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Review Article

Biochemical and Hematological Indexes of Liver Dysfunction in Horses

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ABSTRACT

In the present review, the authors, based on the multiple functions performed by the liver, analyze the multiple biochemical and hematological changes as an expression of altered liver function in the horse. The liver performs important metabolic functions related to the synthesis, degradation, and excretion of various substances. Modification of these functions can be evaluated and diagnosed by determining serum concentrations of several serum analytes, including enzymes and other endogenous substances. Hepatocellular enzymes, such as sorbitol dehydrogenase-SDH and glutamate dehydrogenase-GLDH, are released following hepatocellular necrosis. Hepatobiliary enzymes, such as γ-glutamyl transferase-GGT, increase in response to necrosis, cholestasis, and other alterations in bile conducts. Serum concentrations of mainly endogenous and exogenous substances that the liver should synthesize or eliminate, such as proteins (albumin and globulins), bile acids, urea, glucose, total and direct bilirubin, and coagulation factors, and fibrinogen should be included in the liver function test profile. The interpretation of laboratory tests of liver function will allow the diagnosis of functional loss of the organ. Some of the analytes considered provide information on the prognosis of liver disease. This review will provide an accurate and objective interpretation of the common biochemical and hematological tests in use in the diagnosis of equine hepatic disease patients, aiding still further the veterinary activity on the applied equine clinical cases.

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1. Introduction

The functional liver failure's syndrome covers a board spectrum of clinical, biochemical, and neurophysiological changes. Hepatic failure or insufficiency refers to the liver inability to perform its physiological functions, characterized by deterioration in the synthesis, regulation, and detoxification function [1]. Because the liver is involved in such a wide variety of physiologic functions, any pathologic process may hinder one or several activities without impeding others. What is more, the high reserve capacity of the liver induces it capable of remaining functional albeit large sum of tissue damage in the horse [2]. Despite the ability to regenerate, death, or necrosis of liver cells causes them to be replaced with fibrous tissue. The correct and incontrovertible etiology of chronic liver disease in equine adults, by considering analysis of clinical, ultrasonographic, serum biochemical, hematological, and immunoreactivity data, is rarely identified based in the biochemistry; however, some causes can include cholangiohepatitis, aflatoxicosis, and pyrrolizidine alkaloid toxicity (Senecio spp.), alsike clover, iron toxicity [3], and viral hepatitis as equine hepacivirus (EqHV) [4] and equine parvovirus hepatitis (EqPV-H) in adult horses [5,6], among others [1,7]. Replacement with fibrous tissue is a serious problem and carries out a poor prognostic evaluation since the hepatic function is compromised. However, the prognosis of equine hepatic in-sufficiency depends upon the type and related severity of the underlying disease. Unfortunately, hepatic diseases and liver failure are difficult to diagnose in the early stages, until more than 60% to 80% of the liver is non-functioning [19].

In horses, the most common clinical signs of hepatic insufficiency are represented by, anorexia, weight loss, icterus, fever, hepatic encephalopathy, and depression. On the other hand, the less commonly reported clinical signs include diarrhea, colic, hepatogenic photosensitization, hemorrhagic diathesis, polycythemia, and

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bilateral laryngeal paralysis. In addition, polydipsia, hemolysis, dependent abdominal edema, ascites, tenesmus, and endotoxic shock are rarely possible to observe. The appearance of specific clinical signs of hepatic diseases often reflects the typology of physiological or altered hepatic functions [8,9,19]. Since the functions of the liver are numerous, its diseases and/or failure can affect the fat, protein, and carbohydrate metabolism, the excretion of bile, breakdown and excretion of compounds, toxins' filtration, aged erythrocytes and organisms, storage of vitamins (A, D, and B12) and minerals (copper and iron); among others, changes in coagulation factors, fibrinogen, ammonia, urea (BUN), total bile acids (TBA), bilirubin (BIL), albumin (ALB) and globulins (GLOBs) could indicate although not consistently in all liver dysfunction patients (Mair et al., 2017).These liver function test only become abnormal when approximately 60 - 70% of liver function is lost [19].

