THE UNIVERSITY of EDINBURGH

Edinburgh Research Explorer

Presence of Systemic Inflammatory Response Syndrome Predicts a Poor Clinical Outcome in Dogs with a Primary Hepatitis

Citation for published version:
Kilpatrick, S, Dreistadt, M, Frowde, P, Powell, R, Milne, E, Smith, S, Morrison, L, Gow, AG, Handel, I & Mellanby, RJ 2016, 'Presence of Systemic Inflammatory Response Syndrome Predicts a Poor Clinical Outcome in Dogs with a Primary Hepatitis' PLoS One, vol. 11, no. 1, e0146560. DOI: 10.1371/journal.pone.0146560

Digital Object Identifier (DOI):
10.1371/journal.pone.0146560

Link:
[Link to publication record in Edinburgh Research Explorer](#)

Document Version:
Publisher's PDF, also known as Version of record

Published In:
PLoS One

OPEN ACCESS

RESEARCH ARTICLE

Presence of Systemic Inflammatory Response Syndrome Predicts a Poor Clinical Outcome in Dogs with a Primary Hepatitis

Scott Kilpatrick[1], Margaret Dreistadt[1], Polly Frowde[2], Roger Powell[3], Elspeth Milne[1], Sionagh Smith[1], Linda Morrison[1], Adam G. Gow[1], Ian Handel[1], Richard J. Mellanby[1]*

1 Royal (Dick) School of Veterinary Studies and The Roslin Institute, The University of Edinburgh, Hospital for Small Animals, Easter Bush Veterinary Centre, Roslin, Midlothian, United Kingdom, 2 Davies Veterinary Specialists Limited, Manor Farm Business Park, Higham Gobion, Herts, United Kingdom, 3 PTDS, Unit 2a, Manor Farm Business Park, Higham Gobion, Herts, United Kingdom

* Richard.Mellanby@ed.ac.uk

Abstract

Primary hepatopathies are a common cause of morbidity and mortality in dogs. The underlying aetiology of most cases of canine hepatitis is unknown. Consequently, treatments are typically palliative and it is difficult to provide accurate prognostic information to owners. In human hepatology there is accumulating data which indicates that the presence of systemic inflammatory response syndrome (SIRS) is a common and debilitating event in patients with liver diseases. For example, the presence of SIRS has been linked to the development of complications such as hepatic encephalopathy (HE) and is associated with a poor clinical outcome in humans with liver diseases. In contrast, the relationship between SIRS and clinical outcome in dogs with a primary hepatitis is unknown. Seventy dogs with histologically confirmed primary hepatitis were enrolled into the study. Additional clinical and clinicopathological information including respiratory rate, heart rate, temperature, white blood cell count, sodium, potassium, sex, presence of ascites, HE score, alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin and red blood cell concentration were available in all cases. The median survival of dogs with a SIRS score of 0 or 1 (SIRS low) was 231 days compared to a median survival of 7 days for dogs with a SIRS score of 2, 3 or 4 (SIRS high) (p<0.001). A Cox proportional hazard model, which included all other co-variables, revealed that a SIRS high score was an independent predictor of a poor clinical outcome. The effect of modulating inflammation on treatment outcomes in dogs with a primary hepatitis is deserving of further study.

Introduction

Primary hepatopathies are a common cause of morbidity and mortality in dogs, with a recent study reporting that over 10 per cent of dogs had evidence of chronic hepatitis at post mortem examination [1–3]. Primary hepatitis includes all inflammatory disorders of the hepatic

parenchyma [4]. In contrast to human medicine, where the type of hepatitis is defined by the inciting cause, few causes of chronic hepatitis have been identified in the dog, and the majority of cases are idiopathic [4]. Although primary hepatitis can be readily diagnosed in dogs through histological examination of a liver biopsy, it remains a challenging and difficult disease to treat [1, 5]. Furthermore, it is difficult to offer clients an accurate prognosis at the time of diagnosis [2].

There is growing evidence that systemic inflammatory response syndrome (SIRS) is a common and serious disorder among human patients with liver diseases [6–8]. It has been suggested that the presence of SIRS can lead to a further deterioration in liver function resulting in significant morbidity and mortality [9, 10]. The presence of SIRS can compromise the function of various organ systems resulting in Multiple Organ Dysfunction Syndrome (MODS) [11]. Hospitalised human patients with cirrhosis and SIRS have more severe hepatic encephalopathy (HE), are more likely to develop hepatorenal syndrome and have non-reversible renal dysfunction [12]. In acute liver failure, the presence of SIRS, whether or not precipitated by infection, has been implicated in the progression of HE, reducing the chances of transplantation and conferring a poorer prognosis [13]. Furthermore, higher SIRS scores are related to the development of acute liver failure in patients with pre-existing hepatitis [14].

