Liver Function Tests in Atrial Fibrillation

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ABSTRACT

Numerous known risk factors for atrial fibrillation (AF) exist, but few studies have investigated the link between gastrointestinal and liver disorders. Through a variety of pathways, hepatic and gastrointestinal conditions can increase the risk of both prevalent and incident AF. According to numerous studies, liver dysfunction plays a significant role in the pathogenesis of atrial fibrillation. So, this review article aimed to give an overview of how liver function tests played role in the AF. Albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, gamma-glutamyl transferase, serum bilirubin, and prothrombin time were highlighted in the pathogenesis of AF. However, the 5'-nucleotidase test, alpha-fetoprotein test, mitochondrial antibodies test and more, and liver functions test need to find their pathogenesis in AF. The exact mechanism of action of the liver panel was not reported in the pathogenesis of AF. To control the major liver diseases in AF patients, the therapeutic management of liver function tests is required.

KEYWORDS: Liver function tests; Atrial fibrillation; Pathogenesis, homeophatic.

INTRODUCTION

The heart arrhythmia that occurs most frequently is atrial fibrillation (AF). In the United States of America, this disease is expected to affect 6–12 million people by 2050, and 17.9 million people in Europe by 2060. A major risk factor for ischemic stroke, AF results in severe morbidity and mortality, as well as a significant economic burden. One of the largest epidemics and public health concerns, AF incidence and prevalence have increased over the past 20 years and will continue to rise over the following 30 years, especially in countries with moderate socio-demographic indexes[1].

Numerous known risk factors for AF exist, but few studies have investigated the connection between gastrointestinal and liver disorders. Through a variety of pathways, hepatic and gastrointestinal conditions can raise the risk of both prevalent and incident AF. Inflammation and autonomic regulation may be particularly important. The gastrointestinal system and liver may be adversely affected by the effects of AF and its numerous therapies, leading to considerable morbidity and mortality[2]. In contrast to individuals without cardiac arrhythmia, persons with liver cirrhosis who have AF have greater rates of inpatient mortality, stroke, and acute kidney injury[3].

While liver stiffness was strongly associated with AF, particularly in those without steatosis, fatty liver disease was not linked to either prevalent or incident AF. This link might be caused by venous congestion rather than fibrogenesis,

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although further research is needed to confirm this. In patients with high liver stiffness, particularly in the absence of overt liver disease, we recommend evaluating cardiovascular health[4].

It is unclear how liver disease affects the onset of AF. Huang et al. determined the prevalence of AF in the presence of liver disease and whether, using the model for end-stage liver disease (MELD), increasing liver disease severity is independently related to an increased risk of AF. Patients who have the liver disease have a significant prevalence and incidence of AF. A key indicator of new-onset AF is the severity of the liver disease, as determined by MELD. This great discovery raises the possibility that the pathophysiology of AF and inflammatory and neurohormonal alterations in liver disease interact[5].

MAIN TEXT

Blood tests called liver function tests, commonly referred to as liver panels, liver function panels, liver profile hepatic function panels, and liver function test, examine various enzymes, proteins, and other substances produced by the liver. These tests examine the liver's overall condition. Frequently, many substances are examined simultaneously on a single blood sample. It may be a sign of liver disease if levels of one or more of these substances are above or below normal. According to numerous studies, liver dysfunction plays a significant role in the pathogenesis of AF.