Blood tests are generally very helpful in clinical diagnosis of equine hepatic diseases, but they have a limited prognostic value. In the analysis of the liver profile, some biochemical indices are helpful for prognoses, such as significantly elevated levels of GLOBs (x 13 risk of death at 6 months) and TBA (x 10 risk of death at 6 months) and significantly reduced levels of ALB (x 10 risk of death at 6 months) [10].

Bile acids (BA) are a group of amphipathic steroids synthesized by hepatocytes from cholesterol and excreted into bile. They function to emulsify fat in intestine and facilitate nutrient absorption and are highly conserved via enterohepatic circulation as outlined below [11]. BA concentrations above the reference interval indicate a poor prognosis in UK horses with liver disease [10,12,13]. An experimental study, carried out in 9 horses, evaluated the toxicity of the pyrrolizidine alkaloid, resulting in an increase of BA above 50 µmol/L in 8 of them, which were euthanized for the severity of the disease or died spontaneously; the only surviving horse showed a BA concentration of 33 µmol/L [16]. Delvescovo et al. [14], showed that the survival rate in horses with BA >30 µmol/L was 55%, which is in line with the previously reported 52% survival for cases with BA concentrations of>20 µmol/L [1], confirming the guarded prognostic indicators for all these cases. Moreover, the degree of BA elevation above 30 µmol/L concentrations did not worsen the prognosis for survival up to 6 months after hospital release.

Survival prognosis improves when liver damage is reversible and, in these cases, a single measurement of BA might not provide enough information about the potential for recovery and survival. The prognostic value of BA relies on the fact that the detected loss of hepatic function is permanent or progressive or both. It is conceivable that reversible changes, such as inflammatory infiltration or reversible hepatocyte damage, could temporarily interfere with hepatic function, leading to an increase in BA. In contrast, in cases of serum hepatitis, cholangiohepatitis, neoplasia, Clostridium piliformis infection, and pyrrolizidine alkaloid toxicity are all associated with severe or non-reversible liver damage, a single BA value might be more predictive of survival [14]. In many of these cases, loss of hepatic function is permanent or progressive, or both, and BA are likely to be indicative of extend of the irreparable damage and therefore also of the prognosis. In these cases, a close association between BA, presence and severity of hepatic damage and a negative outcome would be expected [12]. However, BA returned to normal levels in horses that survived liver necrosis from mild to moderate liver disease of unknown etiology, and in these cases, BA might be more indicative of a temporary and potentially reversible compromise of hepatic function corresponding to improved liver function as regeneration occurred [15].This assumption is supported by the low specificity of BA >17 and >20 µmol/L for nonsurvival and the correlation between BA and potentially reversible histological findings such as inflammation and hemosiderin accumulation in Kupffer cells suggesting interference with hepatic function [12].

Table 1
Common findings of hepatobiliary enzymes associated with liver functional abnormalities [8,13,6,4].

Specific Enzymatic Indicators of Liver Disease		
Enzyme	Dynamic	Range (UI/L)
SDH	> 8	2–8
GGT	> 20	5–20
GLDH	> 10	2-10
Arginase	> 4.2	0-4.2

In these latter studies, the predictive value of survival based on pyrrolizidine alkaloid toxicity could not be established for the small number of horses used in the study (only 3 cases). However, BA concentrations exceeded 50 µmol/L and these animals died or were euthanized for the severity of the disease. This supports the hypothesis observed by [16] that high BA concentrations (>50 µmol/L) are associated with the nonsurvival of this disease. In contrast, in cholangiohepatitis and hepatic lipidosis, the survival rate was 79% (15/19 survivors) and 87% (7/8) despite the marked elevations in BA concentrations present in some cases. These findings suggest that the primary disease and the potential for reversible liver damage are important in evaluating the prognostic indicator of elevated BA concentrations. The relationship between prognosis and direct bilirubin (DBIL) has only been reported by Dunkel et al. [12], although in this study only DBIL was measured in 2 horses that did not survive, resulting in low statistical power; and indirect bilirubin (IBIL) was not assessed due to confounding effects of hemolysis and anorexia. Based on the results recorded by Delvescovo et al. [14] the magnitude of the elevation of DBIL could represent a better prognostic indicator than BA concentrations in horses from the eastern United States with hepatic disease and BA >30 µmol/L, furthermore, the DBIL concentration was positively correlated with non-survival.