There is a clear need to clarify the relationship between inflammation and outcome in dogs with a primary hepatitis. A more detailed understanding of the relationship between inflammation and clinical outcomes may lead to novel therapeutic approaches. The aim of this study was to determine the prevalence of systemic inflammation in a cohort of dogs with primary hepatitis, and to then examine the relationship between systemic inflammation and patient survival.

Materials and Methods

Consecutive cases of dogs diagnosed with primary hepatopathies at the Royal (Dick) School of Veterinary Studies or Davies Veterinary Specialists, were considered for inclusion in the study. Cases were only included if the dog had histopathological confirmation of primary parenchymal hepatic disease. Information on the signalment and previous medical treatment was extracted from the clinical records. The histopathological diagnosis was classified according to WSAVA (World Small Animal Veterinary Association) criteria by a board certified pathologist [4]. All blood samples were taken by a veterinary surgeon as part of routine clinical management of each patient. The study was approved by The University of Edinburgh Ethics Research Committee and the owners of the dogs gave permission for their animals' data to be used in this study.

The presence of HE was evaluated using previously described criteria [15]. The dog was considered to have HE if it had clinical signs of lethargy, inappropriate behavior, disorientation, circling, head pressing or seizures [16]. If the dog displayed none of these signs, it was considered not to have HE. The presence of ascites was documented if confirmed by ultrasound evaluation. Details of heart rate, respiratory rate, temperature, haematology profile and biochemistry profile were recorded. A SIRS score was calculated for each dog using methodology previously described [17]. The SIRS score could range from 0–4 as each dog was given 1 point when they met each of the following criteria: respiratory rate greater than 20 min heart rate greater than 120 min; total white blood cell (WBC) count less than 6 or greater than 16 $x10^9$ L and rectal temperature less than 38.1°C or greater than 39.2°C Therefore, a SIRS score could range from 0 to 4.

Survival of the cohort was initially examined using Kaplan Meier analysis. As some of the dogs were alive at the end of follow up, Cox proportional hazard analysis was used to estimate the association between survival and selected co-variates. Initially, a uni-variable analysis was

performed which explored the relationship between survival and SIRS score. To determine if this relationship persisted in the presence of other possible other confounding variables, a multivariable Cox proportional hazard model was constructed which included SIRS score of 0 or 1 (SIRS low) or SIRS score of 2, 3 or 4 (SIRS high), sodium, potassium, sex, ALT, ALP, bilirubin, red blood cell count, presence of ascites, age and HE score. A final model was built based on step wise removal of variables from the initial comprehensive model using AIC as a measure of parameter penalised model fit. To confirm the model structure, the impact on AIC of both dropping each of the final variables and adding back in the dropped variables was investigated. Results are presented as a hazard ratio with 95% CI. Statistical analysis was performed in R statistical software package (R Development Core Team (2012)).

