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Contents

Thrice Monthly Volume 10 Number 9 March 26, 2022

REVIEW

- 2660** Role of metabolites derived from gut microbiota in inflammatory bowel disease
Zheng L, Wen XL, Duan SL

MINIREVIEWS

- 2678** Roles of Wnt/ β -catenin signaling pathway related microRNAs in esophageal cancer
Chu CY, Wang R, Liu XL
- 2687** Animal models applied to acute-on-chronic liver failure: Are new models required to understand the human condition?
Gama JFG, Cardoso LMDF, Lagrota-Candido JM, Alves LA

ORIGINAL ARTICLE

Case Control Study

- 2700** Associations between coagulation factor XII, coagulation factor XI, and stability of venous thromboembolism: A case-control study
Meng Y, Li Y, Ye YJ, Ma Q, Zhang JB, Qin H, Deng YY, Tian HY

Retrospective Cohort Study

- 2710** Nomogram to predict the risk of endoscopic removal failure with forceps/baskets for treating submandibular stones
Huang Y, Liang PS, Yang YC, Cai WX, Tao Q
- 2721** Association between anesthesia technique and complications after hip surgery in the elderly population
Guo LS, Wang LN, Xiao JB, Zhong M, Zhao GF

Retrospective Study

- 2733** Perforating and nonperforating indications in repeated surgeries for Crohn's disease
Shen WS, Huang XH, Liu RQ, Li CY, Li Y, Zhu WM
- 2743** Treatment of *Pneumocystis jirovecii* pneumonia in non-human immunodeficiency virus-infected patients using a combination of trimethoprim-sulfamethoxazole and caspofungin
Wu HH, Fang SY, Chen YX, Feng LF
- 2751** Acute kidney injury in traumatic brain injury intensive care unit patients
Huang ZY, Liu Y, Huang HF, Huang SH, Wang JX, Tian JF, Zeng WX, Lv RG, Jiang S, Gao JL, Gao Y, Yu XX
- 2764** Enucleation combined with guided bone regeneration in small and medium-sized odontogenic jaw cysts
Cao YT, Gu QH, Wang YW, Jiang Q

Clinical Trials Study

- 2773 Determination of the ED₉₅ of intranasal sufentanil combined with intranasal dexmedetomidine for moderate sedation during endoscopic ultrasonography

Zou Y, Li N, Shao LJZ, Liu FK, Xue FS, Tao X

Observational Study

- 2783 Overexpression of Ubiquilin4 is associated with poor prognosis in patients with cervical cancer

Wang LN, Huang KJ, Wang L, Cheng HY

Randomized Clinical Trial

- 2792 Peplau's interpersonal relationship theory combined with bladder function training on patients with prostate cancer

Yang XH, Wu LF, Yan XY, Zhou Y, Liu X

SYSTEMATIC REVIEWS

- 2801 Efficacy of bone grafts in jaw cystic lesions: A systematic review

Wang J, Yao QY, Zhu HY

CASE REPORT

- 2811 Short stature associated with a novel mutation in the aggrecan gene: A case report and literature review

Yin LP, Zheng HX, Zhu H

- 2818 Treatment with sorafenib plus camrelizumab after splenectomy for primary splenic angiosarcoma with liver metastasis: A case report and literature review

Pan D, Li TP, Xiong JH, Wang SB, Chen YX, Li JF, Xiao Q

- 2829 Sarcomatoid intrahepatic cholangiocarcinoma with good patient prognosis after treatment with Huaier granules following hepatectomy: A case report

Feng JY, Li XP, Wu ZY, Ying LP, Xin C, Dai ZZ, Shen Y, Wu YF

- 2836 Sequential occurrence of T790M mutation and small cell lung cancer transformation in EGFR-positive lung adenocarcinoma: A case report

Hong E, Chen XE, Mao J, Zhou JJ, Chen L, Xu JY, Tao W

- 2844 Early diagnosis of Gitelman syndrome in a young child: A case report

Wu CY, Tsai MH, Chen CC, Kao CH

- 2851 Congenital intestinal malrotation with gastric wall defects causing extensive gut necrosis and short gut syndrome: A case report

Wang Y, Gu Y, Ma D, Guo WX, Zhang YF

- 2858 Delusional parasitosis as premotor symptom of parkinson's disease: A case report

Oh M, Kim JW, Lee SM

- 2864** Laninamivir-induced ischemic enterocolitis: A case report
Suzuki C, Kenzaka T
- 2871** Intramural pregnancy after *in vitro* fertilization and embryo transfer: A case report
Xie QJ, Li X, Ni DY, Ji H, Zhao C, Ling XF
- 2878** Bilateral ureteral reimplantation in a patient with an intraperitoneal ectopic bipenis: A case report
Jia YT, Shi BL, Zhang J, Li YY, Zhu J
- 2883** Lumbar disc sequestration mimicking a tumor: Report of four cases and a literature review
Li ST, Zhang T, Shi XW, Liu H, Yang CW, Zhen P, Li SK
- 2895** Parasitic leiomyoma in the trocar site after laparoscopic myomectomy: A case report
Roh CK, Kwon HJ, Jung MJ
- 2901** Giant nontraumatic myositis ossificans in a child: A case report
Xia AN, Wang JS
- 2908** Paradoxical carbon dioxide embolism during laparoscopic hepatectomy without intracardiac shunt: A case report
Jeon S, Hong JM, Lee HJ, Kim Y, Kang H, Hwang BY, Lee D, Jung YH
- 2916** Local hyperthermia combined with chemotherapy for the treatment of multiple recurrences of *undifferentiated pleomorphic sarcoma*: A case report
Zhou YT, Wang RY, Zhang Y, Li DY, Yu J
- 2923** Acute coronary artery stent thrombosis caused by a spasm: A case report
Meng LP, Wang P, Peng F
- 2931** Turner syndrome with primary myelofibrosis, cirrhosis and ovarian cystic mass: A case report
Xu LW, Su YZ, Tao HF
- 2938** Esophageal myoepithelial carcinoma: Four case reports
Lu H, Zhao HP, Liu YY, Yu J, Wang R, Gao JB
- 2948** Ipsilateral hemifacial microsomia with dextrocardia and pulmonary hypoplasia: A case report
Guo R, Chang SH, Wang BQ, Zhang QG
- 2954** Upper gastrointestinal bleeding from a Mallory-Weiss tear associated with transesophageal echocardiography during successful cardiopulmonary resuscitation: A case report
Tang MM, Fang DF, Liu B
- 2961** Malignant struma ovarii with papillary carcinoma combined with retroperitoneal lymph node metastasis: A case report
Xiao W, Zhou JR, Chen D