Therefore, an approach to interpreting abnormal liver function through changes in main biochemical and hematological markers in order to aid subsequent diagnosis was considered in this review.

2. Biochemical Profile of the Equine Hepatic Function

Since before alterations in some laboratory parameters are observed, the liver injury must be massive and since pathological processes can differentially alter liver functions, the laboratory diagnosis of liver failure can be a challenge. Increased serum activities of several intracellular enzymes have been reported to be useful in establishing the diagnosis and prognosis of hepatopathies in the horse [5,17]. Hepatocellular enzymes located in the cytoplasm, like sorbitol dehydrogenase-SDH and arginase or the mitochondria, as soon as glutamate dehydrogenase-GLDH, are released following hepatocellular necrosis. Serum activity of these enzymes depends on the number of hepatocytes injured, the severity of the disorders, and the half-life of the enzyme activities involved in both acute and chronic disease. In fact, since the half-life is very short for the enzymes LDH-5 (<24 hours), SDH (<12 hours), and GLDH (12–14 hours), the increase due to hepatocellular injury is followed by a rapid decrease. Thus, repeated measurements of these enzymes may be useful in determining the progression of acute hepatocellular injury, but less appropriate for the diagnosis of chronic liver injury [8,18]. On the other hand, γ-glutamyl transferase-GGT is mainly released from the biliary epithelium and in cases of inflammation, biliary hyperplasia, or destruction of the epithelium of the bile canaliculi and secondary to the inflammation of cholestatic hepatocytes, it continues to rise for a few days, although liver damage is not present [19]. However, in horses, increased GGT activity may also be associated with hepatocellular damage and liver necrosis [5,17–19] (Table 1).

The identification of increased hepatic-derived enzymes is used to diagnose liver damage, but the magnitude of the increases is not sufficiently reliable to predict prognosis [18]. Prognosis is best assessed by function test abnormalities, in conjunction with the identification of the etiology and the presence or absence of hepatic encephalopathy [1].

Other enzymes located in hepatocytes (aspartate aminotransferase-AST and lactate dehydrogenase isoenzyme 5 (LDH-5) and in the epithelium of the bile ducts (alkaline phosphatase-ALP), although they are often included in hepatobiliary profiles in horses, are not specific for hepatobiliary damage since they can be found in other locations. In fact, AST is also expressed in striated muscle, so other liver-specific enzymes (SDH or GLDH) or muscle-specific enzymes such as creatine kinase (CK) must be used to differentiate between hepatocellular or muscle damage. While the marked increase in both AST and SDH suggests acute or active hepatocellular injury, the increase in AST and CK is indicative of muscle damage. Likewise, ALP is also expressed in bone, kidney, intestine, and placenta, and LDH-5 in kidneys, muscle, myocardium, and red blood cells [1]. In copper-associated liver cirrhosis elevations of ALP, AST, GGT, LDH, and BA and prolongation of Prothrombin Time (PT) were identified. Although the cause of hepatic cop-per accumulation was not identified, Ankringa et al. [20] concluded that excess copper in the liver should be considered in the differential diagnosis of hepatic cirrhosis in the horse. However, in chronic hepatic disease with severe liver fibrosis and despite the reduction of its functionality, the serum activities of hepatic enzymes might remain in the physiological range [2].

Serum concentrations of mainly endogenous and exogenous substances that the liver should synthesize or eliminate (ALB, GLOBs, BA, BUN, GLU, TBIL and DBIL, fibrinogen (FIB) and coagulation factors should be included in the liver function test profile [21,18,22]. Since hepatic tests of functionality become abnormal only after 70% or more of its function is lost [22], biochemical indicators can help narrow the differential diagnosis for hepatic failure and, when evaluated over time, can help predict prognosis. Specific parameters, indicators of hepatic disease, include BA, DBIL, ammonia concentrations, and the ratio between branched amino acids: aromatic amino acids (BCAA/AAA ratio). Nonspecific parameters indicators of liver disease include TBIL, IBIL, BUN, GLOBs, ALB, GLU, prothrombin time (PT) and activated Partial Thromboplastin Time (aPTT), triglycerides (TGs), and FIB.

