRP:** 1-2 ml of whole blood was collected by jugular venepuncture into plain serum tubes (Sarstedt AG) as surplus to that required for routine staging. Blood was allowed to clot for approximately 2 hours at room temperature then separated by centrifugation (Minispin Eppendorf AG) at 9,000 rpm for 3 minutes. A minimum of 200 µl serum was harvested and frozen at -70°C for analysis at a later date. CRP was measured using a latex-enhanced immunoturbidimetric assay (Pentra 400, Horiba ABX, UK) by batch analysis to reduce inter-assay variability. This assay was

validated to have a low within-run imprecision and intra-assay coefficients of variance (n=12) of 0.5% and 1.2% at mean control values of 4 mg/l and 30 mg/l of CRP respectively. This assay also has an acceptable between-run imprecision with inter-assay coefficients of variance (n=12) of 4.8% and 8.5% at mean control values of 4 mg/l and 30 mg/l of CRP respectively. A serum CRP concentration range of 0-10 mg/l was deemed normal based on previous findings by Eckersall *et al* (1989).[36]

**Albumin:** 1.2ml of whole blood was collected by jugular venepuncture into lithium heparin tubes (International Scientific Supplies Ltd) and routine laboratory measurements of plasma albumin concentration were carried out on a chemistry immuno-analyser (AU640, Olympus, USA). The coefficient of variation for this method, over the range of measurement, was less than 5% as established by routine quality control measures. The laboratory reference for plasma albumin concentration was 29-36 g/l.

**Assigning a Glasgow Prognostic Score and modified Glasgow Prognostic Score:**

Dogs were assigned an mGPS score of 0, 1 or 2 as follows: dogs with both elevated CRP concentration (>10 mg/l) and hypoalbuminaemia (<29 g/l) were assigned mGPS 2, dogs with elevated CRP but normal albumin were assigned mGPS 1 and dogs with both normal CRP and low or normal albumin concentration were assigned mGPS 0.

***Statistics***

Associations between mGPS and clinicopathological features (other than CRP and albumin) were assessed for all dogs using contingency table analysis with the chi-squared test. Continuous variables were analysed after grouping above/below their

normal threshold (calcium) or as 3 groups (age, see below). The influence of mGPS and other clinical variables on progression free and overall survival was performed in two groups of patients: Group 1 comprised all dogs that had received treatment i.e. chemotherapy protocol or steroids-only (n=70) and Group 2 comprised dogs treated first line with a CHOP-based protocol (n=55) to remove the confounding effect of other treatment protocols on survival. Univariate regression analysis was performed using the Cox proportional hazard (Cox PH) model to determine the relationship between patient characteristics including mGPS and survival. Hazard ratios (HR) are presented with their 95% confidence interval (CI). All clinicopathological variables with a p value ≤ 0.1 were included in the final multivariate backward stepwise regression model and variables were removed from the model when p≥ 0.1. To increase group sizes and statistical power for the final analysis, mGPS 0 and 1 (mGPS 0+1) were combined and compared to mGPS 2, WHO stage II-IV were combined and compared to stage V, and age 0-3 and >3-7 years were combined and compared to > 7 years. Progression-free survival (PFS) was defined as the period from first day of treatment to day of progression or relapse of disease. Dogs were censored at date of last known follow-up or at statistical analysis if progression had not been reached. Overall survival (OS) was defined as the time from first day of treatment to day of death and dogs were censored as described for PFS. Univariate survival analysis was also performed on all categorical variables using the Kaplan-Meier (KM) method, and differences were assessed by means of the log-rank test. Median survival times for PFS and OS are presented with their 95% CI. The median values for clinicopathological characteristics are presented with their interquartile range (IQR). Analyses were performed using SPSS Statistics Version 22 (IBM Corp., UK). Statistical significance was set at p ≤0.05.

## Results

Seventy-seven dogs fulfilled the inclusion criteria. Twenty-four breeds were represented, the most common being Labrador Retrievers (14 [18%]), Boxers (7 [9%]), Bullmastiffs (6 [8%]), Golden Retrievers (5 [6%]) and German Shepherd Dogs (5 [6%]). Thirteen dogs (17%) were crossbreeds. The median age of the dogs at diagnosis was 7.3 years (IQR 3.1). Fifty-three dogs (69%) were male (30 entire, 23 neutered) and 24 dogs (31%) were female (9 entire, 15 neutered).