- 2969** Occult colon cancer with sepsis as the primary manifestation identified by bone marrow puncture: A case report

Wang HJ, Zhou CJ

ABOUT COVER

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Animal models applied to acute-on-chronic liver failure: Are new models required to understand the human condition?

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Abstract

The liver is a multifaceted organ; its location and detoxifying function expose this organ to countless injuries. Acute-on-chronic failure liver (ACLF) is a severe syndrome that affects the liver due to acute decompensation in patients with chronic liver disease. An infection environment, ascites, increased liver enzymes and prothrombin time, encephalopathy and fast-evolving multiorgan failure, leading to death, usually accompany this. The pathophysiology remains poorly understood. In this context, animal models become a very useful tool in this regard, as understanding the disease may be helpful in developing novel therapeutic methodologies for ACLF. However, although animal models display several similarities to the human condition, they do not represent all ACLF manifestations, resulting in significant challenges. An initial liver cirrhosis framework followed by the induction of an acute decompensation by administering lipopolysaccharide and D-GaIN, potentiating liver damage supports the methodologies applied to induce experimental ACLF. The entire methodology has been described mostly for rats. Nevertheless, a quick PubMed database search indicates about 30 studies concerning ACFL models and over 1000 regarding acute liver failure models. These findings demonstrate the clear need to establish easily reproducible ACFL models to elucidate questions about this quickly established and often fatal syndrome.

Key Words: Liver disease; Acute-on-chronic liver failure; Cirrhosis; Acute decompensate event; Translational study; Animal models

Core Tip: The liver is a multifaceted organ; its location and detoxifying function expose it to countless injuries. Acute-on-chronic failure liver (ACLF) is a severe syndrome that affects the liver due to acute decompensation in patients with chronic liver disease. Animal models become a very useful tool in this regard. However, although they display several similarities to the human condition, they do not represent all manifestations, resulting in significant challenges. A quick PubMed database search indicates about 30 studies concerning ACLF models. These findings demonstrate the need to establish easily reproducible models to elucidate questions about this quickly established and often fatal syndrome.

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INTRODUCTION

The liver is a multifaceted organ that performs various functions, including protein and amino acid metabolism and plasma protein secretion, in addition to lipid oxidation and drug and xenobiotic blood detoxification[1]. Hepatic tissue is susceptible to countless injuries that may lead to liver cirrhosis. Most chronic liver lesions that culminate in cirrhosis processes are reversible, depending on their etiology, the amount of affected liver tissue and appropriate treatment, although this may lead to serious complication or be fatal in some patients[2]. Deaths caused by liver disease have increased by around 400% in the United Kingdom since the 1970s up to 2018[3]. About 2 million people die each year due to liver disease complications, 50% of which are due to liver cirrhosis. This is mostly due to alcohol consumption and non-alcoholic fatty liver diseases in the western world and hepatitis B in China and Asian countries[4]. Acute-on-chronic liver failure (ACLF) was diagnosed in 30% of all cases among 1343 hospitalized patients presenting liver cirrhosis according to a European study carried out between February and September 2011, with a mortality rate of 32.9% at 28 d and 51.2% at 90 d. Patients with liver cirrhosis may experience acute decompensating that leads to ACLF, characterized by ascites, hepatic encephalopathy, gastrointestinal bleeding or a combination of these symptoms[5,6]. The molecular, cellular, and immune mechanisms reported in patients with liver cirrhosis that develop ACLF, however, remain unclear. Therefore, effective therapeutic methodologies become a challenge, generating high costs, with liver transplants comprising the only effective treatment to date.

Animal models concerning hepatic disease have been very useful in preclinical research for decades, comprise an alternative in the understanding of ACLF pathophysiology, as they are reproducible, and are able to adequately mimic some ACLF events. However, many models do not faithfully reproduce human disease and require special management for understanding specific hypothesis. In this context, this review aims to provide an overview of the main animal models used in ACLF research, alongside their pros and cons. Furthermore, pathological events that do reproduce human ACLF are also discussed.

WHAT IS KNOWN ABOUT ACUTE-ON-CHRONIC LIVER FAILURE PATHOPHYSIOLOGY?

The vast majority of patients referred to specialist hepatological centers suffer from acute deterioration during chronic liver disease. Two important conditions are observed in patients with known chronic liver disease who exhibit acute decompensation, namely acutely decompensated cirrhosis and ACLF. The first is a widely accepted condition and refers to the development of ascites, encephalopathy, gastrointestinal hemorrhage, or any combination of these disorders in patients with cirrhosis[5,7]. The second, ACLF, identifies patients with known or unknown chronic liver disease who develop rapid liver function deterioration and high short-term mortality after an acute insult. The definitions of ACLF differ, with most addressing the role of both hepatic and extra-hepatic precipitating events and including extra-hepatic organ failures[8,9]. ACLF, a term suggested by Jalan and Williams in 2002[10], emerged from studies indicating the development of a syndrome associated with a high risk of short-term death (death < 28 d after hospital admission) in patients presenting acutely decompensated cirrhosis. Three major features characterize this syndrome, namely intense systemic inflammation, frequently displaying a close temporal relationship with pro-inflammatory precipitating events (*e.g.*, infections or alcoholic hepatitis) associated with single- or multiple-organ failure. However, the first

ACLF definition was only established by a consensus of the Asian Pacific Association for the study of the liver (APASL) in 2008. Unlike other definitions, this definition does not include extra-hepatic organ failures[7]. Thus, ACLF was defined as an acute hepatic insult in patients with chronic liver disease resulting in jaundice (total bilirubin ≥ 5 mg/dL) and coagulopathy (INR ≥ 1.5), complicated within four weeks by ascites and/or encephalopathy[7]. Thereafter, the North American Consortium for the Study of End-Stage Liver Disease associated ACLF with a 30-d mortality rate of 41% compared to 7% concerning acute decompensation without ACLF[11]. Meanwhile, the European Association Study Liver (EASL) defines ACLF as an acute decompensated liver insult in patients with cirrhosis or chronic liver disease that can often lead to sepsis due to bacterial infection, increasing the requirement for intensive care and resulting in a high 28-d mortality rate ($\geq 15\%$)[12].