2.1. Bile Acids

Bile acids (BA) are present in high concentrations in the portal circulation, are extracted efficiently by the liver, and are normally transported away from the hepatic tissue through the biliary circulation. The enterohepatic circulation normally removes more than 90% of BA concentrations [23]. It is estimated to cycle approximately 40 times a day in ponies [83]. The determination of the total BA (TBA) concentration is considered a highly sensitive assay in cases of hepatic dysfunction, and its increase is an excellent indicator of liver failure but is not specific to the type of liver disease in horses [15]. Normal TBA concentrations in healthy adult horses between 5 and 28 µmol/L have been reported with neither diurnal variations and postprandial increase, nor time-of-day variations [24]. TBA concentrations >20 µmol/L have high sensitivity and positive predictive value for hepatic diseases in horses [1,13]. Indeed, horses with chronic liver disease and persistently increased TBA concentrations > 20 µmol/L have a guarded to poor prognosis [12,1]. Survival rates for horses with TBA >20 µmol/L [1] and >30 µmol/L [14] have been reported to range from 52 and 55%, respectively, which indicates the reserved prognosis in these cases. Milder increases (up to 20 µmol/L) may occur in a few horses without hepatic disease that result anorexic for 2 or more days (20–30 mmol/L) [25]. However, TBA concentrations should not be used as a predictor of prognosis in horses with acute hepatic disease.

An experimental study, carried out in 9 horses, evaluated the toxicity of the pyrrolizidine alkaloid, resulting in an increase of BA above 50 µmol/L in eight of them, which were euthanized for the severity of the disease or died spontaneously; the only surviving horse showed a BA concentration of 33 µmol/L [16]. Delvescovo et al. [14], showed that the survival rate in horses with BA >30 µmol/L was 55%, which is in line with the previously reported 52% survival for cases with BA concentrations of>20 µmol/L [1], confirming the guarded prognostic indicators for all these cases. Moreover, the degree of BA elevation above 30 µmol/L concentrations did not worsen the prognosis for survival up to 6 months after hospital release.

In foals under 1 week of age, the interpretation of TBA concentrations is difficult. Compared with those of healthy adult horses, TBA concentrations in healthy foals are considerably higher during the first 6 weeks of life. In clinically ill neonatal foals, it is particularly important to have healthy controls of the same age or reference values concerning age [83].

2.2. Total, Direct, and Indirect Bilirubin

In normal horses, the TBIL concentration varies between 0.2 and 5.0 mg/dL, with DBIL in the range of 0 to 0.4 mg/dL [14]. Failure of the liver to absorb, conjugate, and/or excrete BIL can lead to increases in IBIL and/or DBIL. However, both anorexia and hemolysis are causes of unconjugated hyperbilirubinemia in healthy horses [15]. The latter condition may be caused by a congenital deficiency of glucuronyl transferase and affected horses may maintain persistent TBIL concentrations of 9 mg/dL or more [26].

Most cases of equine hepatic disease present moderate increases in TBIL concentration (typically 50-150 mmol/L) in which the IBIL often greatly exceeds the DBIL fraction. However, the increased concentrations of IBIL, which occurs in equine hepatic diseases, are associated with acute hepatocellular but do not necessarily indicate the presence of hepatic failure. Similarly, TBIL values may be within physiological ranges in animals with severe chronic disorders of the liver [27].

According to Barton and LeRoy [83] and DeNotta and Divers [28] when serum DBIL concentration is > 25% of the TBIL value, the hepatocellular disease should be considered in the differential diagnosis, and when > 30% of the total value, cholestasis should be considered as well. DBIL concentration is water soluble and detectable in horse's urine (bilirubinuria) only if blood concentrations rise high enough to exceed the renal threshold; therefore, when urine tests are positive for the presence of BIL, cholestatic disease should be suspected [14].

In case of liver damage in horses, most of the BIL is unconjugated and the DBIL/TBIL ratio is usually <0.3. In horses with acute liver failure, the IBIL is the fraction that increases as the IBIL rarely exceeds 25%-35% of the TBIL.