So, this review article aimed to give an overview of liver function tests played role in AF. Albumin, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum bilirubin, and prothrombin time (PT) were highlighted, and their role in the AF is explained in Fig. 1. Different databases including Google Scholar, PubMed, and Science Direct were used to review the literature. September 15, 2022 was the late date of the research. Many keywords were used, such as liver function tests, atrial fibrillation, and pathogenesis. The language of clinical studies was restricted to English. We did not limit the time frame, although more recent studies were favored.
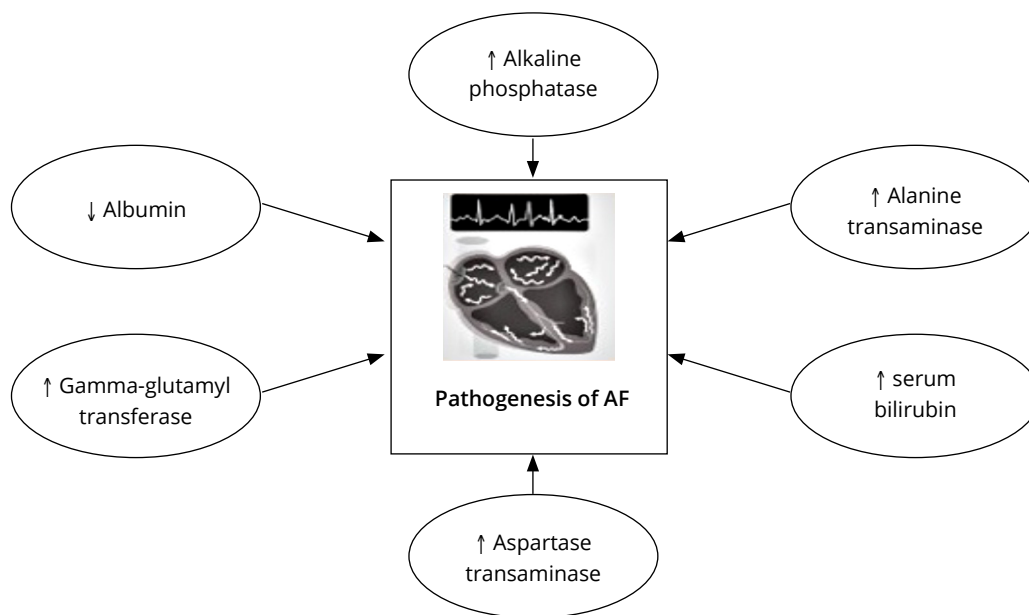

Figure 1. Overall presentation of major liver function test's role in the pathogenesis of atrial fibrillation.

ROLE OF MAJOR LIVER FUNCTION TESTS IN ATRIAL FIBRILLATION

There are many liver function tests, but this review article only included albumin, ALP, ALT, AST, GGT, serum bilirubin, PT, as explained in Table 1.

Table 1. Summary of major liver function tests in - atrial fibrillation.