Results

Eighty cases of histologically confirmed primary hepatopathies were identified. Ten dogs were excluded from the study due to incomplete clinical records. The 70 dogs included in this study comprised of 29 different pure breeds and eight cross-breeds. The sex distribution comprised of 12 entire males, 24 neutered males, 24 neutered females and 10 entire female dogs. The median age was 75 months (range 6 to 180 months). The diagnosis of hepatitis was histologically confirmed from samples collected at post-mortem examination in 9 cases, and from a percutaneous spring-loaded biopsy instrument in 12 cases. Forty nine samples were collected by surgical biopsy techniques. Fifty cases were diagnosed with chronic hepatitis (Fig 1), 10 cases with acute hepatitis, eight cases with cirrhosis (Fig 2) and two cases with copper associated hepatitis (Fig 3). Fifty-seven dogs were dead at follow up and 13 were alive. Seventeen dogs had a SIRS score of 0, 22 had a score of 1, 25 had a score of 2, five had a score of 3 and one dog had a score of 4.
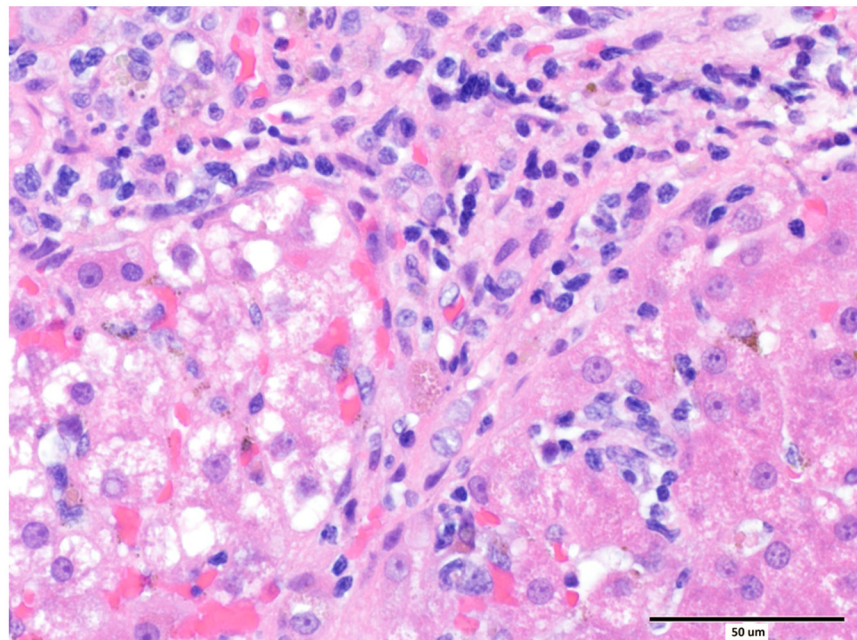

Fig 1. Liver from a case of chronic hepatitis with islands of hepatocytes separated by bands of fibroblasts and collagen, and moderate numbers of macrophages, lymphocytes and plasma cells. Haematoxylin and eosin, scale bar = 50 μm.

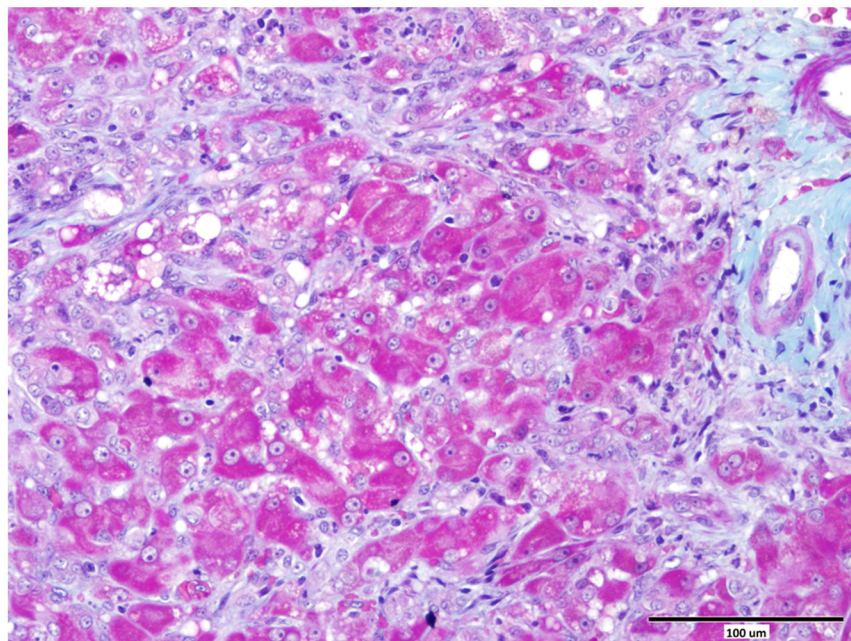doi:10.1371/journal.pone.0146560.g001

Fig 2. Liver from a case of chronic hepatitis and early cirrhosis showing disruption of the lobular architecture and dissecting fibrosis (green). Masson's trichrome, scale bar = 100 μm.