The prevalence of ACLF ranges from 24% to 40% of hospitalized patients with liver cirrhosis. ACLF may develop in patients with previously compensated or decompensated cirrhosis, as well as in patients presenting the underlying chronic liver disease without cirrhosis[13]. Excessive alcohol consumption is also important in an ACLF context, as alcoholic hepatitis results in a high mortality rate and is one of the causes of acute-on-chronic liver injury[14]. Furthermore, over 50% of patients presenting alcoholic cirrhosis exhibit decompensated disease and, in the US, alcohol-associated liver diseases can lead to an indication for liver transplantation[15,16]. In contrast, the reactivation of hepatitis B virus (HBV) is the leading cause of ACLF in the Asian region, with high prevalence where HBV-related acute-on-chronic liver failure (HBV-ACLF) accounts for over 70% of ACLF[17,18]. However, early diagnosis and prevention measures through long-term HBV infection suppression with antiviral agents (such as lamivudine, tenofovir, entecavir or telbivudine) or sustained eradication of hepatitis C virus (HCV) infection in patients with compensated or decompensated cirrhosis can decrease mortality and prevent the development of HBV-ACLF and HCV-related acute-on-chronic liver failure (HCV-ACLF) in this region[19,20]. Patients with chronic hepatitis B or HBV-related cirrhosis are at risk of developing ACLF, with multi-organ failure and high short-term mortality[21]. HBV reactivation could be either a spontaneous setting of treatment cessation[22] or due to intensive chemotherapy or immunosuppressive therapy[23,24], treatment related[25] or reactivation of the occult HBV infection by rituximab (anti-CD20)-based chemotherapy[26-28] or immune restoration after highly active antiretroviral therapy for HIV[29,30]. Similarly, HCV infection reactivation has also been reported, mainly following immune suppressive therapy[31,32]. Drugs such as anti-tuberculosis drugs, methotrexate and antiretroviral drugs in HIV/AIDS-infected individuals have been implicated in triggering liver injury, particularly in the setting of underlying chronic liver disease due to HBV or HCV[31,33-35]. Drugs are seen as a precipitating factor in ACLF, although databases on concerning drugs as an acute insult leading to ACLF are extremely scarce. This factor limits the study and knowledge of the effects of certain drugs and medications in ACLF development. This indicates the need for further data and assessments concerning models on hepatic injury caused by different herbal and medicinal preparations in cirrhosis patients[8].

ACLF pathogenesis is still poorly understood, and will depend on the origin of the condition, the number of organ failures and the patient's past medical history. It can, however, be characterized as a systemic inflammatory syndrome, whose evolution and pathophysiology are directly associated with the involved immune mechanisms, such as those in response to danger associated molecular patterns and pathogen associated molecular patterns (DAMPs and PAMPs, respectively), cytokine production and the inflammatory profile[36]. Patients with hepatitis B (HB) diagnosed with ACLF exhibit an exacerbated innate and adaptive inflammatory response evidenced by increased ROS (reactive oxygen species) production by macrophages and neutrophils, increased TLR4 expression and high blood cytokine levels. The induction of cytokine storms has been associated with interleukin 33 (IL-33) up-regulation, an important DAMP associated with disease severity[36,37]. The source of this inflammatory response exacerbation, however, remains unknown. Another event consists in the formation of the NLRP3 inflammasome, as reported in a study on 70 HB patients presenting ACLF. This is composed of a NOD-like receptor family, pyrin domain containing 3 (NLRP3), an intracellular PAMP receptor responsible for activating Caspase-1 that, consequently, cleaves pro-inflammatory IL-1 β and IL-18 cytokines[38]. Immune system cells involved in the inflammatory response play a key role in the ACLF-caused mechanism, as the neutrophil-leucocyte ratio is an indicator of ACLF death severity[39]. In addition, the large liver cell death that occurs in ACLF may be closely related to mitochondrial damage, mainly in organ and multi-organ failure. In three CANONICAL studies in cirrhotic patients with ACLF was observed changes in mitochondrial markers associated with ACLF follow up[40-42]. The increase of fingerprints in metabolomics assays demonstrated the fatty acylcarnitines (FA) was raised, suggesting impairment in β -mitochondrial oxidation that can cause decreasing of the FA-derived energy in peripheral organs, and then, cell death and organ failure[40]. In addition, immunometabolism was required with the increased of GDF15 and FGF21, as wells as the up-regulation of inflammatory cytokines (e.g. MIP-1 α/β , MCP-1, IL-1 α and IL-6) and ultra-structural changes with cristae rarefaction in mitochondrial morphology of the peripheral blood mononuclear cells[41,42]. These findings together indicate the impairment of mitochondrial function through the energy expenditure by systemic inflammation. Xue and coworkers demonstrated that mitofusin2 (Mfn-2) can regulated the autophagy and apoptosis levels, as well as decreasing reactive oxygen species (ROS)[43].