Authors	Year	Liver functional tests	The main finding of major liver function tests in - atrial fibrillation (AF)
Wang et al.[7]	2021	Albumin	Dose-response meta-analysis suggests that low serum albumin level is associated with an increased risk of atrial fibrillation.
Liao et al.[9]	2020	Albumin	The serum albumin level was independently inverse associated with incident AF in a linear pattern.
Zhong et al.[10]	2022	Albumin	Low albumin levels in male patients are independently associated with paroxysmal AF.
He et al.[11]	2006	Albumin	Paroxysmal AF was associated with hypoalbuminaemia.
Mukamal et al.[12]	2006	Albumin	Higher levels of fibrinogen and lower levels of albumin were prospectively associated with a higher risk of AF, even accounting for their relationship with the risk of cardiovascular disease.
Liu et al.[14]	2016	Alkaline phosphatase	Elevated alkaline phosphatase levels may help identify high-risk symptomatic hemorrhagic transformation in ischemic stroke patients with atrial fibrillation and/or rheumatic heart disease.
Yagi et al.[15]	2022	Alkaline phosphatase	High serum alkaline phosphatase levels, even those in the normal range, were significantly associated with an increased risk of cardiovascular events, especially heart failure admission in patients with AF.
Saito et al.[19]	2022	Alanine transaminase	Low alkaline phosphatase may reflect aging, sarcopenia, and malnutrition and be independently associated with a high risk of all-cause mortality in patients with AF.
Sinner et al.[20]	2013	Alanine transaminase, aspartate transaminase	Elevated transaminase concentrations (alanine transaminase, aspartate transaminase) are associated with increased AF incidence.
Makar et al.[21]	2008	Alanine transaminase	Elevated alanine transaminase is common among patients with AF, although new and persistent elevation greater than twice the upper limit of normal is uncommon.
Alonso et al.[22]	2014	Alanine transaminase, aspartate transaminase	Levels of aspartate transaminase , and to a lesser extent alanine transaminase, showed a U-shaped association with AF risk, with higher AF risk among individuals in the two extremes of the distribution in minimally adjusted models.
Alonso et al.[22]	2014	Gamma-glutamyl transferase	Higher levels of liver enzymes, mainly gamma-glutamyl transferase, were associated with an increased risk of AF.
Ndrepepa et al.[24]	2017	Gamma-glutamyl transferase	In patients with coronary artery disease, elevated gamma-glutamyl transferase activity is independently associated with the presence of AF.
Ndrepepa et al.[24]	2017	Gamma-glutamyl transferase	In patients with coronary artery disease, elevated gamma-glutamyl transferase activity is independently associated with the presence of AF.
Lee et al.[26]	2017	Gamma-glutamyl transferase	A strong correlation between raised gamma-glutamyl transferase levels and an increased risk of AF, particularly in non-obese individuals.
Tekin et al.[27]	2013	Gamma-glutamyl transferase	Serum γ-gamma-glutamyl transferase activity is independently associated with chronic nonvalvular AF.
Demir et al.[29]	2013	Serum bilirubin	Revealed a relationship between serum bilirubin and nonvalvular AF.
Chen et al.[30]	2019	Serum Bilirubin	Higher serum bilirubin levels were associated with AF recurrence in paroxysmal AF patients following catheter ablation.
Liu et al.[31]	2020	Total bilirubin	Total bilirubin levels are nonlinearly associated with initial ischemic stroke in patients with non-valvular AF.
Huang et al.36	2018	Prothrombin time	The PT of the international normalized ratio is determined by multiple variables in patients with AF receiving rivaroxaban. Rivaroxaban-treated patients with AF having different international normalized ratio values may have similar clinical outcomes.

Albumin

The most prevalent plasma protein, albumin serves a variety of biological purposes, such as regulating colloidal osmotic pressure, binding to both endogenous and foreign chemicals, and having antithrombotic properties. In acute and chronic diseases, plasma albumin frequently decreases and offers reliable, powerful information about the prognosis[6]. Hypoalbuminemia may represent an underappreciated modifiable risk factor given the physiological characteristics of serum albumin, which include anti-inflammatory, antioxidant, anticoagulant, and antiplatelet aggregation action, as well as a colloid osmotic influence[7].

In human plasma, albumin is the most common protein. A significant indicator of malnutrition, inflammation, or cachexia, hypoalbuminemia is typically defined as 35 g/L. It has also been recognized as a reliable biomarker for a variety of non-cardiovascular and cardiovascular diseases in the general population or patients with coexisting diverse comorbidities. A study found a 36% reduction in the incidence of AF for 10-g/L serum albumin, indicating a substantial negative linear connection between serum albumin and AF risk. The majority of the subgroup and sensitivity analyses produced stable results, indicating the reliability of conclusions. Additional research is required to determine how increasing serum albumin levels can prevent AF[8].

Liao et al. reported that the level of serum albumin was linearly and independently inversely correlated with the incidence of AF. Serum albumin is potential causal role in the aetiology of AF, but it was not supported by two-sample Mendelian randomization (MR) analysis. To rule out any causative link and evaluate any potential role of serum albumin in the prevention of AF, additional studies are required[9].

Similarly, Zhong et al. observed that paroxysmal AF and low ALB levels in male patients were related, but not causally related. TG, TC, HDL-C, and LDL-C were all positively correlated with albumin levels. These results showed that low blood lipid profiles and hypoproteinemia may work in concert to contribute to the pathological development of paroxysmal AF. Additionally, a prospective cohort design would be necessary to look at the underlying connections between these diseases[10].