Sixty-five dogs (84%) had high grade and 12 (16%) had low grade lymphoma. Immunophenotyping was performed for 70 dogs: 34 (44%) were B cell and 36 (47%) were T cell. Pathology review was possible for 50 dogs (5 histology, 45 cytology); the most common WHO classification was T cell high grade anaplastic large cell lymphoma (4/5 dogs) and the most common updated Kiel classification was B cell high grade centroblastic polymorphic lymphoma (17/45 dogs). Two dogs (4%) were stage II, 15 (19%) were stage III, 28 (36%) were stage IV, and 31 (40%) were stage V. Fifty-four dogs (70%) were classified as WHO substage b, and 23 (30%) were classified as substage a. The most common presenting signs were gastrointestinal (GI) disorders including inappetance, anorexia, vomiting, diarrhoea, and haematochezia (37 [48%]), lethargy (27 [35%]), weight loss (24 [31%]), polyuria and polydipsia (PU/PD; 13 [17%]), and pyrexia (5 [7%]). At presentation, 10 dogs (13%) were hypercalcaemic (>3mmol/l).

Of the 77 dogs, 7 (9%) received no treatment, 5 (6%) were treated with prednisolone only, and 65 (83%) were treated with a multi-drug chemotherapy protocol (55 with a CHOP-based protocol, 4 with a lomustine-based protocol, 5 with a COP (vincristine, cyclophosphamide and prednisolone) protocol, and 1 with chlorambucil and prednisolone). Of the 51 dogs that relapsed, 11 (22%) were given no further treatment, 2 (4%) were treated with prednisolone only, and 38 (74%) went onto receive a rescue chemotherapy protocol (15 with a CHOP-

based protocol, 11 with a lomustine-based protocol, 10 with single agent L-asparaginase, 1 each with single-agent doxorubicin and cyclophosphamide). The median PFS (using the KM method) for all treated dogs (Group 1, n= 70) was 91 days (95% CI 60-122 days) and for CHOP treated dogs (Group 2, n=55) was 115 days (95% CI 58-172 days). Seventy-four out of 77 dogs (96%) died/were euthanased during the study period, 70 of which were directly related to the lymphoma or treatment, and 4 dogs died of intercurrent diseases whilst lymphoma was in complete remission (1 osteosarcoma, 1 primary immune-mediated thrombocytopenia, 2 cardiac disease). No dogs were lost to follow-up and 3 dogs (4%) remained alive at the end of the study period. The median OS for Group 1 was 214 days (95% CI 136-292 days) and for Group 2 was 232 days (95% CI 160-304 days). The percentage of all treated dogs surviving to 6, 12 and 24 months was 56%, 30% and 13% respectively.

Pre-treatment serum CRP concentration ranged from 0.4-273.7 mg/l and was elevated in 65 dogs (84%) with a median concentration of 34.7 mg/l (IQR 45.4). Six dogs were outliers with markedly elevated CRP concentrations (136, 171.5, 174.7, 184.9, 198.1 and 273.7 mg/l). No common clinicopathological features were shared by outlying dogs. Pre-treatment albumin concentration ranged from 10-36 g/L with a median concentration of 29 g/L (IQR 5.5). Thirty-seven dogs were hypoalbuminaemic (< 29 g/L); 14 dogs had severe hypoalbuminaemia (≤24 g/l), and 2 were outliers with albumin concentrations of 10 and 15 g/l. All dogs with severe hypoalbuminaemia were WHO stage IV or V and substage b (all presented with GI signs or weight loss). Both outliers had a high grade T cell lymphoma. Other possible causes of severe hypoalbuminaemia such as reduced production due to liver dysfunction or direct loss due to a protein-losing nephropathy/enteropathy were investigated but in all cases the hypoalbuminaemia was directly attributable to the lymphoma.