Another important issue concerning the knowledge and studies of the events that lead to ACLF development in humans is directly related to the current pandemic scenario caused by the new coronavirus disease 2019 (COVID-19). The hallmark of ACLF is excessive systemic inflammation, and patients with ACLF exhibit higher levels of inflammatory markers and pro-inflammatory cytokines—IL-6, IL-1 β , and IL-8. Systemic inflammation inducers can be exogenous or endogenous and viruses have been described previously as triggering inflammation[13]. A cytokine storm has been reported in patients with COVID-19, characterized by increased IL-2, IL-7, G-SCF and TNF- α [44]. Thus, it is believed that the excessive inflammatory response associated with COVID-19 can serve as a trigger for ACLF in patients with underlying chronic liver disease, which could justify the increase in liver disease patient deaths[45]. However, other mechanisms may also contribute to ACLF development in COVID-19 patients, such as hypoxic changes and iatrogenic causes such as drugs and ventilation, exacerbating underlying liver disease[46,47]. A case study reported the development of ACLF precipitated by severe acute respiratory syndrome coronavirus-2 infection (SARS-CoV-2) in a patient with HBV-related cirrhosis without no previous anti-viral treatment. The authors suggest that the SARS-CoV-2 infection induced systemic inflammatory response syndrome, and the resultant immune dysregulation could have precipitated ACLF, in turn. Since the patient had not been on nucleoside analogs treatment for HBV prior to admission, it is possible that the ACLF was caused by HBV flare in a context of uncontrolled inflammation and dysbalance of innate and adaptive immune responses triggered by the SARS-CoV-2 infection[48]. This highlights the importance of the treatment in patients with HBV and other chronic liver disease in the current pandemic status worldwide. Nevertheless, long-term follow-up clinical studies are required to explore the potential relationship between ACLF development in COVID-19 patients[45].

Despite these relevant facts concerning ACLF pathophysiology, the low number of patients assessed to date, its poor diagnosis and the use of different methodological analyses are still a challenge in understanding this condition. Focused research on strategies to prevent and treat this potentially reversible syndrome are, thus, paramount. Therefore, animal models comprise a helpful tool, as they are reproducible, easy to manage and are able of mimicking several ACLF mechanisms.

ANIMAL MODELS IN LIVER RESEARCH

As described previously, acute and chronic liver diseases are frequent and potentially lethal conditions, displaying a high worldwide prevalence[49]. The development of new therapeutic strategies, drugs and the definition of effective potential biomarkers depends on understanding liver damage pathogenesis and progression, which can be investigated by making use of suitable animal models. Liver injury is highly complex and the absence of adequate animal models able to faithfully reproduce human liver disease characteristics limits the understanding of the mechanisms underlying this condition and treatment[50,51]. Rodent animal models are preferred in preclinical liver research, mainly in ACLF assessments, due to easy to maintain and breed in captivity, the genetic similarity to human, similar liver morphology and simple management concerning the use of genetic manipulation tools[52]. In contrast, large animal models, like pigs, previously used mostly in acute liver failure modeling, now play an important role in the assessment of various acute and chronic liver diseases[51]. Non-human primate models like baboons (*Papio hamadryas*) are also widely applied due proximity of the human condition, for example, as alcohol-caused liver disease (ALD) models. They displaying significant similarity to the pathogenesis of this disease, *i.e.*, inducing fatty liver and fibrosis, and high annexin-2 Levels, directly associated to the final stage of the disease in humans, as well as fibrinolysis and high risk of bleeding[53]. Furthermore, Rhesus monkeys also significantly reproduce the pathology, biochemistry markers and genetic expression of human ALD[54]. However, after a deep and thorough data review, we observed that no primate non-human models have been reported in the literature concerning ACLF research, and that rodent (rats and mice) models are the most assessed (Table 1).

Animal models as important contributors to the understanding of ACLF

Animal models are useful in understanding the mechanisms surrounding immune responses and multiorgan failure in inflammatory and systemic syndromes[55]. Many studies have attempted to comprehend this inflammatory scenario[56-62]. With the aim of mimicking the human disease, techniques able to induce ACLF, resulting in a chronic liver insult and, finally, a precipitating event, have been developed. It is important to note that the main precipitating events comprise the reactivation of hepatitis viral or acute hepatitis A virus infection, acute alcoholic hepatitis or acute bacterial infection in Asian patients and alcoholism and bacterial infection that aggravate chronic cirrhosis conditions in the western world[20]. In this context, most ACLF animal models induce chronic cirrhosis and a posterior acute insult, usually through the administration of Lipopolysaccharide (LPS), LPS/D-Galactosamine hydrochloride (D-GaIN) or ethyl alcohol (EtOH), in order to reproduce events of bacterial infection (Figure 1). However, few animal ACLF models have been established to date (described in the next section).