The median survival time of the 70 dogs was 38.5 days (95% CI 20–215). To explore the relationship between a systemic inflammatory response and survival, the median survival of dogs with a SIRS low and dogs with a SIRS high was estimated. The median survival of SIRS low dogs was 231 days (95% CI 78-not available/ days) and median survival of SIRS high was 7
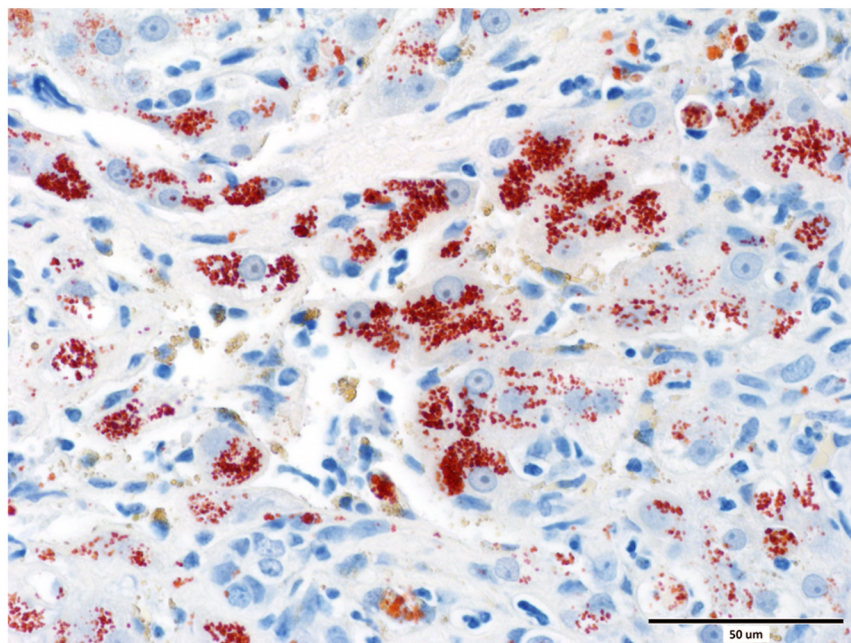

Fig 3. Liver from a case of chronic hepatitis with intracytoplasmic copper accumulation in hepatocytes. Rhodanine red, scale bar = 50 μm.
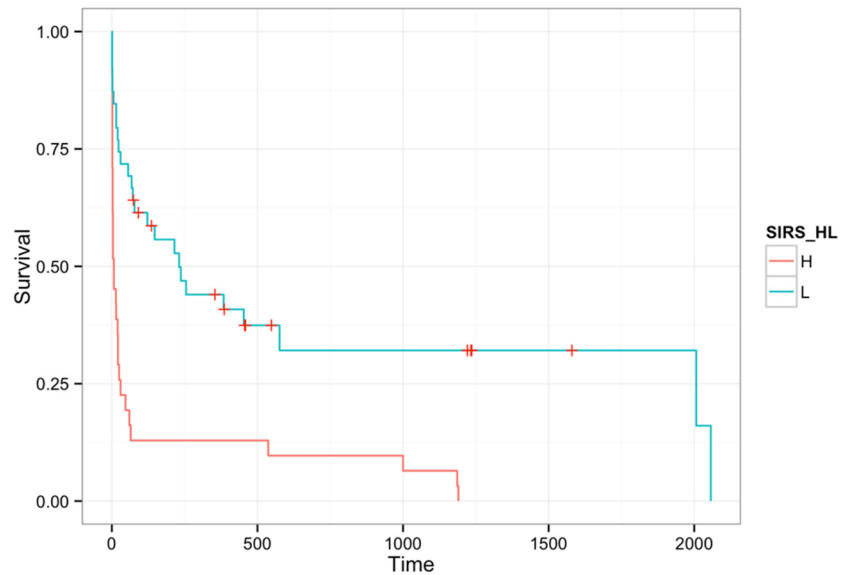
Fig 4. Kaplan-Meier plot of survival time in days by SIRS high (red solid line) and SIRS low (blue dotted line). Tick marks show censored events.

doi:10.1371/journal.pone.0146560.g004

days (95% CI 3-25/ days) (p<0.001) ([Fig 4](#)). To assess whether this relationship persisted in the presence of other co-variates, a Cox proportional hazard model was built. The initial model included SIRS high or low, presence of ascites, HE score, sex, sodium, potassium, ALT, ALP, bilirubin, age, sex and red blood cell count ([S1 File](#)). The final model after variable selection included SIRS, bilirubin, red blood cell concentrations and age ([Table 1](#)). The impact of variables dropped from the model was confirmed by calculating the impact on model fit (Δ AIC) when they were individually added back into the model ([Table 2](#)).