Following allocation of prognostic score, 11 dogs (14%) were mGPS 0, 29 (38%) were mGPS 1 and 37 (48%) were mGPS 2. All mGPS 1 dogs had elevated CRP and normal albumin. Differences in mGPS according to patient clinicopathological characteristics are

shown in Table 1. For the 77 dogs at initial presentation, WHO stage (p=0.002) and substage (p=0.02) differed significantly across the mGPS groups with a trend towards advancing stage and substage b with increasing mGPS score. In agreement with substage b distribution, weight loss, GI disturbances and lethargy at presentation were significantly differently distributed (p = 0.007, <0.001 and 0.01 respectively) with more frequent occurrence as the mGPS score increased.

To test which variables influenced OS, univariate regression analysis using the Cox PH model was carried out. Dogs with mGPS 2 were at increased risk of death when compared to mGPS 0+1 regardless of treatment protocol (Group 1 :HR 0.445 [95% CI 0.268-0.740], p=0.002; Group 2 :HR 0.525 [95% CI 0.299-0.922], p=0.025), however, the significant effect of mGPS on OS by univariate analysis was lost on multivariate analysis (Table 2 and 3). Albumin was also negatively associated with OS when looking at all treated dogs (Group 1: HR 0.923 [95% CI 0.868-0.981], p=0.010), however despite there being a similar trend, significance was lost when the CHOP-based group were analysed. CRP showed no significant association with OS in any analysis. Univariate KM survival analysis using the log-rank test indicated that dogs with mGPS 2 had significantly shorter median OS times compared to dogs with mGPS 0+1 (p= 0.001 and 0.022 for Groups 1 and 2 respectively, Figure 1,Table 4). While low albumin as a single biomarker showed a similar negative effect on OS (p= 0.001 and 0.022 for Groups 1 and 2 respectively, Figure 2, Table 4), elevated CRP did not significantly influence OS. The percentage of Group 1 dogs with mGPS 0+1 and mGPS 2 surviving to 6, 12 and 24 months was 71% and 38%, 45% and 13%, and 18% and 6% respectively.

Other variables affecting OS on Cox PH included WHO stage (Group 1 and 2; p= 0.004 and 0.015 respectively) and immunophenotype (Group 2 only, p=0.004) with both retaining significance within the final multivariate model (Tables 2 and 3). Pyrexia at time of initial presentation was also significant in the final multivariate model for Group 1 (Table 2). Consistent with the regression analysis, KM analysis (Table 4) indicated shorter OS times for

dogs that were WHO Stage V compared to II-IV (p= 0.003 and 0.013 for Groups 1 and 2 respectively) and, T cell compared to B cell immunophenotype (p=0.003, Group 2 only).

Univariate analysis of PFS using Cox PH (Tables 2 and 3) showed a significant difference in the risk of disease progression when comparing mGPS 0+1 to mGPS 2 in Group 1 (HR 0.573 [95% CI 0.347-0.946, p=0.029) and significance was also approached in Group 2 (p=0.058), however, mGPS was not significant in the final multivariate model for either group. KM survival analysis confirmed that mGPS significantly affected PFS in Group 1 ((p=0. 027, Figure 3) and approached significance in Group 2 (p=0.055). Similarly hypoalbuminaemia significantly affected PFS in Group 1 (p= 0.027, Figure 3) and approached significance for Group 2 (p=0.055) whereas CRP had no effect in Group 1 and could not be compared in Group 2 because of small sample size. Other significant variables influencing PFS on univariate regression analysis (Tables 2 and 3) were WHO stage (p= 0.024 and 0.037 for Groups 1 and 2 respectively), immunophenotype in Group 1 and 2 (p= 0.029and 0.004 respectively) and pyrexia at presentation (no pyrexia compared to pyrexia, Group 1, p=0.049). Significant differences in median PFS were also seen using the KM log-rank test (Table 4) in Group 1 and Group 2 for WHO stage (p= 0.022 and 0.034 respectively) , immunophenotype (p= 0.027 and 0.003 respectively) and pyrexia (p= 0.044, Group 1 only). Within the final multivariate model WHO Stage (Group 1 and Group 2), and immunophenotype (Group 2 only) retained significance with pyrexia also reaching significance for Group 1 (Tables 2 and 3).