According to previous research, hypoalbuminaemia significantly links with heart disorders and is a separate risk factor for paroxysmal AF patients. Although the relationship between hypoalbuminemia and paroxysmal AF was still unclear, He et al. enhance new knowledge about its origin and treatment options for paroxysmal AF patients[11].

Mukamal et al. concluded that, even after accounting for their relationship to the risk of cardiovascular disease, greater levels of fibrinogen and lower levels of albumin were prospectively linked to a higher risk of AF. These results back up the theory that inflammation plays a role in the genesis of AF[12]. Aksoy et al. explained that a reliable diagnostic to predict the onset of AF after coronary artery bypass grafting was the novel inflammatory measure C-reactive protein/albumin ratio (CAR)[13].

Alkaline phosphatase

ALP is frequently used in clinical practice as a marker of liver impairment. Serum ALP levels were also linked to an increased risk of cardiovascular events, ischemic/hemorrhagic strokes, and small cerebral vascular disease. High-risk symptomatic hemorrhagic transformation in ischemic stroke patients with AF and/or rheumatic heart disease may be identified with the use of elevated ALP levels, but more research with higher cohorts was required to pinpoint findings[14]. Moreover, Yagi et al. explained that, even within the normal range, high serum ALP levels were strongly linked to a higher risk of cardiovascular events, particularly heart failure admission in patients with AF[15].

Alanine transaminase and aspartate aminotransferase

The enzyme ALT promotes gluconeogenesis, a crucial metabolic process that produces glucose and energy. It is mostly found in the liver and skeletal muscles. Alanine is converted into -ketoacids by ALT, which is mostly present in the liver. Serum ALT is frequently assessed in clinical settings, and greater levels are observed in conditions affecting the liver and skeletal muscles, likely as a result of the enzyme's release into the bloodstream by injured cells[16-18].

In several cardiovascular diseases, extremely low ALT may be a sign of ageing, frailty, sarcopenia, and malnutrition. However, the relationship between low ALT and patients's characteristics, cardiovascular mortality, and all-cause mortality

in the population with AF was not well understood. Saito et al. found that low ALT may be an independent risk factor for a high risk of all-cause death in patients with AF and may reflect age, sarcopenia, and malnutrition. Low ALT may be a helpful screening tool for identifying people with AF who will have poor clinical outcomes[19].

Increased incidence of AF is linked to higher transaminase concentrations of ALT and AST. Unknown are the mechanisms by which higher mean transaminase concentrations were linked to incident AF[20]. Patients with AF frequently have elevated ALT, but only rarely they have new or sustained elevations that are larger than twice the upper limit of normal (ULN). These elements make it challenging to distinguish between incident increases taken on by comorbidities and medication-induced liver injury in the context of a new therapy[21].

In minimally adjusted models, levels of AST and, to a lesser extent, ALT demonstrated a U-shaped correlation with AF risk, with increased AF risk among individuals in the two extremes of the distribution. After potential confounders were taken into account, the relationships were reduced[22].

The baseline GGT level was positively associated with the AF risk in a log-linear manner. The authors found no significant association between ALT or AST and the risk of AF. However, further well-designed prospective studies are needed to confirm these findings and elucidate the pathophysiological mechanisms[23].

Gamma-glutamyl transferase

Higher levels of liver enzymes, particularly GGT, were linked to an increased risk of AF in this community-based prospective analysis. Further investigation is warranted on the processes behind this association[22]. Elevated GGT activity was independently linked to the prevalence of AF in people with coronary artery disease. A circulating marker of the risk for AF may be GGT[24]. Through AF, the GGT level was strongly linked to cardioembolic stroke. The findings of this study may shed light on why GGT is linked to stroke[25].

Another population-based investigation found a strong correlation between raised GGT levels and an increased risk of AF, particularly in non-obese individuals[26]. Additionally, serum γ-GGT activity was independently associated with chronic nonvalvular AF[27].