Discussion

In this large two centre study, we have examined for the first time, the relationship between SIRS, a simple marker of inflammation, and clinical outcome in dogs with primary hepatitis The central finding of this study was that the dogs with a primary hepatitis and a SIRS score of 2, 3 or 4 had a significantly worse clinical outcome than dogs with a SIRS score of 0 or 1. This provides evidence that the presence of systemic inflammation is associated with a poorer clinical outcome in dogs, which is similar to human patients with liver disease. The presence of SIRS was a major predictor of multiple organ failure and strongly correlated with short term mortality in patients with alcoholic hepatitis [7]. In addition, SIRS has recently been associated with acute on chronic liver failure (ACLF) [18].

Table 1. Hazard Ratios and 95% confidence interval for terms in final Cox proportional hazard model. Δ AIC is the increase in AIC if the term is dropped from the model. A positive Δ AIC equates to a poorer model fit.

	Hazard Ratio (95% CI)	Δ AIC
SIRS	3.575 (1.857–6.884)	13.3
Bilirubin	1.003 (1.001–1.005)	5.98
Red blood cell	0.768 (0.596–0.990)	2.14
Age	0.909 (0.827–1.000)	1.94

doi:10.1371/journal.pone.0146560.t001

Table 2. Δ AIC for terms not included in final model when added back in final model. A positive Δ AIC equates to a poorer model fit.

	Δ AIC
Sodium	0.03
Potassium	1.77
Sex	2.75
Ascites	1.94
HE score	4.77
ALP	1.98
ALT	0.68

doi:10.1371/journal.pone.0146560.t002

Inflammation may be associated with a poor outcome in dogs and humans with liver disease for several reasons. Intestinal bacterial overgrowth and altered gut permeability in patients with liver disease is hypothesised to lead to increased translocation of bacteria and endotoxin into the portal circulation [9]. Factors leading to SIRS development in liver disease include the impaired phagocytic function of the reticuloendothelial system which allows endotoxin to reach the systemic circulation in high concentrations [13]. Lipopolysaccharide (LPS) concentrations in the peripheral and portal circulation have been shown to be increased in people with liver cirrhosis. Importantly, LPS concentrations have been shown to predict mortality in patients with alcoholic hepatitis[7]. Endotoxin can activate monocytes and release pro-inflammatory cytokines which have been implicated in the development of hepatic complications such as HE, ascites and variceal bleeding [19]. The disturbances in systemic and hepatic haemodynamics in alcohol-related liver failure (ACLF) have also been associated with dysregulated inflammation, multi-organ failure and marked activation of the sympathetic nervous system [7]. These abnormalities predict high mortality rates in these patients [8].

In our study, the proportion of dogs which had an infection was not accurately defined. In a recent study of human patients with alcoholic hepatitis and SIRS, over 60% of patients had no evidence of infection, based on clinical or microbiological criteria [8]. Understanding the pathophysiology of sterile inflammation in patients with liver disease, with the ambition of developing targeted therapies, is one of the major challenges in contemporary hepatology.

Predicting the course and prognosis of disease is an important part of veterinary and human clinical practice and the development of new prognostic markers with documented significance is an important focus of human and veterinary research. Various factors have been demonstrated as negative prognostic indictors in dogs with primary hepatitis [20]. These include jaundice, abdominal fluid wave, microhepatica, ascites, enlarged portal lymph nodes, hypoalbuminemia and left shift of neutrophils in the peripheral blood [1]. Consistent with our study, total serum bilirubin was a negative prognostic indicator in idiopathic canine chronic hepatitis [2]. High bilirubin concentrations have also been documented to be associated with a negative outcome in human patients [21, 22]. Furthermore, our prognostic link with low red blood cell count is consistent with the prediction of poor post-surgical survival associated with reduced red blood cell counts in human patients with primary liver cancer [23] and end stage liver disease [24].

Another finding of this study was that abnormal serum sodium concentrations were not commonly observed in dogs with primary hepatitis. This observation contrasts with the findings from studies of humans with liver disease where hyponatremia is frequently observed [25–27]. For example, in a prospective study of 997 patients with cirrhosis the prevalence of low serum sodium concentration, defined as a serum sodium ≤135 mmol/l, ≤130 mmol/l, ≤125 mmol/l or ≤120 mmol/l, was 49.4%, 21.6%, 5.7%, and 1.2%, respectively [28]. Borroni et al.

reported hyponatraemia in 29.8% of patients admitted for management of cirrhosis, as defined by a serum sodium concentration of ≤130 mmol/l [29]. Furthermore, the prevalence of hypo-natremia was 26% in a population of paediatric patients with end stage liver disease awaiting liver transplantation (as defined by a serum sodium concentration of ≤130 mmol/l) [30]. It remains unclear why humans frequently develop hyponatraemia with liver disease while dogs do not. We hypothesise that the differences may reflect the different causes of liver disease in dogs compared to humans.

