How to interpret and manage abnormal liver blood test results in older people

Abstract

Ageing impairs liver function and reduces the liver's regenerative capacity. With the predicted increase in the older population, the burden of liver disease will proportionally rise in this age group. Elevated levels of liver enzymes in an otherwise asymptomatic older individual (≥65 years) are a common observation and positively associated with the metabolic syndrome, whereas a decline in albumin levels is linked with a rise in all-cause and liver-specific mortality. Deranged liver function tests do not always indicate liver disease, nor do normal liver function tests exclude liver disease. Therefore, clinicians need to consider individual patient risk factors during the assessment of abnormal liver function tests. This article discusses various liver function tests, their pathophysiology, and the approach to interpret and manage common abnormalities in liver function test results and liver disease in the older population.

Key words: LFT; Liver enzymes; Liver function tests; Older people; Review

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Introduction

Deranged liver function test results in older people is a frequently encountered clinical problem, and the prevalence is twice (16%) that of the younger population (8%) (Fleming et al, 2011; Lala et al, 2020). Liver function tests are part of routine clinical assessment and the third most commonly requested blood test in primary care; over 10 years, 25% of the resident population of Tayside Scotland had liver function tests (Donnan et al, 2007). Asymptomatic liver function test measurement, alongside a 6% predicted rise in the UK ageing population by 2038 (Office for National Statistics, 2019), is likely to have a significant impact on clinical practice.

As the liver ages, its total blood volume reduces by 35% compared to that in people younger than 40 years (Kim et al, 2015). This causes a reduction in functional cell mass, translating into a lower regenerative capacity (Kim et al, 2015; Cieslak et al, 2016). The liver is central to systemic lipid and glucose metabolism, steroid biosynthesis, homeostasis and insulin signalling (Hunt et al, 2019). Hence the risk of metabolic liver diseases demonstrates a positive linear association with age (Liu et al, 2018). The effect of this change may be mediated by ageing physiology, promoting the development of fibrosis. Age-related changes in the liver include dysregulation of hepatic energy metabolic pathways, lipofuscin accumulation, dysfunction of hepatic endothelial cells and increased oxidative stress, increased susceptibility to age-related diseases, insulin resistance, diabetes, non-alcohol fatty liver disease and the harmful effects of alcohol (Kim et al, 2015). Consequently, modern lifestyle choices promoting obesity and increased alcohol consumption (Williams et al, 2014) have led to an increase in non-viral liver disease in western populations. Over the last decade, there has been a worrying trend of increasing alcohol misuse among older people, with an exponential rise (>90%) in alcohol-related hospital admissions in people aged 65 years and over (Rao et al, 2016). Older people with at-risk drinking behaviours are increasingly prone to liver disease, which may progress rapidly as a result of associated age-related changes in liver physiology.

What are the liver function tests?

Liver function tests have been used in clinical practice since the 1950s to diagnose and treat liver disease. The standard liver function test panel includes liver enzymes (alanine

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aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transferase) and markers of liver function (bilirubin and albumin). In the setting of acute liver failure, prothrombin time can be a useful marker.

Aspartate aminotransferase and alanine aminotransferase transfer amino groups from aspartate and alanine to ketoglutaric acid and are markers of hepatocellular liver injury, but in reality, can be non-specific (Karmen et al, 1955). Alanine aminotransferase is more liver-specific whereas aspartate aminotransferase is present in cardiac and skeletal muscles, kidney, pancreas, lung and brain, as well as in the liver. An isolated rise in aspartate aminotransferase levels can be the result of cardiac or skeletal muscle disease (Kwo et al, 2017). Gamma-glutamyl transferase is a marker of oxidative stress and subclinical inflammation (Liu et al, 2018). The primary source of gamma-glutamyl transferase is the liver, although tissues such as the intestine, prostate and pancreas produce gamma-glutamyl transferase albeit at low levels, it is not present in bone (Newsome et al, 2018). Alkaline phosphatase is mainly present in the hepatocytes' canalicular membrane and is involved in hydrolysis of phosphate esters (Kwo et al, 2017). Other tissues that secrete alkaline phosphatase are bone, intestines, kidneys and white blood cells. However, a concomitant rise in gamma-glutamyl transferase supports the idea that an elevated alkaline phosphatase level is hepatic in origin. Aminotransferases (alanine aminotransferase and aspartate aminotransferase) usually remain within the reference range, whereas gamma-glutamyl transferase and alkaline phosphatase can rise with age. Serum bilirubin levels may gradually decline as a result of reduced muscle mass and haemoglobin (Tajiri and Shimizu, 2013; Kim et al, 2015). In patients who have hepatocellular liver injury, elevation of transaminase levels (alanine aminotransferase, alanine aminotransferase) is the predominant finding, whereas gamma-glutamyl transferase and alkaline phosphatase levels are elevated in patients with cholestatic liver injury.

