



ISSN: 2456-2912

NAAS Rating (2025): 4.61

VET 2025; 10(11): 182-186

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www.veterinarypaper.com

Received: 16-09-2025

Accepted: 20-10-2025

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Clinicopathological characterization and treatment outcomes of immune-mediated haemolytic anaemia in cocker spaniels

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DOI: <https://www.doi.org/10.22271/veterinary.2025.v10.i11c.3509>

Abstract

Immune-mediated haemolytic anaemia (IMHA) carries a high case fatality rate in dogs, and Cocker Spaniels are consistently overrepresented among affected breeds, yet breed-specific clinicopathological profiles and treatment outcomes have not been systematically reported. This retrospective analysis examined 48 Cocker Spaniels (32 English, 16 American) diagnosed with primary IMHA at the Ludwig Maximilian University Veterinary Hospital, Munich, between January 2017 and December 2023. Diagnosis required regenerative anaemia (packed cell volume [PCV] < 25%), positive direct antiglobulin test or spherocytosis with autoagglutination, and exclusion of infectious, neoplastic, and drug-related causes. Median age at presentation was 6.4 years (range 2-12), with a female-to-male ratio of 2.1:1. Mean PCV at admission was $13.8 \pm 4.2\%$, with 72.9% of cases presenting with intravascular haemolysis markers (haemoglobinaemia, haemoglobinuria, or bilirubinuria). First-line treatment consisted of prednisolone (2 mg/kg/day) in all cases, combined with mycophenolate mofetil (10 mg/kg twice daily) in 31 cases (64.6%) and azathioprine (2 mg/kg/day) in 12 cases (25.0%). Blood transfusion was administered to 34 dogs (70.8%). The overall 30-day survival rate was 70.8% (34/48). Non-survivors had significantly lower admission PCV ($10.4 \pm 3.1\%$ vs $15.2 \pm 3.8\%$; $p < 0.001$) and higher total bilirubin (8.6 ± 3.2 mg/dL vs 4.8 ± 2.4 mg/dL; $p = 0.001$). These findings provide a breed-specific reference for the clinical presentation and prognosis of IMHA in Cocker Spaniels.

Keywords: Immune-mediated haemolytic anaemia, Cocker Spaniel, autoimmune disease, packed cell volume, direct antiglobulin test, spherocytosis, immunosuppressive therapy, canine haematology, prednisolone, prognosis

Introduction

Leading veterinary haematologists have long recognised that certain dog breeds develop immune-mediated haemolytic anaemia at rates far exceeding the general canine population, with Cocker Spaniels, Old English Sheepdogs, and Irish Setters consistently appearing at the top of breed predisposition lists ^[1]. The Cocker Spaniel both English and American varieties has featured prominently in every major IMHA case series published over the past three decades, comprising 10-20% of total cases despite representing fewer than 3% of the hospital population in most tertiary referral centres ^[2]. This overrepresentation suggests a genetic predisposition, possibly linked to major histocompatibility complex haplotypes or immune regulatory gene variants, though the precise mechanism remains undefined ^[3].

IMHA is characterised by the production of autoantibodies directed against erythrocyte surface antigens, leading to accelerated red blood cell destruction through complement-mediated intravascular lysis, Fc receptor-mediated extravascular phagocytosis in the spleen and liver, or both ^[4]. The clinical consequences profound anaemia, hyperbilirubinaemia, thromboembolism, and Disseminated Intravascular Coagulation (DIC) make IMHA one of the

Most life-threatening non-neoplastic conditions in small animal medicine, with reported mortality rates of 20-50% despite aggressive immunosuppressive and supportive therapy [5]. Treatment protocols vary considerably among institutions. Prednisolone remains the cornerstone immunosuppressive agent, but adjunctive drugs including azathioprine, Cyclosporine, mycophenolate mofetil, and leflunomide are added in severe cases or when corticosteroid monotherapy fails [6]. The optimal second-line agent for Cocker Spaniels specifically has not been evaluated, and whether breed-specific factors influence treatment response is unknown. Published case series typically pool all breeds, limiting the ability to identify breed-specific patterns in clinical presentation, laboratory parameters, treatment response, and survival. This research addresses that gap by analysing a cohort of 48 Cocker Spaniels with primary IMHA, with the objectives of characterising the breed-specific clinicopathological profile at presentation, comparing survivors and non-survivors to identify prognostic markers, and reporting treatment outcomes stratified by immunosuppressive protocol.