Several studies in human patients with liver disease have examined the role of circulating biomarkers as adjunctive markers of systemic inflammation, such as LPS, procalcitonin and C reactive protein [31–33]. Cytokines, including interleukin-6 (IL-6), interleukin-8 (IL-8) and tumour necrosis factor (TNF), are key mediators of the inflammatory response [11]. Several studies have measured circulating cytokine concentrations in patients with liver disease. One marker that has been investigated in some detail is IL-6 [34–36]. Increased serum concentrations of IL-6 have been found in people with different inflammatory diseases and has been correlated with the severity of disease, prognosis and outcome [37]. Higher circulation levels of IL-6 were significantly associated with a higher risk of developing hepatocellular carcinoma [38]. IL-6 has also been shown to be a useful prognostic marker for canine critical care patients [39].

Our study demonstrates the need to understand more about the development of systemic inflammation in dogs with liver disease and to establish whether reducing systemic inflammation improves outcomes.

Conclusion

In conclusion, a high SIRS score was associated with poorer long term survival in our study of dogs with primary hepatitis Our study demonstrates the need to understand more about the causes and consequences of inflammation in dogs with liver disorders. Our study demonstrates the need to understand more about the development of systemic inflammation in dogs with liver disease and to establish whether reducing systemic inflammation improves patient outcomes. The impact of ameliorating inflammation in patients with hepatitis is ill defined. Although prednisolone is widely used as a first line treatment for hepatitis in both dogs and humans, its therapeutic benefits remain ill-defined in both species [40–43].

Supporting Information

S1 File. Clinical and biochemical data from the 70 dogs with histologically confirmed hepatitis reported in this study.
(XLSX)

Acknowledgments

We would like to thank the veterinary surgeons, nurses and owners involved in the care of the animals included in this study.

Author Contributions

Conceived and designed the experiments: RJM SK. Performed the experiments: SK RJM. Analyzed the data: SK RJM IH. Contributed reagents/materials/analysis tools: SK MD PF RP EM SS AGG IH RJM LM. Wrote the paper: SK MD PF RP EM SS AGG IH LM RJM.

References

1. Poldervaart JH, Favier RP, Penning LC, van den Ingh TS, Rothuizen J. Primary hepatitis in dogs: a retrospective review (2002–2006). J Vet Intern Med. 2009; 23(1):72–80. doi: 10.1111/j.1939-1676.2008.0215.x PMID: 19175724

2. Gomez Selgas A, Bexfield N, Scase TJ, Holmes MA, Watson P. Total serum bilirubin as a negative prognostic factor in idiopathic canine chronic hepatitis. Journal of veterinary diagnostic investigation: official publication of the American Association of Veterinary Laboratory Diagnosticians, Inc. 2014; 26 (2):246–51.

3. Watson PJ, Roulois AJ, Scase TJ, Irvine R, Herrtage ME. Prevalence of hepatic lesions at post-mortem examination in dogs and association with pancreatitis. J Small Anim Pract. 2010; 51(11):566–72. doi: 10.1111/j.1748-5827.2010.00996.x PMID: 20973784

4. Cullen JM. Summary of the World Small Animal Veterinary Association standardization committee guide to classification of liver disease in dogs and cats. The Veterinary clinics of North America Small animal practice. 2009; 39(3):395–418. doi: 10.1016/j.cvsm.2009.02.003 PMID: 19524786

5. Fuentealba C, Guest S, Haywood S, Horney B. Chronic hepatitis: a retrospective study in 34 dogs. The Canadian veterinary journal La revue veterinaire canadienne. 1997; 38(6):365–73. PMID: 9187802

6. Shawcross DL, Sharifi Y, Canavan JB, Yeoman AD, Abeles RD, Taylor NJ, et al. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. J Hepatol. 2011; 54(4):640–9. doi: 10.1016/j.jhep.2010.07.045 PMID: 21163546

7. Michelena J, Altamirano J, Abraldes JG, Affo S, Morales-Ibanez O, Sancho-Bru P, et al. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. Hepatology. 2015.