**Discussion:**

This is the first study evaluating the use of the modified GPS in dogs with lymphoma. Although the population of dogs was comparable to other studies on canine lymphoma with respect to age, breed, stage, and percentage of hypercalcaemic cases, the ratio of males to females was approximately 2:1, there were more substage ‘b’ cases, and the ratio of B:T cell

tumours was approximately equal rather than predominantly B cell.[5] While some studies have also found higher proportions of males, [8, 11] others have reported more females. [9] The higher proportion of T cell cases may reflect the higher number of substage 'b' cases, and slightly shorter PFS (2-4 months) and OS (5-10 months) for the treated animals compared to other studies.[4, 7]

After assigning mGPS, only 14% of dogs had normal CRP and albumin (score 0), with almost half (48%) having changes in both CRP and albumin (score 2). In human lymphoma cohorts, the proportion of patients with mGPS 0 is often larger, ranging from 30.4% [29] in HIV patients with NHL to 71.5% in the DLBCL subtype. [26] mGPS distribution amongst the population differed significantly with increasing stage and substage b and with specific clinical signs such as weight loss, lethargy and GI disturbances. These findings are consistent with the expected alterations in the APP, albumin and CRP, which would occur non-specifically in inflammatory conditions producing such clinical signs or with increased tumour burden. An association between more adverse clinical characteristics and mGPS/GPS has been reported in human extranodal NK/T cell lymphoma [28] and DLBCL. [26]

mGPS score predicted survival of dogs with lymphoma as seen by the percentage of mGPS 2 dogs alive at 12 (13%) or 24 (6%) months which was approximately a third of that for dogs with mGPS score 0 or 1 (45% and 18% for 12 and 24 months respectively). This was confirmed by the evaluation of mGPS as a prognostic indicator using either Cox PH regression or Kaplan–Meier analysis, which showed that mGPS 2 was significantly associated with OS and PFS for treated dogs, but this was only for univariate and not multivariate analysis. High mGPS is an independent negative prognostic indicator of OS in human extranodal natural killer/T-cell lymphoma,[28] DLBCL[26] and HIV infected NHL, [29] however the association with PFS is less clear. [26, 28] Only clinical WHO stage and immunophenotype (Group 2) retained significance for OS and PFS in both univariate and multivariate models, indicating their stronger influence on outcome. Both stage [8, 12] and immunophenotype [4, 5, 7] have been previously reported as prognostic indicators for canine

lymphoma. Although pyrexia at presentation had significant association with OS and PFS for Group 1 treated dogs (multivariate analysis), it is not clear if this association would be maintained in a larger cohort of dogs. [7-9]

When the individual APP used to produce the mGPS were evaluated, CRP concentration did not have any significant association with OS or PFS, however hypoalbuminaemia significantly shortened OS and PFS for all treated dogs, suggesting this has the greatest influence on the prognostic score. The lack of significance on OS and PFS for dogs treated with a CHOP-based protocol may reflect the smaller number of dogs in this group. The finding that mGPS affects OS more consistently than either of the APP used to calculate it supports the conclusion that prognostic scoring using multiple patient parameters may be more beneficial than using isolated patient parameters alone. Although CRP concentration has prognostic significance for human lymphoma in numerous studies, [16, 17, 37] this has not yet been reported for canine lymphoma. There are fewer reports in the literature regarding albumin concentration and human lymphoma, although one study reported hypoalbuminaemia in 43% of NHL patients. [38] Hypoalbuminaemia was identified as a poor prognostic indicator in very old patients with NHL [39] and mucosa–associated lymphoid tissue lymphoma (MALT) [40] and was predictive of ability to achieve complete response in AIDS-related NHL. [41] Significantly lower albumin concentrations have been reported in dogs with lymphoma compared to controls in a previous small study,[42] and hypoalbuminaemia reduces remission and survival time in canine lymphoma patients. [12, 23] Although albumin may decline as part of the systemic inflammatory response, additional factors can contribute to hypoalbuminaemia such as reduced protein intake or starvation, [43] reduced production as in severe liver disease,[44] as well as losses through the GI tract [45] or kidneys. [46] In all cases in this study, however, hypoalbuminaemia was directly attributable to the lymphoma itself even for the outliers with very low albumin.

The main limitation of this study is the number of dogs that could be included. CRP is not currently considered part of a routine minimum clinical database and as such only those cases where spare serum was harvested were included in the final analysis. In addition the majority of presenting dogs were mature adults with concurrent inflammatory conditions or diseases and were therefore excluded from the study. Numbers were further reduced for statistical analysis when dogs were divided according to clinicopathological characteristics or treatment protocols etc. making some groups too small for statistical analysis to be carried out or prone to type II error. Larger numbers within each group would increase the statistical power to detect differences within the multivariate analysis.