It is essential to emphasise that because of the indolent nature of liver disease, especially in apoptotic conditions such as non-alcoholic fatty liver disease and alcohol-related liver disease, a patient can have advanced liver disease but still have normal results of liver function tests (Newsome et al, 2018). This review discusses the observed derangement of liver function tests in the older population (≥65 years), the clinical implications, including management, and briefly describes the common causes of liver disease in this cohort.

Liver function tests in asymptomatic older people in community settings

Despite liver function being the third most commonly requested blood test in primary care, data on the true prevalence of impaired liver function test results in the otherwise asymptomatic population is lacking. Mild elevation of liver enzyme levels in healthy patients is a commonly reported incidental abnormality. One in six older adults (≥75 years) is said to have at least one abnormal liver function test (aspartate aminotransferase, alanine aminotransferase or bilirubin) (Fleming et al, 2011) (**Table 1**).

A population-based study from the USA reported 8.9% and 4.9% of healthy individuals had an elevated alanine aminotransferase or aspartate aminotransferase level respectively; high body mass index, waist circumference and alcohol intake were common causes (Ioannou et al, 2006). Donnan et al (2007) conducted a population-based cohort study (ALFIE) to determine the natural history of impaired liver function test results. They showed that 21.7% of participants reported having at least one deranged liver function test result and, of these, only 1.14% developed liver disease (median follow up of 3.7 years). Those with mild elevations of aspartate aminotransferase, alanine aminotransferase or gamma-glutamyl transferase levels had up to four times the risk (hazard ratio 4.23, 95% confidence interval 3.55–5.04) of developing liver disease over 5 years. This risk was 13 times higher when severe elevations of both alanine aminotransferase or aspartate aminotransferase and gamma-glutamyl transferase levels were observed. The Birmingham and Lambeth Liver Evaluation Testing Strategies study highlighted similar findings: fewer than 5% of cases with abnormal liver test results had an acute or chronic liver condition, and only 1.3% of patients had a severe liver problem (Lilford et al, 2013). A caveat of these studies is a lack of long-term follow up, which is essential to predict the natural history of chronic liver disease.

Table 1. Distribution of impaired liver function test results among older people (≥75 years) in the community

Liver function test	Sample size (*n*)	% abnormal test results (95% confidence interval)
Aspartate aminotransferase	*n*=12826	3.3 (3.0–3.7)
≤2 upper normal limit		2.9 (2.6–3.2)
≥2 upper normal limit		0.5 (0.4–0.6)
Alkaline phosphatase	*n*=13499	9.2 (8.7–9.7)
≤2 upper normal limit		8.3 (7.8–8.8)
≥2 upper normal limit		0.9 (0.8–1.1)
Bilirubin	*n*=12690	5.4 (5.0–5.8)
≤2 upper normal limit		5.1 (5.0–5.8)
≥2 upper normal limit		0.3 (0.2–0.5)
Aspartate aminotransferase and alkaline phosphatase	*n*=12794	0.7 (0.6–0.9)
Aspartate aminotransferase and bilirubin	*n*=12021	0.3 (0.2–0.5)
Alkaline phosphatase and bilirubin	*n*=12648	0.5 (0.4–0.7)
Aspartate aminotransferase, alkaline phosphatase and bilirubin	*n*=11994	0.07 (0.03–0.14)
Any (aspartate aminotransferase, alkaline phosphatase or bilirubin)	*n*=13546	16.1 (15.4–16.7)

From Fleming et al (2011)

Multimorbidity is expected after the age of 65 years and becomes almost universal in people aged 90 years or over. Most of the reported increase in morbidity and mortality linked to abnormal liver enzyme levels in older people relates to systemic diseases rather than the liver. Donnan et al (2007) found low albumin levels to be a strong predictor of all-cause mortality in their study (mean age of 62 years; ratio 2.65, 95% confidence interval 2.47–2.85) and the decline in albumin levels with increasing age is correlated with an increased risk of all-cause and cardiovascular mortality (Schalk et al, 2006).

Up to 50% of people with cirrhosis first present with decompensated liver disease and may not have deranged liver enzymes (Williams et al, 2014). A diagnosis of cirrhosis confers an increased risk of liver-related morbidity and mortality (Sharma et al, 2014). There is little evidence to help the physician decide on further diagnostic workup for abnormal liver function test results in older people (Oh and Hustead, 2011) and the diagnostic accuracy of liver function tests in isolation is questionable. Adding non-invasive investigations and diagnostic tools, such as identifying risk factors for liver disease, may increase the yield of diagnosing liver disease and minimise the risk of harm (Donnan et al, 2007; Aragon and Younossi, 2010). Extensive undue investigation in otherwise healthy individuals can provoke anxiety, result in unnecessary exposure to invasive procedures like liver biopsy or endoscopy and has cost implications for healthcare services (Aragon and Younossi, 2010).