Table 1 Current experimental acute-on-chronic liver failure animal models

Animal model	Liver chronic induction	Fibrosis establishment	AD	Immune response observed	Clear methodology randomized study	Ref.
Female Wistar rats	HSA subcutaneous and i.v.	Yes	LPS/D-GaIN i.p.	Inflammatory cytokines	Unclear methodology regarding randomization ¹ , n = 60	Wang <i>et al</i> [56], 2012; Gao <i>et al</i> [83], 2016
Male NZ rabbit	CCl ₄ in oil i.p.	Yes	Not described	Not described	Unclear methodology	Zhu <i>et al</i> [71], 2013
Female Wistar rats	HSA subcutaneous and i.v.	Yes	LPS/D-GaIN i.p.	Inflammatory pathway through cytokines increase	Unclear methodology regarding randomization ¹ , n = 15	Yang <i>et al</i> [57], 2014
Female SD rats	CCl ₄ in oil i.p.	Yes	LPS/D-GaIN i.p.	Not described	Unclear methodology	Zhang <i>et al</i> [67], 2014
Female Wistar rats	BD ligation	Yes	ischemia 70% liver reduction	Inflammatory cytokines	Unclear methodology regarding randomization, n = 10	Hu <i>et al</i> [58], 2014
Male SD rats	CCl ₄ in oil i.p.	Yes	LPS/D-GaIN i.p.	Treg/Th17 imbalance	Unclear methodology regarding randomization ¹ , n = 80	Ni <i>et al</i> [59], 2017
Male Wistar rats	Cholestasis induced by BD ligation	Yes	Not described	CD45 ⁺ up regulation	Unclear methodology regarding randomization ¹ , n = 20	Gilsanz <i>et al</i> [60], 2017
Male Wistar rats	PS i.p.	Yes	LPS/D-GaIN i.p.	Inflammatory cytokines	Unclear methodology regarding randomization ¹ , n = 10 e 60	Li <i>et al</i> [61], 2017
Wistar rats	BD ligation	Yes	LPS i.p.	Not described	Unclear methodology regarding randomization ¹ , n = 6/8	Nataj, <i>et al</i> [80], 2018
Wistar or SD rats	CCl ₄ or TAA or BD ligation	Yes	LPS i.p.	Neutrophil infiltration and NET	Unclear methodology regarding randomization ¹ , n = 6-9	Tripathi <i>et al</i> [69], 2018
Male C57BL/6J	CCl ₄ in olive oil i.p.	Yes	Ethyl alcohol	Inflammatory cytokines and neutrophil infiltration	Unclear methodology regarding randomization ¹	Furuya, <i>et al</i> [14], 2019; Schwarzkopf <i>et al</i> [73], 2020
Male SD rats	CCl ₄ in oil i.p.	Yes	LPS/D-GaIN i.p.	Not described [†]	Unclear methodology regarding randomization ¹ , n = 10	Xue <i>et al</i> [43], 2019
Male SD rats	CCl ₄ in oil i.p.	Yes	LPS/D-GaIN i.p.	Not described ^{†§}	Unclear methodology regarding randomization ¹ , n = 10	Xie <i>et al</i> [68], 2019
Male C57BL/6J	CCl ₄ in oil i.p.	Yes	<i>Klebsiella pneumonia</i> i.p.	Increase in IL-6 and IFN- γ pathway	Unclear methodology regarding randomization ¹ , n = 4-8	Xiang, <i>et al</i> [70], 2020
SD rats	BD ligation	Yes	LPS i.p.	Inflammatory cytokines	Unclear methodology	Monteiro <i>et al</i> [62], 2021

¹There is no methodological description of the randomization that has been used. [†]The mitochondrial function was assessed relating with cell damage and systemic inflammatory response. [§]This model shows increased of vacuoles and damage liver mitochondrial, and downregulation in adenosine triphosphate and adenosine diphosphate source. AD: Acute decompensation; NZ: New Zealand; SD: Sprague Dawley; HAS: Human albumin serum; PS: Porcine serum; i.p.: Intraperitoneal injection; i.v.: Intravenous injection; TAA: Thioacetamide Administration; LPS: Lipopolysaccharide; D-GaIN: D-Galactosamine Hydrochloride; BD: Bile Duct; CCl₄: Carbon Tetrachloride; NET: Neutrophil extracellular trap; Treg: Regulatory T cell; Th17: T helper 17 lymphocyte.

Chemically induced ACLF animal models: Carbon tetrachloride in combination with LPS/GaIN

A widely applied model used to induce chronic lesions consist in the use of carbon tetrachloride (CCl₄) as a hepatocellular damage inducer. This model leads to liver steatosis due to CCl₄ covalent binding to cell metabolites, resulting in Ca²⁺ sequestration and K⁺/Na²⁺ channel imbalances in an anaerobic environment and cytochrome P450 (CYP450) action [63]. Liver CCl₄ metabolism occurs through carbonyl chloride and free radicals formation (*i.e.*, [•]CCl₃), the latter binding to protein and lipids in the cell cytosol, even though no acid nucleic binding occurs [64]. Thus, toxicity due to CCl₄ administrations is similar to alcohol-induced toxicity. Furthermore, fibrosis following significant liver destruction is also noted in this model, evidenced by increased hydroxyproline content and liver function failure, comprising increased alanine aminotransferase (ALT) and aspartate transaminase (AST) activities [63, 65]. Aiming to mimic ACLF events, CCl₄ in combination with the administration of D-GaIN, with or without LPS, is the mostly used to induce chronic liver injury (Table 1). LPS is a bacterial endotoxin capable of activating Kupffer cells and stimulating TNF- α and an immune response by the NF- κ B