8. Mehta G, Mookerjee RP, Sharma V, Jalan R. Systemic inflammation is associated with increased intrahepatic resistance and mortality in alcohol-related acute-on-chronic liver failure. Liver Int. 2015; 35 (3):724–34. doi: 10.1111/liv.12559 PMID: 24703488

9. Abdel-Khalek EE, El-Fakhry A, Helaly M, Hamed M, Elbaz O. Systemic inflammatory response syndrome in patients with liver cirrhosis. Arab journal of gastroenterology: the official publication of the Pan-Arab Association of Gastroenterology. 2011; 12(4):173–7.

10. Thabut D, Massard J, Gangloff A, Carbonell N, Francoz C, Nguyen-Khac E, et al. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. Hepatology. 2007; 46(6):1872–82. PMID: 17972337

11. Nystrom PO. The systemic inflammatory response syndrome: definitions and aetiology. J Antimicrob Chemoth. 1998; 41:1–7.

12. Cazzaniga M, Dionigi E, Gobbo G, Fioretti A, Monti V, Salerno F. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. J Hepatol. 2009; 51(3):475–82. doi: 10.1016/j.jhep.2009.04.017 PMID: 19560225

13. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. Hepatology. 2000; 32(4 Pt 1):734–9. PMID: 11003617

14. Shin HS, Kim SP, Han SH, Kim do Y, Ahn SH, Han KH, et al. Prognostic indicators for acute liver failure development and mortality in patients with hepatitis A: consecutive case analysis. Yonsei medical journal. 2014; 55(4):953–9. doi: 10.3349/ymj.2014.55.4.953 PMID: 24954323

15. Salgado M, Cortes Y. Hepatic encephalopathy: diagnosis and treatment. Compendium. 2013; 35(6): E1–9; quiz E10.

16. Tivers MS, Handel I, Gow AG, Lipscomb VJ, Jalan R, Mellanby RJ. Hyperammonemia and systemic inflammatory response syndrome predicts presence of hepatic encephalopathy in dogs with congenital portosystemic shunts. PLoS One. 2014; 9(1):e82303. doi: 10.1371/journal.pone.0082303 PMID: 24392080

17. Hauptman JG, Walshaw R, Olivier NB. Evaluation of the sensitivity and specificity of diagnostic criteria for sepsis in dogs. Vet Surg. 1997; 26(5):393–7. PMID: 9381665

18. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013; 144(7):1426–37, 37 e1–9. doi: 10.1053/j.gastro.2013.02.042 PMID: 23474284

19. Bolognesi M, Merkel C, Bianco S, Angeli P, Sacerdoti D, Amodio P, et al. Clinical significance of the evaluation of hepatic reticuloendothelial removal capacity in patients with cirrhosis. Hepatology. 1994; 19(3):628–34. PMID: 8119687

20. Weingarten MA, Sande AA. Acute liver failure in dogs and cats. J Vet Emerg Crit Care (San Antonio). 2015; 25(4):455–73.

21. Gupta RK, Yadav SK, Rangan M, Rathore RK, Thomas MA, Prasad KN, et al. Serum proinflammatory cytokines correlate with diffusion tensor imaging derived metrics and 1H-MR spectroscopy in patients with acute liver failure. Metab Brain Dis. 2010; 25(3):355–61. doi: 10.1007/s11011-010-9206-x PMID: 20838864

22. Puri K, Nobili V, Melville K, Corte CD, Sartorelli MR, Lopez R, et al. Serum bilirubin level is inversely associated with nonalcoholic steatohepatitis in children. Journal of pediatric gastroenterology and nutrition. 2013; 57(1):114–8. doi: 10.1097/MPG.0b013e318291fefe PMID: 23518490

23. Xie X, Yao M, Chen X, Lu W, Lv Q, Wang K, et al. Reduced red blood cell count predicts poor survival after surgery in patients with primary liver cancer. Medicine. 2015; 94(8):e577. PMID: 25715259

24. Li C, Wen TF, Yan LN, Li B, Yang JY, Xu MQ, et al. Risk factors for in-hospital mortality of patients with high model for end-stage liver disease scores following living donor liver transplantation. Annals of hepatology. 2012; 11(4):471–7. PMID: 22700628

25. Garg H, Kumar A, Garg V, Sharma P, Sharma BC, Sarin SK. Clinical profile and predictors of mortality in patients of acute-on-chronic liver failure. Dig Liver Dis. 2012; 44(2):166–71. doi: 10.1016/j.dld.2011.08.029 PMID: 21978580

26. Guevara M, Baccaro ME, Torre A, Gomez-Anson B, Rios J, Torres F, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. The American journal of gastroenterology. 2009; 104(6):1382–9. PMID: 19455124

27. Cordoba J, Ventura-Cots M, Simon-Talero M, Amoros A, Pavesi M, Vilstrup H, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). J Hepatol. 2013.