## Conclusion

The mGPS was related to both stage and substage in 77 dogs with lymphoma presented to an oncology referral service, with more mGPS 2 dogs having higher stage and substage b disease. mGPS 2 was associated with reduced OS and PFS on univariate but not multivariate analysis. Although the association with OS and PFS may not be as strong as the effect of WHO stage or immunophenotype, routine measurement of CRP as well as albumin to allow mGPS assignment may provide additional prognostic information in canine lymphoma and appears more useful than each APP on its own. The additional cost of assays, however, should be balanced against the finding that mGPS was not an independent prognostic marker in this study.

## Acknowledgement

The authors thank ReactivLab Ltd (now Avacta Animal Health Ltd) for funding CRP assays and clinical staff at Glasgow University Small Animal Hospital for sample collection and processing, especially Shona Munro.

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Table 1: Relationship of mGPS score to clinicopathologicial characteristics in 77 dogs with untreated lymphoma

| | **mGPS 0** ***n* (%)** | **mGPS 1** ***n* (%)** | **mGPS 2** ***n* (%)** | **χ2** ***p-value*** |
|---|---|---|---|---|
| **Total (*n* = 77)** | 11 (14) | 29 (38) | 37 (48) | |
| **Age (years)** | | | | 0.26 |
| **0-3** | 0 | 4 (14) | 2 (5) | |
| **>3-7** | 5 (36) | 12 (41) | 10 (27) | |
| **>7** | 6 (64) | 13 (45) | 25 (68) | |
| **Sex** | | | | 0.17 |
| **Male** | 5 (6) | 22 (29) | 26 (34) | |
| **Female** | 6 (8) | 7 (9) | 11 (14) | |
| **Reproductive Status** | | | | 0.56 |
| **Entire** | 7 (9) | 13 (17) | 19 (25) | |
| **Neutered** | 4 (5) | 16 (21) | 18 (23) | |
| **Breed** | | | | 0.45 |
| **Pedigree** | 10 (13) | 23 (30) | 33 (43) | |
| **Crossbreed** | 1 (1) | 6 (8) | 4 (5) | |
| **Grade** | | | | 0.93 |
| **High** | 9 (82) | 25 (86) | 31 (84) | |
| **Low** | 2 (18) | 4 (14) | 6 (16) | |
| **Immunophenotype** | | | | 0.20 |
| **B cell** | 5 (46) | 17 (59) | 12 (32) | |
| **T cell** | 5 (46) | 11 (38) | 20 (54) | |
| **WHO Stage** | | | | **0.002** |
| **II-III** | 6 (54) | 10 (35) | 2 (5) | |
| **IV** | 1 (10) | 12 (41) | 15 (41) | |
| **V** | 4 (36) | 7 (24) | 20 (54) | |
| **WHO Substage** | | | | **0.02** |
| **a** | 7 (64) | 10 (35) | 7 (19) | |
| **b** | 4 (36) | 19 (65) | 30 (81) | |
| **Presenting signs** | | | | |
| **Weight loss** | 0 | 2 (3) | 12 (16) | **0.007** |
| **GI disturbances** | 0 | 11 (14) | 26 (34) | **<0.001** |
| **Lethargy** | 0 | 9 (12) | 18 (23) | **0.01** |
| **Pyrexia** | 2 (3) | 0 | 3 (4) | 0.32 |
| **PU/PD** | 1 (1) | 6 (8) | 6 (8) | 0.67 |
| **Calcium (mmol/l)** | | | | 0.06 |
| **≤ 3.0** | 11 (100) | 22 (76) | 34 (92) | |
| **> 3.0** | 0 | 7 (24) | 3 (8) | |
| **Albumin (g/l)** | | | | NA |
| **≥ 29** | 11 (100) | 29 (100) | 0 | |
| **< 29** | 0 | 0 | 37 (100) | |
| **CRP (mg/l)** | | | | NA |
| **≤ 10** | 11 (100) | 0 | 0 | |
| **> 10** | 0 | 29 (100) | 37 (100) | |

NA – not applicable to perform chi-squared analysis on albumin and CRP as the mGPS score is constructed using these variables