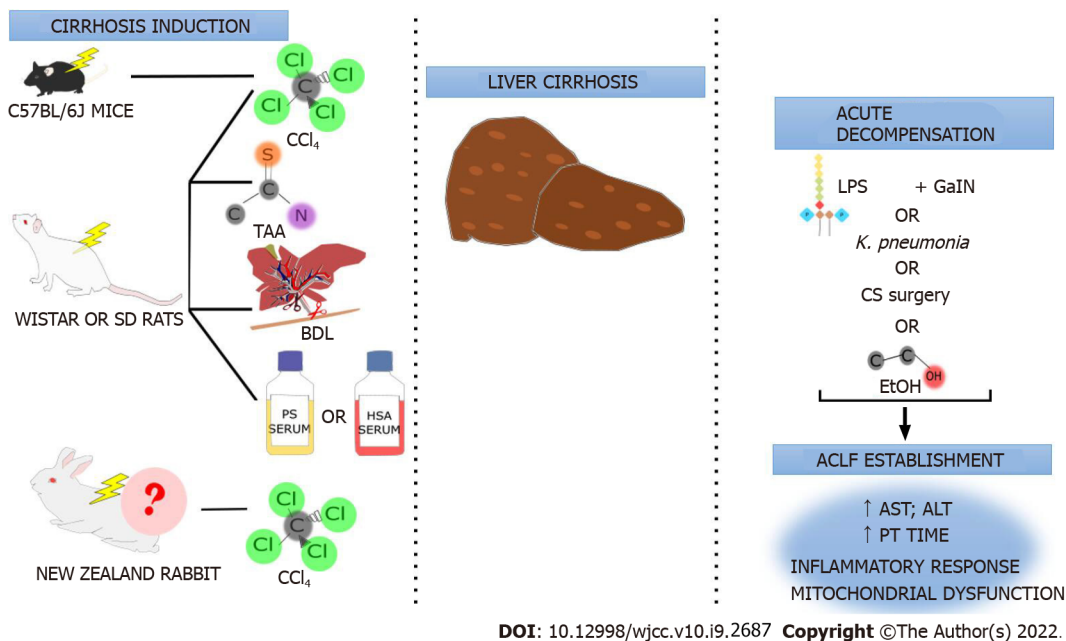


Figure 1 Acute-on-chronic liver failure animals models based on a literature review. Liver injury models applying chemical, biological and surgery induction leading to cirrhosis and subsequent acute decompensation with lipopolysaccharide or Galactosamine hydrochloride or both associated, *Klebsiella pneumonia* i.p. injection or Ethyl alcohol (EtOH), and CS surgery to Acute-on-chronic Liver Failure (ACLF) induction in rats or acute decompensation with EtOH in mice. Intense fibrosis and Aspartate aminotransferase, Alanine aminotransferase serum levels, an inflammatory response and impairment of mitochondrial function are observed. Unclear and non-reproducible data concerning the ACLF rabbit model induced by Carbon tetrachloride are described. SD: Sprague Dawley; HAS: Human albumin serum; PS: Porcine serum; TAA: Thioacetamide Administration; CS: Cecal slurry; BDL: Bile duct ligation; CCl₄: Carbon tetrachloride; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PT: Prothrombin time; ACLF: Acute-on-chronic liver failure.

pathway, while D-galactosamine is able to potentiate this response by depleting the uridine nucleotides and interfering in protein synthesis, leading to acute insults as a precipitating event[66]. The major challenge verified in this model consists in determine differences between CCl₄ and LPS/GaIN administration time and doses for ACLF induction. In one study, female Sprague-Dawley (SD) rats (180-200 g) were administered intraperitoneal (i.p.) CCl₄ dissolved in olive oil (10%) twice a week for ten weeks. After cirrhosis confirmation, the animals received 0.70 g/kg body weight (BW) D-GaIN i.p.[67]. ACLF was confirmed due to increased AST and ALT activities and higher bilirubin and plasma ammonia levels associated with changes consistent with necrosis as revealed by histological analyses. However, modified CCl₄ doses were administered according to the liver function index and animal body weight [67]. In another study, ACLF was induced in male SD rats (150 - 170 g) by the i.p. injection of 1.5 mL/kg of CCl₄ dissolved in vegetable oil (40%) twice a week for ten weeks. After cirrhosis establishment, LPS (100 µg/kg) and D-GaIN (0.5 g/kg) were i.p. administered[43]. In addition to the same biochemistry and histopathology events observed as in the first study, a macroscopic analysis also detected granules and severe liver surface adhesions, as well as increased B-cell lymphoma 2 (BCL-2) and BCL-2-associated X protein apoptosis regulator genes, which could probably be handled with the control of mitochondrial damage *via* Mtn-2[43,67]. Immune responses are also a target for investigation. Thus, another study evaluated male SD rats (160-180 g) received i.p. injections comprising CCl₄ in peanut oil (1/1 w/v) once every three days for two months (1.5 mL/kg BW during the 1st month and 2 mL/kg BW during the 2nd month). Subsequently, 500 mg/Kg BW D-GaIN and 80 µg/Kg BW LPS were i.p. administered, resulting in a Treg/Th17 ratio imbalance, necrosis and fibrotic tissue as revealed by histological assessments[59]. In addition to intense inflammatory response, the HIF-1α shows an important role in development of ACLF and the mitochondrial function was impairment. These findings was observed in a study with ACLF induced by i.p. CCl₄ in vegetable oil (1.5 mL/kg) 3 days in 4 wk, in male SD rats (approximately 200 g), and then i.p. of LPS (100 µg/kg) in combination with D-GaIN (0.5 g/kg)[68]. These models show enhanced histopathological evidences; AST and ALT levels and prothrombin time (PT) was raised, as well as the liver mitochondrial ultrastructure was damage with nuclear fragmentation[68]. Its corroborated the energy expenditure due the oxidative stress and systemic inflammation[40,42]. Tripathi and collaborators reported that CCl₄ is capable of inducing advanced chronic liver injury, as Wistar rats (50-75 g) subjected to CCl₄ inhalation and receiving phenobarbital (0.3 g/L) in drinking water presented micronodular cirrhosis with ascites after 15 or 16 wk. Subsequently, LPS (from obtained from *Escherichia coli*, O111:B4 - 1 mg/kg) was i.p. injected to induce an acute insult in the decompensated cirrhosis group 4 h prior to a hemodynamic study and 24 h prior in the compensated cirrhosis group[69]. LPS administration was more effective in the decompensated cirrhosis animals, resulting in portal hypertension and increased neutrophil infiltration

and neutrophil extracellular trap (NET), as well as a high inflammatory response and aggravated fibrosis[69]. Male C57BL/6J mice have also been reported as an ACLF model with disease induced by CCl₄ i.p. (0.2 mL/Kg/twice a week, for 8 wk). Then, a double dose CCl₄ injection (0.4 mL/kg) was administered. After that, *klebsiella pneumonia* (strain 43816- ATCC, Manassas, VA) was i.p. injected in order to mimic bacterial infection in ACLF[70]. This model was able to develop the main observed pathophysiological features of ACLF in humans, such as chronic/acute liver injury, bacterial infection and multiorgan failures. Rabbits have also been described as an ACLF model mimicking the condition of this disease. In one investigation, New Zealand Rabbits injected i.p. with CCl₄ displayed changes in biochemical markers after 10 wk, including ALT, AST, albumin and prothrombin levels, as well as altered liver morphology, reflecting fibrosis consistent with cirrhosis, revealed by HE- and Masson-stained analyses, following the administration of intravenously-injected D-GaIN[71]. It is important to note that the methodology applied in the model described in a previous study carried out with male New Zealand rabbits (2.73 ± 0.05 kg and 100 d old) that did not induce ACLF, only cirrhosis, by the intragastric administration of CCl₄ once a week during 16 wk[71,72]. Therefore, rabbits have not yet been established as an ACLF model.