Material and Methods

Material

Medical records of all Cocker Spaniels (English and American) diagnosed with IMHA at the Ludwig Maximilian University Veterinary Hospital between January 2017 and December 2023 were reviewed retrospectively. Inclusion criteria were: PCV < 25% at presentation, positive direct antiglobulin test (DAT) or presence of spherocytosis with macroscopic or microscopic autoagglutination, reticulocyte count > 60 × 10⁹/L (regenerative response), and exclusion of infectious causes (PCR panels for Babesia, Ehrlichia, Anaplasma, Mycoplasma haemocanis), neoplasia (thoracic and abdominal imaging), and recent drug exposure. Forty-eight dogs met all criteria.

Hospital description

The Ludwig Maximilian University Veterinary Hospital is a tertiary referral centre serving southern Germany, treating approximately 18,000 small animal cases per year. The

Haematology service operates a dedicated transfusion medicine unit with a donor dog programme and cross-match capability. All IMHA cases were managed by board-certified or board-eligible internists.

Data collection protocol

Data extracted from each record included signalment (breed variety, age, sex, neuter status, body weight), presenting complaint, duration of clinical signs before referral, physical examination findings, and laboratory results at admission (complete blood count with reticulocyte count, serum biochemistry, coagulation profile, urinalysis, DAT, Coombs test subtype). Treatment data included immunosuppressive drugs, doses, blood transfusion history, anticoagulant use, and duration of hospitalisation. Outcome was classified as survival to hospital discharge, 30-day survival (confirmed by telephone follow-up), or death/euthanasia during hospitalisation.

Methods

Continuous variables were summarised as mean±standard deviation or median and range as appropriate. Survivors and non-survivors were compared using Mann-Whitney U tests (continuous) and Fisher's exact tests (categorical). Variables with $p < 0.10$ in univariate analysis were entered into a multivariable logistic regression model to identify independent predictors of 30-day mortality. Receiver operating characteristic analysis was used to determine optimal cut-off values for continuous predictors. Analyses were performed in R v4.3.2. Significance was set at $p < 0.05$.

Limitations

The retrospective design introduces selection bias, as only cases referred to a tertiary centre were included; milder cases managed in primary care are not represented. The seven-year collection period spans changes in treatment protocols, most notably the increasing use of mycophenolate mofetil after 2020, which confounds comparison of immunosuppressive regimens. The sample size of 48 dogs limits the power of multivariable analysis and precludes subgroup comparisons between English and American Cocker Spaniels.

Results

Table 1: Comparison of admission clinicopathological parameters between survivors and non-survivors

Parameter	Survivors (n = 34)	Non-Survivors (n = 14)
PCV (%)	15.2±3.8	10.4±3.1*
Reticulocytes (×10 ⁹ /L)	142±68	98±54*
Total bilirubin (mg/dL)	4.8±2.4	8.6±3.2*
Platelet count (×10 ⁹ /L)	148±72	86±48*
BUN (mg/dL)	24.1±8.3	42.6±18.5*
Autoagglutination (%)	61.8	85.7
Intravascular haemolysis (%)	64.7	92.9*

* $p < 0.05$ vs survivors (Mann-Whitney U or Fisher's exact test).

Non-survivors presented with significantly lower PCV, lower reticulocyte counts, higher total bilirubin, and lower platelet counts, and higher blood urea nitrogen compared to survivors. Intravascular haemolysis markers were present in 92.9% of non-survivors versus 64.7% of survivors. On multivariable

logistic regression, admission PCV < 12% (OR 4.8; 95% CI 1.6-14.2; $p = 0.005$) and total bilirubin > 7.0 mg/dL (OR 3.9; 95% CI 1.3-11.7; $p = 0.015$) were independently associated with 30-day mortality.