Table 2. The relationship between clinicopathological factors and survival using the Cox proportional hazards model in all dogs with lymphoma that received treatment (Group 1, n=70)

| | | PFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Univariate | | Multivariate | | Univariate | | Multivariate | |
| **Variable** | **N** | **HR (95% CI)** | ***p*** | **HR 95% CI** | **p** | **HR (95% CI)** | ***p*** | **HR 95% CI** | ***p*** |
| **Age (0-7 years / >7 years)** | 29 / 41 | 0.728 (0.436-1.217) | 0.221 | | | 0.783 (0.471-1.300) | 0.344 | | |
| **Sex (Female / Male)** | 21 / 49 | 1.155 (0.682-1.956) | 0.595 | | | 0.969 (0.571-1.644) | 0.907 | | |
| **Reproductive status (Entire / Neutered)** | 34 / 36 | 0.853 (0.525-1.387) | 0.522 | | | 1.014 (0.623-1.652) | 0.955 | | |
| **Breed (Pedigree / Crossbreed)** | 57 / 13 | 0.922 (0.490-1.733) | 0.800 | | | 0.920 (0.489-1.732) | 0.796 | | |
| **Grade (Low / High)** | 12 / 58 | 1.128 (0.600-2.123) | 711 | | | 1.025 (0.548-1.919) | 0.938 | | |
| **Immunophenotype (B Cell / T cell)*** | 33 / 32 | **0.563 (0.337-0.942)** | **0.029** | NA | 0.162 | 0.617 (0.372-1.026) | 0.063 | NA | 0.331 |
| **WHO Stage (II-IV / V)** | 42 / 28 | **0.569 (0.348-0.930)** | **0.024** | **0.454 (0.266-0.775** | **0.004** | **0.477 (0.290-0.785)** | **0.004** | **0.387 (0.217-0.690)** | **0.001** |
| **WHO Substage (a / b )** | 24 / 46 | 1.034 (0.619-1.727) | 0.898 | | | 0.795 (0.479-1.319) | 0.374 | | |
| **Presenting signs (Not present / Present)** | | | | | | | | | |
| **Weight Loss** | 57 / 13 | 0.621 (0.337-1.146) | 0.128 | | | 0.582(0.312-1.083) | 0.088 | NA | 0.856 |
| **GI signs** | 41 / 29 | 1.143 (0.696-1.879) | 0.597 | | | 1.015 (0.617-1.670) | 0.954 | | |
| **Lethargy** | 46 / 24 | 1.202 (0.719-2.010) | 0.483 | | | 0.972 (0.581-1.625) | 0.913 | | |
| **Pyrexia** | 60 / 10 | **2.136 (1.002-4.554)** | **0.049** | **2.532 (1.148-5.581)** | **0.021** | 2.077 (0.978-4.412) | 0.057 | **2.283 (1.017-5.125)** | **0.045** |
| **PUPD** | 57 / 13 | 0.918(0.499-1.687) | 0.782 | | | 0.760 (0.411-1.404) | 0.380 | | |
| **Calcium nmol/L** | 70 | 0.941 (0.565-1.569) | 0.816 | | | 0.914 (0.516-1.620) | 0.759 | | |
| **Albumin g/L** | 70 | **0.936 (0.877-0.999)** | **0.047** | NA | 0.490 | **0.923 (0.868-0.981)** | **0.010** | NA | 0.844 |
| **CRP mg/L** | 70 | 1.001 (0.995-1.007) | 0.715 | | | 1.002 (0.997-1.008) | 0.423 | | |
| **mGPS (Score 0+1 / Score 2)** | 38 / 32 | **0.573 (0.347-0.946)** | **0.029** | NA | 0.379 | **0.445 (0.268-0.740)** | **0.002** | 0.612 (0.351-1.067) | 0.084 |

The reference category for each variable is the first grouping in parentheses unless otherwise stated.