Another experimental model comprises the ACLF induction by chronic i.p. CCl₄ injection and an acute insult with EtOH administered *via* an intragastric cannula, resulting in a condition resembling human alcoholic hepatitis[14,73]. Briefly, 12-wk-old C57BL/6J male mice were categorized into a control group receiving an olive oil i.p. injection and an experimental group receiving a CCl₄ i.p. injection (0.2 mL/kg) twice a week during 6 wk to induce liver fibrosis. The experimental group was then submitted to surgical intragastric intubation, beginning at EtOH 16 g/kg/day, gradually increasing to 25 g/kg/day. The CCl₄ associated with EtOH was able to mimic an acute-on-chronic injury, resulting in intense inflammation, hypoxia and opportunist infection by *E. coli* and *Candida sp.*, as well as chromatin and DNA modifications with epigenetic gene dysregulation. This model is, however, difficult to reproduce, due to the applied surgery and an approximate mortality rate of 30%.

It is noteworthy that CCl₄ has been widely applied to induce hepatotoxicity in experimental studies, although it is toxic. According to the National Institute of Health chemistry database (PubChem) CCl₄ is a clear, colorless, volatile and very stable chlorinated hydrocarbon and its inhalation (> 200-250 ppm CCl₄ for > 4 h) leads to accumulation mainly in fatty tissues and may result in nervous system depression, lung, kidney and liver damage and increased cancer susceptibility[74]. The intoxication level and affected tissue, however, may vary with exposure time and amount. Although no direct data concerning humans are available, animal experiments have indicated that toxic CCl₄ metabolites are produced in reactions catalyzed by CYP450 oxygenases (*e.g.*, CYP2E1; CYP3A)[74,75].

Chemically induced ACLF animal model: Thioacetamide in combination with LPS

Administration i.p. of Thioacetamide (TAA) also has been used to induce ACLF. In one assessment, male SD rats (150-200 g) received 250 mg/kg of TAA dissolved in saline twice a week for ten weeks to induce compensated cirrhosis without ascites development[69,76]. The animals subsequently received i.p. LPS injection obtained from *Escherichia coli* O111:B4 - 1 mg/kg) 24 h prior to a hemodynamic study. Increased liver enzymes, portal hypertension worsening and fibrosis were noted, similar to the human condition[69]. This is the only study to date applying TAA alongside LPS to induce ACLF in an animal model as an alternative methodology to CCl₄ administration. However, TAA, a crystalline solid, is highly toxic following inhalation or dermal contact and is carcinogenic to humans[77], requiring care to avoid researcher, laboratory and environmental contamination.

Surgery protocol to reproduce the human ACLF condition

In addition to chemical ACLF induction, surgery can also be used to establish ACLF. An obstructive jaundice model was developed in female Wistar rats (200-250 g) through bile duct ligation (BDL) by the dissociation of the common bile duct of the hepatoduodenal ligament[58], through a double ligature using surgical threads at the proximal end of the common bile duct, followed by a layered suturing of the abdominal wall to close the abdominal cavity[58,78]. Reduced-size hepatic is-chemia/reperfusion injury was performed, leading to cholestasis (0 min, 15 min, 30 min and 45 min of ischemia), followed by a choledochoduodenostomy to relieve this condition. A reduction of the 70% in the hepatic area was observed. This model was able to reproduce certain ACLF pathological features, such as increased AST, ALT and total bilirubin levels after the obstruction surgery[58]. Another study demonstrated that microsurgery applied to induce cholestasis also mimics certain pathological ACLF events. For example, male Wistar rats (200-400 g) have been submitted to an extra-hepatic biliary tract dissection through hepatic lobe and lobe ligament sectioning[60,79]. This technique is most applied in human secondary biliary hepatic cirrhosis and atresia assessments, but is also capable of inducing ACLF syndrome events, such as histological and biochemistry aspects and an international normalized ratio (INR) of up to 1.5. In addition, an increase in CD45⁺ leucocyte infiltration was also observed[60]. Recent studies have suggested the bile duct obstruction Wistar rat model followed by the i.p. injection of a single dose of LPS (1 mg/kg, extracted from *Salmonella typhimurium*)[80] or bile duct-obstructed SD rats followed by an i.p. injection of LPS (0.03 mg/kg BW). It was obtained from *Klebsiella pneumoniae* 28 d after cirrhosis as confirmed ACLF models presenting systemic disease. Alternatively, to induce acute decompensation, animals received a single intravenous LPS dose obtained from *Escherichia coli* O111:B4 - 6.25 mg/kg BW

3 wk after bile duct obstruction[62]. Using a similar methodology, common bile duct ligation was performed in SD rats for 28 d, with cirrhosis displaying ascites established on the 25th day. The animals were then injected with LPS 1 mg/kg obtained from *Escherichia coli* (O111:B4)[69]. An increase in plasma enzyme levels and splenomegaly were observed, mimicking pathological events and inducing the inflammasome (*e.g.* IL-1 β ; IL-18), as noted in the human syndrome[62,80]. Although these methodologies result in similar conditions to the human disease, the need for surgical procedures and animal survival maintenance make them more challenging and costly, requiring previous surgical knowledge.