2.3. Ammonia

Physiological values for ammonia in the range of 13 to 108 µg/dl in healthy horses have been reported. Blood ammonia concentrations can range from slightly above normal to more than 1000 µmol/L, and higher concentrations at admission were associated with nonsurvival in one retrospective report including 36 cases [29].

Hyperammonemia contributes to hepatic encephalopathy in equine patients with liver failure; however, hyperammonemia can

also be caused by gastrointestinal (GI) disorders, poisoning, or inborn metabolic defects. However, patients with hepatic failure have other metabolic complications that do not occur in patients with other causes of hyperammonemia. Hyperammonemia results when ammonia from portal circulation is not metabolized to BUN within the liver and enters the systemic circulation. Raised plasma ammonia affects gluconeogenesis, causing the utilization of branched-chain amino acids. The resultant decrease in the ratio of branched chain to aromatic amino acids (BCAAs to AAAs ratio) affects neurotransmission and may give rise to hepatic encephalopathy or, very rarely, peripheral neuropathy which can lead to unusual complications such as gastric impaction (and colic) or laryngeal paralysis [30].

Although circulating ammonia concentrations can be increased in equine patients with hepatic failure, they do not correlate well with the severity of hepatic encephalopathy, except in portocaval shunts [31]. Hyperammonemia with clinical signs of encephalopathy is occasionally also recorded in horses with acute GI disease, without evidence of concurrent hepatic diseases [29,32,33]. In such cases, hyperammonemia is caused by the increased production of ammonia in the GI tract in combination with increased gut permeability that facilitates ammonia absorption in the horse [34].

Increased blood TBA and ammonia concentrations, with hepatic enzymes' activity usually normal, and signs of hepatic encephalopathy without liver failure have been re-ported in Morgan horses at weaning; this profile, related to an inherited defect in a trans-porter protein at the mitochondrial level that, causes deficiency in ornithine, necessary for urea synthesis, has been identified. This process is characterized by a syndrome of hyperammonemia, hyperornithinemia, and normocitrullinuria [35].

2.4. Branched and Aromatic Amino Acids Ratio

Serum concentrations of branched-chain amino acids (BCAA), leucine, isoleucine, and valine are decreased, while the concentrations of the aromatic amino acids (AAAs) phenylalanine, tyrosine, and tryptophan are increased in patients with advanced liver diseases, resulting in a low of BCAAs/AAAs ratio of plasma amino acids in human cirrhotic patients [36]. A low ratio of branched and aromatic amino acids has been associated with hepatic encephalopathy; hence, a decrease below 2.5 in this ratio has been associated with an increased risk of developing signs of hepatic encephalopathy in horses [37,38]. The imbalance of amino acids tends to become more marked with the progression of hepatic diseases, and aminograms are useful for assessing the prognosis of human cirrhotic patients with or without hepatocellular carcinoma, as have been showed in humans [39].

2.5. Urea and Creatinine

Because the liver is primarily responsible for removing ammonia from the circulation and converting it to BUN for renal excretion, increases in blood ammonia concentration or a decrease in BUN concentration ($<$ 9 mg/dL) may be indicative of chronic hepatocellular disease in the horse [40,83]. Decreased plasma BUN is associated with severe hepatopathies, therefore in these conditions, the measurement of serum BUN concentration has a prognostic value and might be served as a useful screening test for the detection of hepatic insufficiency in these horses [2]. Creatinine is also sometimes low in the liver disease cases for unknown reasons but per-haps due to washout associated with polydipsia. Low concentrations of creatinine in human cirrhotic patients have been related to the presence of protein-calorie malnutrition, reduced muscle mass, altered creatinine production in the liver, and increased excretion of creatinine in the renal tubules of human patients [41]. Although in horses, decreased liver function, advanced age, and reduced muscle mass can maintain creatinine concentration within the physiological range, animals hospitalized for acute liver disease may show prerenal azotemia secondary to dehydration and hypovolaemia, such as colic or diarrhoea [42].