Serum bilirubin

The breakdown of hemoglobin produces bilirubin, a metabolic byproduct that needs to be processed for proper elimination. Lower risks of coronary heart disease and cardiovascular disease are linked to high levels of bilirubin[28]. Demir et al. revealed a relationship between serum bilirubin and nonvalvular AF[29]. Numerous cardiovascular disorders have been linked to bilirubin. Uncertainty surrounds the connection between bilirubin and AF. The authors explained the link between bilirubin and AF recurrence following catheter ablation. The neutrophil counts and total bilirubin levels had a favorable correlation. However, there was no correlation between voltage, left atrial diameter, or total bilirubin level. Following catheter ablation, higher serum bilirubin levels were linked to AF recurrence in patients with paroxysmal AF[30]. Patients with non-valvular AF had a nonlinear relationship between total bilirubin levels and initial ischemic stroke[31].

Prothrombin time

A prolonged peak PT (≥ 20 s) could indicate an increased risk of bleeding in Japanese patients with non-valvular AF using rivaroxaban, and both trough and peak plasma soluble fibrin levels were decreased in comparison to baseline. Regardless of prior anticoagulant history, PT and plasma-soluble fibrin are both useful indicators of coagulation status in individuals on rivaroxaban[32].

Furthermore, another study observed that PT, the international normalized ratio (PT-INR), and activated partial thromboplastin time (aPTT) ratios were not linked to bleeding incidents in Asian AF patients using rivaroxaban or dabigatran. Patients on rivaroxaban had a decreased risk of ischemic stroke/systemic embolism (IS/SE) when their INR was less than 1.5. For patients using rivaroxaban with an INR < 1.5, proper dosages of direct oral anticoagulants and patient compliance should be confirmed[33].

In the past, oral anticoagulation with vitamin K inhibitors, particularly warfarin, has been the most effective treatment for preventing stroke in patients with AF. However, these treatments have now been replaced by "direct oral anticoagulants," such as factor X inhibitors, due to their drawbacks and side effects. Duarte et al. provided a concise overview of AF and the use of rivaroxaban, as well as compared the PT/INR in AF patients taking this oral anticoagulant, depending on the amount of time that had passed since the drug's last administration and the time of blood sample venipuncture. In contrast to warfarin, the authors concluded that to appropriately interpret a laboratory test to evaluate hemostasis, notably PT and its derivatives, the time interval between drug consumption and blood collection from patients using rivaroxaban must be known[34].

In the same way, the most common method for monitoring warfarin medication in people with AF is the PT, which is also known as the INR. A better indicator of the actual level of anticoagulation might be found in prothrombin activation fragment F1.2, which measures in-vivo thrombin production. In patients with AF, the association between F1.2 and INR was investigated. There is a significant amount of variability in this association between decreasing thrombin production as assessed by the F1.2 level and increasing anticoagulation intensity as indicated by the INR. At equal INR readings, older anticoagulated patients have greater F1.2 values than younger patients. It's unclear whether these differences have any clinical importance. In addition to the INR's ability to represent anticoagulation intensity, the F1.2 measurement could also do so[35].

Also, several factors influence the PT of the INR in AF patients using rivaroxaban. Patients with AF who are on rivaroxaban and have a range of INR values may experience comparable clinical results[36].

CONCLUSIONS

This review article concluded that albumin, ALP, ALT, AST, GGT, serum bilirubin, and PT played a significant role in - AF. However, the 5'-nucleotidase test, alpha-fetoprotein test, mitochondrial antibodies test and more, and liver functions test need to find their pathogenesis in AF. The exact mechanism of action of the liver panel was not reported in the pathogenesis of AF. To control the major liver diseases in atrial fibrillation patients, the therapeutic management of the liver function tests is required.

CONFLICT OF INTEREST

Nothing to declare.

FUNDING

This study was not supported by any funding.

DATA AVAILABILITY STATEMENT

Data derived from public domain resources.

AUTHORS' CONTRIBUTION

All authors contribute equally.

ACKNOWLEDGMENTS

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