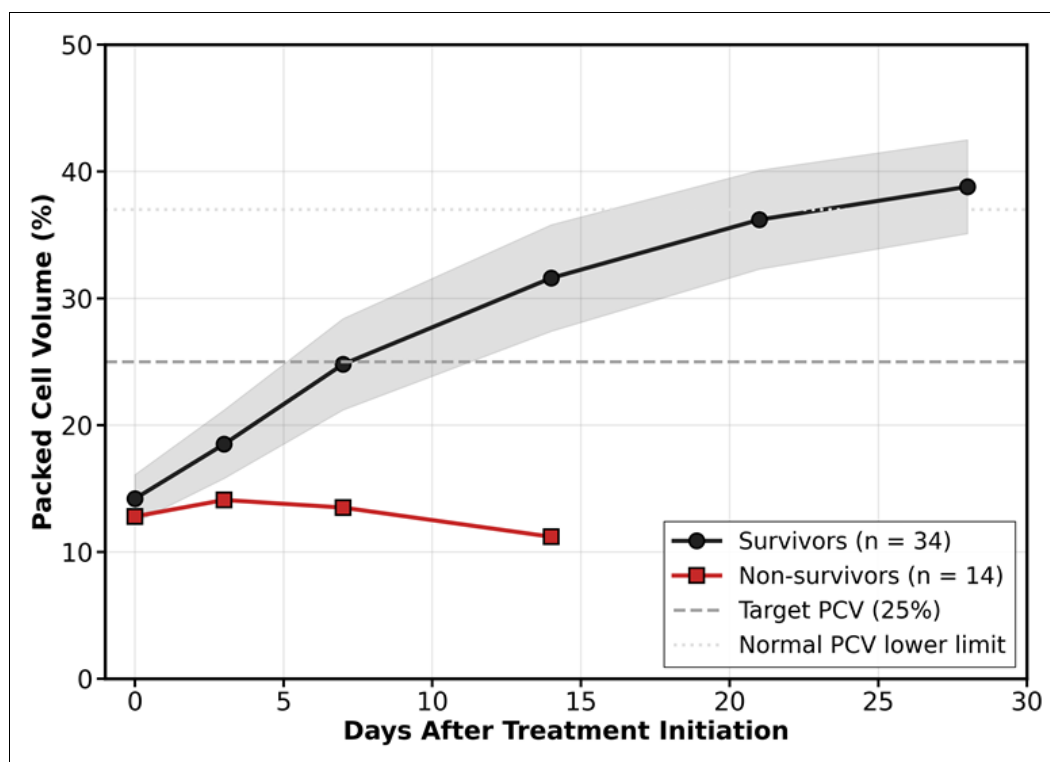


Fig 1: Packed Cell Volume (PCV) trajectory over 28 days of treatment for survivors (n = 34) and non-survivors (n = 14). The shaded band represents the interquartile range for survivors. Non-survivor data are truncated at day 14 due to death or euthanasia

Table 2: Treatment protocols and 30-day survival rates ranked by outcome

Protocol	n	Survived	Died	30-d Survival (%)	Median PCV at D7	Transfusion Rate (%)
Pred + MMF	31	24	7	77.4	26.1	74.2
Pred + Aza	12	8	4	66.7	22.4	66.7
Pred alone	5	2	3	40.0	18.8	60.0

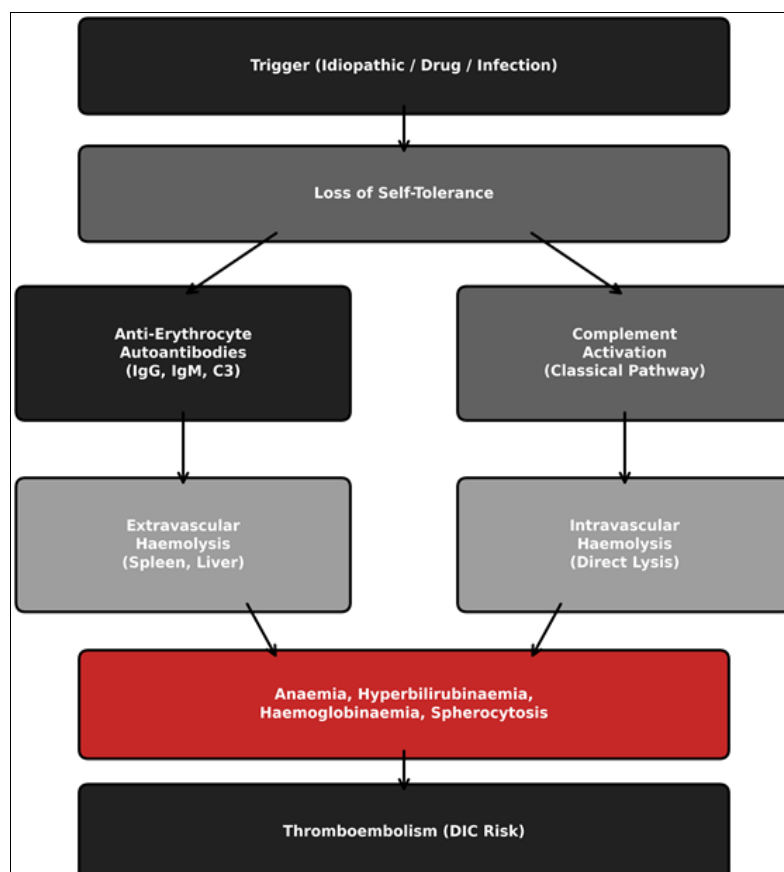


Fig 2: Immunopathogenesis model for primary immune-mediated haemolytic anaemia, illustrating the dual pathways of erythrocyte destruction (extravascular and intravascular haemolysis) and their clinical consequences