2.6. Albumin and Gobulins

Since ALB has a long plasma half-life (19–20 days), hypoalbuminemia in horses is rare, and it is more common in horses with chronic (18%) than acute (6%) hepatic disorders. Indeed, a decreased functional hepatic parenchyma most likely explains the low ALB concentration in patients with chronic hepatic disease. Since concentrations $<$ 2.0 g/dL are not common even in severe equine liver disease [1], hypoalbuminemia is neither a sensitive nor a specific test for hepatic failure in the horse. ALB concentration in foals is significantly higher in the neonatal foals, on the day of the birth (less than 12 hours old), so it is important to use age-based references to assess liver profile during this early period [43,44].

In contrast, GLOBs are increased in 48% of horses with liver failure. Hyperglobulinemia is probably produced because of systemic immunostimulation by gut-derived antigenic material following the loss of Kupffer cells in the liver [45]. Hyperglobulinemia (polyclonal gammopathy or increased β-globulins) can develop in horses with severe acute or chronic liver disease. Although the total protein concentration may be normal, the albumin/globulin ratio is usually decreased [1,46]. Hyperglobulinemia, in association with other clinicopathologic indicators of liver disease, is an important indicator of marked liver injury, and the magnitude of the increase in serum globulin concentration has prognostic relevance. Serum globulin concentrations greater than 45 g/L are worrisome and values up to 60 to 70 g/L justify a guarded prognosis [1]. However, it must be kept in mind that the in-crease in GLOBs must be interpreted in conjunction with other indicators of liver disease, such as liver enzymes, to support the diagnosis of liver disease/insufficiency.

However, hypergammaglobulinemia has also been associated with monoclonal gammopathy in B-cell lymphomas in horses. In fact, Badial et al. [47] on histopathological examination of tissue samples collected during necropsy in three horses revealed neoplastic lymphocytes in the lymph nodes and perivascular infiltrates in the intestinal tract, kidney, heart, and liver. These three animals were diagnosed with B-cell lymphoma characterized by small to intermediate lymphocytes with concurrent tissue and blood involvement and monoclonal gammopathy of IgG isotypes.

Commonly, impaired liver function reduces the capacity for protein synthesis, so that the ALB and α- and β-GLOB fractions decrease. However, total GLOBs may increase due to increased α -GLOB production as part of the acute phase response, β-GLOB production under inflammatory conditions, liver disease, or parasitism; and γ-GLOB by chronic antigenic stimulation associated with infection. While polyclonal gammopathy is common in chronic bacterial infections or autoimmune pathologies or liver cirrhosis [48], some forms of neoplasia (lymphoma or myeloma) can cause monoclonal gammopathy in the region of β- or γ-GLOBs ([49–51]; Gianetto et al., 2022).

Common variable immunodeficiency (CVID) is a rare condition in adult horses characterized by hypogammaglobulinemia and increased susceptibility to parasitic and bacterial infections, including recurrent respiratory diseases, septicemia, hepatitis, and meningitis B. burgdorferi has been speculated to be the cause of hepatitis in other cases of equine neuroborreliosis [52]. Indeed, Pecoraro et al. [53] identified one case of neuroborreliosis associated to Borrelia burgdorferiin a CVID horse related with hepatitis.

Table 2
Common findings of biochemical parameters and coagulation times associated with liver functional abnormalities ([13]; Dunkell et al., 2011; [31,57]).

Specific Biochemical Indicators of Liver Disease		
Parameter	Dynamic	Range
TBA	> 15	< 15 µmol/L
DBIL	> 0.4	0.1–0.4 mg/dL
DBIL/TBIL	> 0.2	< 0.2
Ammonia	> 108	13–108 µmol/L
BCAA/AAA ratio	< 3.5	3.5–4.5
Bilirubinuria	Positive	Negative
Nonspecific Biochemical Indicators of Liver Disease		
TBIL	> 2.1	0.5–2.1 mg/dL
IBIL	> 2.0	0.3–2.0 mg/dL
BUN	< 10	10–29 mg/dL
GLOBs	> 3.8	2.3–3.8 g/dL
ALB	< 2.9	2.9–3.6 g/dL
GLU	< 71	71–122 mg/dL
PT	> 14	12–14 sec
APTT	> 35	24–35 sec
TG	> 65	14–65 g/dL
FIB	> 400 (inflammation) < 200 (liver chronic disease)	200–400 mg/dL

2.7. Glucose

Although changes in blood GLU concentrations are rarely observed in horses with chronic hepatic disease, hypoglycemia (GLU < 60 mg/dL) can occur in massive acute liver failures of horses [54,55], with liver necrosis, lipidosis, neoplasia, and cirrhosis, being more frequent in foals with hepatic failure than in adult horses. It is likely that as anorexia progresses in liver failure, glycogen stores are depleted, and thus gluconeogenesis and subsequent glycolysis occur from increased glucagon secretion [13]. Hypoglycemia, associated with chronic liver disease in horses, is indicative of a guarded prognosis [1].