28. Angeli P, Wong F, Watson H, Gines P, Investigators C. Hyponatremia in cirrhosis: Results of a patient population survey. Hepatology. 2006; 44(6):1535–42. PMID: 17133458

29. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. Dig Liver Dis. 2000; 32(7):605–10. PMID: 11142560

30. Carey RG, Bucuvalas JC, Balistreri WF, Nick TG, Ryckman FR, Yazigi N. Hyponatremia increases mortality in pediatric patients listed for liver transplantation. Pediatric transplantation. 2010; 14(1):115–20. doi: 10.1111/j.1399-3046.2009.01142.x PMID: 19254244

31. Aleksandrova K, Boeing H, Nothlings U, Jenab M, Fedirko V, Kaaks R, et al. Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. Hepatology. 2014; 60(3):858–71. doi: 10.1002/hep.27016 PMID: 24443059

32. Martinez D, Palmer C, Simar D, Cameron BA, Nguyen N, Aggarwal V, et al. Characterisation of the cytokine milieu associated with the up-regulation of IL-6 and suppressor of cytokine 3 in chronic hepatitis C treatment non-responders. Liver Int. 2015; 35(2):463–72. doi: 10.1111/liv.12473 PMID: 24461080

33. Wu HL, Kao JH, Chen TC, Wu WH, Liu CH, Su TH, et al. Serum cytokine/chemokine profiles in acute exacerbation of chronic hepatitis B: clinical and mechanistic implications. J Gastroenterol Hepatol. 2014; 29(8):1629–36. doi: 10.1111/jgh.12606 PMID: 24730549

34. Kilpatrick S, Gow AG, Foale RD, Tappin SW, Carruthers H, Reed N, et al. Plasma cytokine concentrations in dogs with a congenital portosystemic shunt. The Veterinary Journal. 2014.

35. Weaver JD, Huang MH, Albert M, Harris T, Rowe JW, Seeman TE. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology. 2002; 59(3):371–8. PMID: 12177370

36. Tilg H, Wilmer A, Vogel W, Herold M, Nolchen B, Judmaier G, et al. Serum levels of cytokines in chronic liver diseases. Gastroenterology. 1992; 103(1):264–74. PMID: 1612333

37. Jiang X, Zhang Y, Miao X, Li Z, Bao Z, Wang T. Detection of IL-6 by magnetic nanoparticles grown with the assistance of mid-infrared lighting. Molecular medicine reports. 2013; 7(1):73–6. doi: 10.3892/mmr.2012.1136 PMID: 23117195

38. Hammad LN, Abdelraouf SM, Hassanein FS, Mohamed WA, Schaalan MF. Circulating IL-6, IL-17 and vitamin D in hepatocellular carcinoma: potential biomarkers for a more favorable prognosis? Journal of immunotoxicology. 2013; 10(4):380–6. doi: 10.3109/1547691X.2012.758198 PMID: 23350952

39. Schuttler J, Neumann S. Interleukin-6 as a prognostic marker in dogs in an intensive care unit. Veterinary clinical pathology / American Society for Veterinary Clinical Pathology. 2015; 44(2):223–8. doi: 10.1111/vcp.12255 PMID: 25866911

40. Rambaldi A, Saconato HH, Christensen E, Thorlund K, Wetterslev J, Gluud C. Systematic review: glucocorticosteroids for alcoholic hepatitis—a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. Alimentary pharmacology & therapeutics. 2008; 27(12):1167–78.

41. Mathurin P, O'Grady J, Carithers RL, Phillips M, Louvet A, Mendenhall CL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut. 2011; 60(2):255–60. doi: 10.1136/gut.2010.224097 PMID: 20940288

42. Thursz MR, Richardson P, Allison M, Austin A, Bowers M, Day CP, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. The New England journal of medicine. 2015; 372(17):1619–28. doi: 10.1056/NEJMoa1412278 PMID: 25901427

43. Favier RP, Poldervaart JH, van den Ingh TS, Penning LC, Rothuizen J. A retrospective study of oral prednisolone treatment in canine chronic hepatitis. The Veterinary quarterly. 2013; 33(3):113–20. doi: 10.1080/01652176.2013.826881 PMID: 23937599