Last but not least: Albumin serum-induced ACLF

Studies have demonstrated that the albumin, the most abundant protein in the human serum, metabolized in the liver and secreted to the plasma can be an alternative to treat decompensated cirrhosis, although it can become hepatotoxic when an imbalance in albumin levels occurs. Thus, albumin may induce cirrhosis events both when interacting with LPS or when undergoing irreversible alkalization by drug metabolism[81,82]. Therefore, human albumin serum (HSA) is a potential model for liver damage. In order to develop HSA-induced ACLF, female Wistar rats (180-220 g) were challenged with a subcutaneous HSA injection diluted in saline (8 g/L) and the same volume of incomplete Freund's adjuvant for four times (0.5 mL containing 4 mg HSA). Next, 4 mg HSA were injected into the animal tail veins twice/week for six weeks[56]. After the establishment of immune cirrhosis, the animals received 400 mg/kg of D-GaIN and 100 μ g/kg LPS, both *i.p.*, inducing acute decompensation in chronic liver disease, leading to changes in liver histology and increased serum enzymes and several inflammatory markers, such as IL-6, IL-18 and HMGB-1. It is important to note that both NF- κ B and TNF- α play an important role in HMGB-1-mediated responses[56,57,83,84], similar to human ACLF. Since the HSA ACLF model results in high mortality rates, it was developed a rat model using porcine serum (PS), resulting in better induction of pathophysiological events[56,61]. Male Wistar rats (120-150 g) received 0.5 mL *i.p.* PS twice/week for 11 wk and developed liver fibrosis as revealed by hepatic hydroxyproline levels. Then, following the induction of immune cirrhosis, LPS was *i.p.* injected at 50 μ g/kg followed by 600 mg/kg *i.p.* of D-GaIN thirty minutes later, in order to induce acute liver insult on chronic liver damage[61]. This ACLF model presented several similarities with human ACLF, such as increased inflammatory marker (TNF- α , IL-6), plasma enzyme (AST, ALT) and ammonia levels, as well as higher prothrombin times consistent with coagulation function impairment [20,61]. Therefore, ACLF induced by serum albumin showed to be a good model and comprises an alternative to better understand ACLF physiopathology. However, the PS model may be more adequate, it induces a closer response to the human condition, easier to manipulate and results in lower mortality rates compared to the other mentioned models.

DISADVANTAGES AND CHALLENGES OF ACLF ANIMAL MODELS

Due to the complexity of liver injury, the understanding of underlying liver disease mechanisms and their treatment has been limited by the lack of satisfactory animal models. Currently, no model has been able to completely capture the corresponding human acute and chronic liver disorder[52,61,85].

The ideal ACLF model should combine bacterial infection and high short-term mortality. As described previously, several existing ACLF models have been developed by combining chronic and acute liver injury[70]. Chronic injury is most commonly induced by the injection of CCl₄ or *via* BDL surgery, whereas acute injury is induced by the injection of D-GaIN/LPS. The principle of these models is to reproduce the bi-factorial disease profile comprising chronic liver injury, which leads to the development of progressive liver fibrosis, and a precipitating event inducing further organ injury, resulting in ACLF and considerable mortality. This is not, however, entirely consistent with ACLF pathogenesis, and the surgery required for the BDL model is difficult. The clinical situation is often more complex, and different modulating factors may occur concurrently or sequentially[86]. Typically, 50% of patients develop bacterial infection as an ACLF complication, although the (initial) precipitating event was non-inflammatory[87].

The significant challenge to develop an ACLF model is the ability to unite all the clinical characteristics observed in humans, as this is a multifactorial disease with multiple precipitators and complications and, therefore, varying disease phenotypes and organ failures, making it almost impossible to develop a single experimental model capable of triggering all of the most important clinical features [86]. In a recent study by Xiang and coworkers (2020), the authors developed a new ACLF model that could sequentially reproduce three important clinical ACLF disease factors. To this end, a severe liver injury model was prepared by combining chronic injury (CCl₄ injection), acute hepatic insult (injection of a CCl₄ double dose), and systemic bacterial infection (*i.p.* injection of bacteria *Klebsiella pneumoniae*). The findings indicate that this severe liver injury model developed acute-on-chronic liver injury, bacterial infection, multi-organ injury, and high mortality, some of the features of clinical ACLF. The authors highlight that the single bacterial infection step is crucial in inducing multi-organ failure in this model, as chronic-plus-acute liver injury did not drive the full course of ACLF in mice without bacterial infection[70]. In contrast, Schwarzkopf and coworkers developed a model combining chronic liver

disease (CCl₄/EtOH or CYP2D6-linked adenovirus (ADV)-induced autoimmune hepatitis) with different precipitating events [two EtOH binges or i.p. polymicrobial infection by cecal slurry (CS)]. After 7 wk of CCl₄/EtOH, ACLF was induced with two alcohol binges (alcohol gavage with 31.5% Vol.) with an interval of 3 days between binges. Mice mortality was observed, as well as systemic inflammation and significant elevation of serum ALT levels alongside other ACLF features[73]. According to the authors, polymicrobial sepsis by CS is closer to human infection-triggered ACLF than the *K. pneumonia* injection employed by Xiang[70,73]. These variabilities in current data also significantly interfere with the development of a standardized ACLF animal model. Furthermore, it is not yet possible to identify all ACLF precipitants, as over 40% of patients who develop ACLF exhibit no known precipitant, requiring further knowledge of ACLF activation events[22].

CONCLUSION

Animal models are helpful in understanding human diseases and play a relevant role in preclinical research, as they are capable of reproducing major pathophysiological events that occur in humans. ACLF mechanisms remain unclear, displaying a poor diagnosis and high mortality rates worldwide, it becomes relevant to highlight current animal models and how they can elucidate ACLF mechanisms. These models are also crucial in testing new drugs and novel bioengineering and genetic therapies, as the only effective therapy to date is liver transplantation. In this context, few viable livers are available and the quick clinical evolution of this condition was observed. Currently, rats are the most widely applied models (Figure 1), as their maintenance and management is simple compared to other models (Table 1). Furthermore, ACLF induced by PS combined with LPS/D-GaIN seems to be the most adequate methodology in the establishment of an ACLF animal model. However, further studies are required, as controversies concerning model designs, reproducibility and safety are still noted. In addition, the animal models are incapable to reproduce all manifestation of ACLF condition due to different causes of pathology. For example, the HBV infection model remains a challenge, because of use of transgenic mice that were capable to support virus replication or virus products. Thus, understanding current models in order to establish a safe and easily reproducible model to study complementary alternatives to liver transplantation is paramount.

FOOTNOTES

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