2.8. Clotting Parameters

Decreased synthesis of most pro-coagulant, anticoagulant, and fibrinolytic proteins, as well as reduced platelet number and function, are associated with hepatic failure in the horse. Thus, the evaluation of haemostatic function requires the determination of platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen concentration, and fibrin degradation products (FDPs). The reduction in the synthesis of factors II, V, VII, IX, X, XI, and XII is represented at the laboratory level by the prolongation of the PT and APTT. Because factor VII has the shortest half-life and is dependent on vitamin K, abnormalities are seen primarily in PT. In general, a 50% to 70% decrease in the concentration of these factors is necessary for changes to be detectable. Peek and Divers [56] concluded that coagulation abnormalities are not always detectable in all horses with hepatic disease, including obstructive biliary disease and insufficiency. This could be contradictory since it is well known that BA and vitamin K are necessary for the synthesis of coagulation factors II, VII, IX, and X and inhibitors of proteins C and S [56]. Natural anticoagulants such as antithrombin III (AT III) and proteins C and S are also produced in the liver. Decreased hepatic clearance of plasminogen activators, such as tissue plasminogen activator, can result in fibrinolysis [45]. In a population of 65 horses, Johns and Sweeney [57] identified at least one abnormality in a routine coagulation profile (platelet count, PT and APTT times, AT III activity, fibrin degradation products (FDPs), and FIB concentration) in 58% of horses. Although coagulation abnormalities occur in horses with liver disease, these investigators observed no clinical evidence of a bleeding diathesis. Surprisingly, in those horses with fulminant liver disease, platelet counts remained within reference intervals.

Although bleeding is not the most common clinical manifestation in these patients [57], the horse should still be carefully monitored during and after the biopsy. However, 10 of 50 horses with clinicopathologic evidence of liver disease [13] showed clinical signs of epistaxis, bruising, and petechiae, although coagulation indices were not measured. In this same way, West [15] reported that 12 of 40 horses with liver disease evidenced mucosal petechiae or nosebleeds.

2.9. Triglycerides

In situations of negative energy balance, excessive movement of fatty acids out of fat tissue, leads to high blood TGs levels, although hepatic failure, secondary to lipidosis, rarely occurs unless there is visible lipemia in horses [58]; therefore, elevated TGs levels alone should not be used to diagnose hepatic lipidosis and liver failure.

2.10. Fibrinogen

Both in cases of parenchymal insufficiency and diffused intravascular coagulation (DIC) the concentrations of FIB can decrease. In addition, FIB is an acute phase protein indicative of acute inflammatory processes, so cholangiohepatitis can raise the levels of this analyte [59]. Indeed, low iron and high FIB plasma concentrations are both sensitive indicators of systemic inflammation in horses (sensitivity of 90 and 82%, respectively) [60]. Therefore, to correctly interpret blood FIB concentrations, it is important to consider the existence of concomitant liver failure [1]. Although it is rare even to develop hypofibrinogenemia in severe hepatopathies, dysfibrinogenemia, with the production of an abnormal fibrinogen molecule, is much more common [61] (Table 2).

3. Hematologic Abnormalities in Impaired Liver Function

Anemia or polycythemia may occur in horses with hepatic insufficiency. Anemia may be related to chronic inflammation in the presence of liver abscesses or neoplasia or with hemolysis. The anemia of chronic disease is caused by marrow suppression of red blood cell production. Inflammation also leads to a decrease in iron absorption, total iron binding capacity (TIBC)/transferrin, transferrin saturation, and an increase in ferritin to secure iron out of circulation. At the same time, inflammatory cytokines (predominantly IL-6) stimulate hepcidin production by the liver [62]. Hepcidin binds to the iron exporter (ferroportin) induced by the in-

Table 3
Common findings of hematological parameters associated with liver functional abnormalities [80–82].