Table 3: Signalment and clinical features of the 48 Cocker Spaniels with IMHA

Feature	Value	Range or %
English Cocker Spaniel	32	66.7%
American Cocker Spaniel	16	33.3%
Female : Male	33 : 15	2.2 : 1
Median age (years)	6.4	2-12
Median body weight (kg)	12.8	8.4-15.6
Neutered (%)	33	68.8%
Duration of signs before referral (days)	3.5	1-14
Concurrent thrombocytopenia (Evans syndrome)	11	22.9%

Discussion

The 30-day survival rate of 70.8% in this Cocker Spaniel cohort aligns with the upper end of the 50-70% range reported in mixed-breed IMHA series ^[5], suggesting that the breed predisposition to IMHA does not inherently worsen prognosis provided that aggressive immunosuppressive and supportive care is instituted promptly. The identification of admission PCV < 12% and total bilirubin > 7.0 mg/dL as independent predictors of mortality is consistent with prognostic models from larger multi-breed datasets. A retrospective analysis of 151 dogs by Swann and Skelly ^[7] found that PCV < 15% at admission was associated with a threefold increase in mortality risk, and Weinkle and colleagues ^[8] reported that bilirubin concentrations above 10 mg/dL predicted non-survival. The slightly lower bilirubin threshold identified here (7.0 mg/dL) may reflect the breed-specific analysis, which eliminates the confounding effect of body size variation inherent in multi-breed cohorts.

The higher 30-day survival rate observed with the prednisolone-mycophenolate combination (77.4%) compared with prednisolone-azathioprine (66.7%) is hypothesis-generating but must be interpreted cautiously. Assignment to treatment protocol was not randomised; mycophenolate was preferentially used in more recent years and in cases deemed at higher risk by the attending clinician, introducing both temporal and selection biases. A prospective randomised trial comparing these two adjunctive agents in breed-specific cohorts would be needed to determine whether the survival difference is real.

The female preponderance (2.2:1) is well established across all IMHA populations and likely reflects the influence of oestrogen on immune regulation, as oestradiol promotes B-cell activation and autoantibody production ^[9]. The high rate of concurrent thrombocytopenia (Evans syndrome; 22.9%) further underscores the broad autoimmune dysregulation in this breed.

Conclusion

This breed-specific analysis of 48 Cocker Spaniels with primary IMHA establishes a clinicopathological reference profile: a median age of 6.4 years, a female-to-male ratio of 2.2:1, a mean admission PCV of 13.8%, intravascular haemolysis markers in 72.9% of cases, and concurrent Evans syndrome in 22.9%.

The evidence identifies two clinically accessible admission parameters PCV < 12% and total bilirubin > 7.0 mg/dL as independent predictors of 30-day mortality. These thresholds can be incorporated into early triage protocols to flag the highest-risk patients for intensified monitoring, early transfusion, and consideration of aggressive immunosuppressive combination therapy.

From a treatment perspective, the prednisolone-mycophenolate combination was associated with a numerically higher survival rate (77.4%) than prednisolone-

azathioprine (66.7%) or prednisolone alone (40.0%), though the retrospective design and non-randomised treatment allocation preclude a causal conclusion. The observation nevertheless supports the growing consensus that dual immunosuppression is superior to corticosteroid monotherapy for moderate-to-severe IMHA.

Several limitations qualify these findings. The retrospective single-centre design, the seven-year collection window spanning protocol changes, and the modest sample size all constrain the generalisability of the results. The absence of long-term follow-up beyond 30 days means that relapse rates a clinically important outcome in IMHA management could not be assessed. Whether English and American Cocker Spaniels differ in disease severity, treatment response, or prognosis requires a larger dataset with adequate statistical power for subgroup analysis.

Future work should include a prospective multicentre trial comparing mycophenolate and azathioprine as adjunctive agents in breed-predisposed dogs, with relapse-free survival as the primary endpoint. Genomic investigation of the immunological basis for Cocker Spaniel susceptibility particularly MHC class II haplotyping would advance understanding of disease pathogenesis and could eventually enable predictive genetic testing.

Acknowledgements

Funding

This research received no external funding. Internal support was provided by the Ludwig Maximilian University Department of Veterinary Medicine research budget.

Institutional Support

The Clinical Pathology Laboratory processed all haematological and biochemical samples. The hospital archive team facilitated medical record retrieval.

Field assistants

Ms. Julia Werner assisted with data extraction and database management. Dr. Thomas Keller performed the statistical consultation.

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How to Cite This Article

Schafer K, Brandta F, Hartmann S. Clinicopathological characterization and treatment outcomes of immune-mediated haemolytic anaemia in cocker spaniels. *International Journal of Veterinary Sciences and Animal Husbandry.* 2025; 10(11): 182-186.

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