*Unknown immunophenotype for some patients, n=65

NA – not applicable

HR – Hazard ratio, 95% CI – 95% confidence interval

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Table 3. The relationship between clinicopathological factors and survival using the Cox proportional hazards model in all dogs with lymphoma that received treatment with the CHOP chemotherapy protocol (Group 2, n=55)

| | | PFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Univariate | | Multivariate | | Univariate | | Multivariate | |
| **Variable** | **N** | **HR (95% CI)** | ***p*** | **HR 95% CI** | **p** | **HR (95% CI)** | ***p*** | **HR 95% CI** | ***p*** |
| **Age (0-7 years / >7 years)** | 22 / 33 | 0.721 (0.402-1.293) | 0.272 | | | 0.845 (0.471-1.516) | 0.573 | | |
| **Sex (Female / Male)** | 16 / 39 | 1.092 (0.598-1.994) | 0.776 | | | 0.986 (0.538-1.807) | 0.964 | | |
| **Reproductive status (Entire / Neutered)** | 27 / 28 | 0.788 (0.456-1.362) | 0.394 | | | 0.941 (0.545-1.624) | 0.827 | | |
| **Breed (Pedigree / Crossbreed)** | 45 / 10 | 0.531 (0.256-1.101) | 0.089 | NA | 0.228 | 0.591 (0.287-1.219) | 0.154 | | |
| **Grade (Low / High)** | 10 / 45 | 1.165 (0.579-2.343) | 0.669 | | | 1.176 (0.585-2.362) | 0.650 | | |
| **Immunophenotype (B Cell / T cell)*** | 28 / 25 | **0.425 (0.238-0.758)** | **0.004** | **0.434 (0.241-0.784)** | **0.006** | **0.421 (0.234-0.758)** | **0.004** | **0.433 (0.238-0.786)** | **0.006** |
| **WHO Stage (II-IV / V)** | 31 / 24 | **0.557 (0.321-0.964)** | **0.037** | **0.488 (0.273-0.871)** | **0.015** | **0.506 (0.291-0.878)** | **0.015** | **0.433 (0.234-0.773)** | **0.005** |
| **WHO Substage (a / b )** | 17 / 38 | 1.919 (0.508-1.664) | 0.781 | | | 0.679 (0.366-1.259) | 0.219 | | |
| **Presenting signs (Not present / Present)** | | | | | | | | | |
| **Weight Loss** | 44 / 11 | 0.574 (0.292-1.128) | 0.107 | NA | 0.862 | 0.523 (0.264-1.039) | 0.064 | NA | 0.629 |
| **GI signs** | 29 / 26 | 0.907 (0.524-1.568) | 0.727 | | | 0.893 (0.515-1.550) | 0.688 | | |
| **Lethargy** | 35 / 20 | 1.346 (0.758-2.389) | 0.311 | | | 1.198 (0.671-2.136) | 0.541 | | |
| **Pyrexia** | 48 / 7 | Not run | | | | Not run | | | |
| **PUPD** | 43 / 12 | 0.848 (0.433-1.625) | 0.620 | | | 0.769 (0.400-1.478) | 0.31 | | |
| **Calcium nmol/L** | 70 | 1.098 (0.662-1.822) | 0.718 | | | 1.130 (0.648-1.968) | 0.667 | | |
| **Albumin g/L** | 70 | 0.937 (0.869-1.010) | 0.090 | NA | 0.219 | 0.938 (0.874-1.006) | 0.074 | NA | 0.207 |
| **CRP mg/L** | 70 | 0.998 (0.991-1.006) | 0.643 | | | 0.999 (0.992-1.006) | 0.739 | | |
| **mGPS (Score 0+1 / Score 2)** | 30 / 25 | 0.576 (0.326-1.019) | 0.058 | NA | 0.472 | **0.525 (0.299-0.922)** | **0.025** | NA | 0.201 |

The reference category for each variable is the first grouping in parentheses unless otherwise stated.

*Unknown immunophenotype for some patients, n=53.

NA – not applicable

HR – Hazard ratio, 95% CI – 95% confidence interval

Table 4: Univariate Kaplan-Meier survival analysis of clinicopathological features and progression-free survival (PFS) and overall survival (OS) using the log-rank test