Nonspecific Hematological Indicators of Liver Disease		
Hematocrit (%)	Anemia: Chronic inflammation Hemolysis Polycythemia: Secondary absolute erythrocytosis	32–48 (Hot-blooded) 24–44 (Cold-blooded)
White blood cells (10^3/μL)	Leukocytosis (infection or inflammation) Leukopenia (endotoxemia)	5.2–10.1
Platelets (10^3/μL)	Thrombocytopenia	100–300

hibition of iron entry into plasma from ferroportin-rich cells (enterocytes or macrophages). The resulting hypoferremia is a common response to systemic infections or generalized inflammatory disorders that primarily serve as a defense mechanism by limiting the availability of iron to invading organisms [63]. Persistent hypoferremia during inflammatory processes is the cause of anemia of chronic disease [64].

However, a rare fulminant intravascular hemolytic syndrome with prominent near-death hemoglobinuria has been reported in horses with hepatic failure in horses [65]. Although the mechanism by which liver pathology leads to intra-vascular hemolysis is unknown, BA values or its salts are considered hemolytic factors in horses [15]. In humans, bile salts bind to the outer layer of the lipid bilayer of the erythrocyte membrane, causing a preferential release of phospholipids and subsequent lysis [66].

In contrast, in horses that develop acute hepatic necrosis, hematocrit (PCV), iron concentrations, and percent iron saturation may remain elevated. Secondary absolute erythrocytosis results from increased stimulation of erythroid precursors as a physiological response to hypoxia from low ambient oxygen concentration, inadequate oxygen exchange due to pulmonary disease, abnormal hemoglobin affinity for oxygen, administration of exogenous substances like erythropoietin (EPO) or paraneoplastic production of EPO by tumors [67,68]. Two types of tumors associated with erythrocytosis in horses are hepatoblastoma (Beeler-Marfisi et al., 2000; [69–71]) and carcinoma ([72,73]; Beeler-Marfisi et al., 2000). Erythrocytosis in this type of neoplasm is usually associated with paraneoplastic production of EPO of tumor origin [74].

Leukocytosis with neutrophilia may be shifted to the right or the left. The right shift may accompany glucocorticoid-mediated stress [1]; the shift to the left responds to the systemic inflammatory response following the loss of Kupffer cells [1]. Examples of leukocytosis are cholelithiasis associated with recur-rent colic [75], cholangiohepatitis [59], and other liver diseases [76]. In contrast, leukopenia with neutropenia is a common finding in infectious diseases directly related to the liver [10].

According to Durham et al. [1], erythrocytosis and leukocytosis are significant indicators of poor prognosis in horses with liver disease. The association between erythrocytosis and poor prognosis is probably related to dehydration in those cases with worse clinical status. Furthermore, these same investigators revealed an increased risk of non-survival in association with WBC $>$ 10.0 $\times$ 109/L compared to reference ranges.

Liver dysfunction can lead to thrombocytopenia from splenic sequestration in an enlarged spleen, secondary to portal hypertension or from decreased thrombopoietin production in the damaged liver [77]. In humans [78], and dogs [79], thrombocytopenia and impaired platelet function are hall-marks of chronic liver disease and cirrhosis. In horses these mechanisms are unknown. (Table 3)

4. Conclusions

Biochemical and hematological analyses allow the diagnosis of different pathologies related to liver function in horses. The alteration of different biochemical analytes, like enzymes related to liver function, and the increase or decrease of different hematological parameters are not always specific to each type of disease. This is mainly because the excesses or defects of different parameters evaluated do not always occur in the same proportions. There are cases of altered liver function that can present a different magnitude of enzymatic or hematological modifications. Therefore, it is necessary, for a correct diagnosis, to carefully assess complete hematochemical variables, including the best-known enzyme activities, an expression and proof of correct and physiological liver function. In this way, veterinarians dedicated to the equine clinic can formulate a correct differential diagnosis of liver disorders from other diseases, and apply adequate treatment and prognosis.

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