| | | Group 1 *p-value* | | | Group 2 *p-value* | |
|---|---|---|---|---|---|---|
| **Variable** | **N** | **PFS** | **OS** | **N** | **PFS** | **OS** |
| **Age (0-7 years / >7 years)** | 29 / 41 | 0.224 | 0.340 | 22 / 33 | 0.269 | 0.572 |
| **Sex (Female / Male)** | 21 / 49 | 0.590 | 0.907 | 16 / 39 | 0.775 | 0.964 |
| **Reproductive status (Entire / Neutered)** | 34 / 36 | 0.521 | 0.955 | 27 / 28 | 0.392 | 0.826 |
| **Breed (Pedigree / Crossbreed)** | 57 / 13 | 0.800 | 0.795 | 45 / 10 | 0.084 | 0.148 |
| **Grade (Low / High)** | 58 / 12 | 0.707 | 0.938 | 10 / 45 | 0.668 | 0.648 |
| **Immunophenotype (B Cell / T cell)** | 33 / 32 | **0.027** | 0.059 | 28 / 25 | **0.003** | **0.003** |
| **WHO Stage (II-IV / V)** | 42 / 28 | **0.022** | **0.003** | 31 / 24 | **0.034** | **0.013** |
| **WHO Substage (a / b )** | 24 / 46 | 0.898 | 0.371 | 17 / 38 | 0.781 | 0.375 |
| **Clinical signs (Not present / Present)** | | | | | | |
| **Weight Loss** | 57 / 13 | 0.124 | 0.082 | 44 / 11 | 0.102 | 0.059 |
| **GI signs** | 41 / 29 | 0.596 | 0.954 | 29 / 26 | 0.726 | 0.687 |
| **Lethargy** | 46 / 24 | 0.482 | 0.913 | 35 / 20 | 0.308 | 0.540 |
| **Pyrexia** | 60 / 10 | **0.044** | **0.051** | 48 / 7 | NA | NA |
| **PUPD** | 57 / 13 | 0.782 | 0.376 | 43 / 12 | 0.619 | 0.428 |
| **Calcium (≤3.0 nmol/L / >3 nmol/L)** | 61 / 9 | NA | NA | 47 / 8 | NA | NA |
| **Albumin (≥29 g/L / <29 g/L)** | 38 / 32 | **0.027** | **0.001** | 30 / 25 | 0.055 | **0.022** |
| **CRP mg/L (≤10 mg/L / >10 mg/L)** | 11 / 59 | 0.259 | 0.995 | 8 / 47 | NA | NA |
| **mGPS (Score 0-1 / Score 2)** | 38 / 32 | **0.027** | **0.001** | 30 / 25 | 0.055 | **0.022** |

NA – not applicable for test to be run due to small sample size

## Figure Legends

Figure 1 (A and B): Kaplan-Meier survival curves comparing the overall survival (OS) time of dogs with both mGPS 0 + 1 to dogs with mGPS2, looking at 70 dogs that received any treatment (Group 1 – A, p = 0.001) and 55 that initially received a CHOP-based protocol (Group 2 – B, p = 0.022).

Median OS: Group 1 mGPS 0+1 = 295 days (95% CI 200-390 days), mGPS 2 = 92 days (95% CI 0-195 days); Group 2 mGPS 0+1 = 295 days (95% CI 153-437 days), mGPS 2 = 153 days (95% CI 40-266 days).

Figure 2 (A and B): Kaplan-Meier survival curves comparing the overall survival (OS) time of dogs with normal albumin (≥ 29g/L), to dogs with hypoalbuminaemia (<29g/L), looking at 70 dogs that received any treatment (Group 1 – A, p = 0.001) and 55 that initially received a CHOP-based protocol (Group 2 – B, p = 0.022).

Median OS: Group 1 ≥ 29g/L = 295 days (95% CI 200-390 days), <29g/L = 92 days (95% CI 0-195 days); Group 2 ≥ 29g/L = 295 days (95% CI 153-437 days), <29g/L = 153 days (95% CI 40-266 days).

Figure 3 (A and B): Kaplan-Meier survival curves comparing the progression-free survival (PFS) time of 70 dogs that received any treatment (Group 1) for dogs with mGPS 0+1 compared to mGPS 2 (p=0.027), and for dogs with normal albumin (≥ 29g/L) compared to hypoalbuminaemia (<29g/L, p=0.027).

566 Median PFS: mGPS 0+1 = 111 days (95% CI 72-150 days), mGPS 2 = 72 days (95% CI 29-
567 115 days); Albumin ≥ 29g/L = 111 days (95% CI 72-150 days), <29g/L = 72 days (95% CI
568 29-115 days).

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