Historically, liver biopsy was considered the gold standard to establish aetiology and severity of liver disease (Berger et al, 2019), but recently more reliable non-invasive markers of liver fibrosis, such as enhanced liver fibrosis tests and fibroscan, have become available (Loomba and Adams, 2020). Although the evidence on non-invasive assessment of liver fibrosis in cohorts of older people is limited, it does show promising results and should be considered as part of routine clinical assessment for patients with impaired liver function test results in the presence of relevant risk factors (Salles et al, 2009; Dong et al, 2016). Early diagnosis of liver fibrosis provides an opportunity to intervene and is the most effective way of preventing progression of liver disease (Roberts et al, 2019). Common causes of impaired liver function test results in otherwise asymptomatic older individuals and a brief guide to management is given in Tables 2 and 3.

Table 2. Common causes of deranged liver function test results in otherwise asymptomatic older people	
■ Non-alcoholic fatty liver disease ■ Alcohol-related liver disease ■ Drug-induced liver injury ■ Autoimmune hepatitis	
Isolated rise in alkaline phosphatase levels	■ Vitamin D deficiency ■ Paget disease ■ Osteomalacia
Isolated rise in gamma-glutamyl transferase levels	■ Obesity ■ Smoking ■ Alcohol excess ■ Diabetes

Table 3. Management of deranged liver function test results in otherwise asymptomatic older people	
Clinical history	Take a history of ■ Alcohol intake ■ Baseline body mass index ■ Recent change in weight ■ Type 2 diabetes ■ Recent change in medication ■ History of over the counter medications, illicit drugs, herbal medications ■ History of intravenous drug use
Features of metabolic syndrome	Identify the common features of metabolic syndrome ■ Central obesity ■ Hypertension ■ Diabetes ■ Insulin resistance ■ Dyslipidaemia ■ Obstructive sleep apnoea
Further investigations	Based on individual risk factors ■ Request investigations to establish aetiology ■ Non-invasive tests to stratify stage of liver disease (fibroscan, enhanced liver fibrosis test)

Liver function tests in hospitalised older people

In 2017, 22.2% of all hospital admissions in England were of people older than 75 years. Of these, 81% had a single hospital admission, and 96% had one emergency visit in the last year of their life. Cancer, dementia, chronic obstructive pulmonary disease, acute heart disease and liver disease were the most common indications for hospitalisation and mortality (Public Health England, 2020). Hospitalised older adults often have a low functional reserve, increased risk of recurrent hospital admissions and mortality. The prevalence of chronic liver disease rises with age and significantly impacts functional status, quality of life, risk of multimorbidity and mortality in older age (Klausen et al, 2017).

Shah et al (2010) found that 16% (n=2172) of hospitalised patients (≥75 years) had at least one elevated liver function test result (aspartate aminotransferase 3.3%, alkaline phosphatase 9.2%, bilirubin 5.4%). A history of diabetes or dementia was associated with elevated aspartate aminotransferase and alkaline phosphatase levels, while a history of heart attack was related to an elevated alkaline phosphatase level. Sepsis (32.5%) was the most common cause of impaired liver function test results, followed by alcohol-related

liver disease (22%), malignancy (10%), congestive heart failure (5%) and drug-induced liver injury (4.7%) (Shah et al, 2010).

Hospitalised older people (mean age 78 years) with serum albumin level <33 g/litre had 3.2-fold (odds ratio 3.23) increased risk of inpatient mortality (Silva et al, 2009). In a cohort of patients with COVID-19 (mean age 66 years±15 years) those with at least one elevated liver function test result were 3.5 times more likely to die or be transferred to intensive care than those with normal liver function test results (Piano et al, 2020).

The management of patients with deranged liver function test results in hospital settings involves treating the underlying cause, which is often a systemic disease like sepsis. It is vital to consider the presenting and past medical history, risk factors for liver disease and clinical signs while requesting further workup. The early involvement of specialist geriatric teams in managing older patients who are hospitalised as a result of any cause improves the outcome and facilitates early discharge (Totten et al, 2011).

Chronic liver disease in old age

The prevalence of chronic liver disease in older age is rising in line with an increasing life expectancy favouring an ageing population. Unfortunately, these patients often present at a late stage because of the paucity of symptoms in early disease. Alcohol-related liver disease and non-alcoholic fatty liver disease are the commonest aetiologies in developed nations influenced by western lifestyles (Frith et al, 2008).

Alcohol-related liver disease

In the UK, 53% of men and 38% of women over the age of 60 years are current alcohol drinkers and, of all patients diagnosed with alcohol-related liver disease, 28% are older than 60 years (Frith et al, 2008). The risk of liver disease rises in proportion with an increase in alcohol intake and doubles for any given alcohol intake once body mass index is >35 kg/m^2 (Newsome et al, 2018). Excess alcohol consumption is on the rise in older people, but alcohol metabolism reduces because of the decline in activity of the enzymes which metabolise alcohol, which increases the risk of alcohol-related liver disease (Kim et al, 2015). Alcohol is associated with acceleration of liver fibrosis in concomitant hepatitis C virus infection and increases adverse events as a result of polypharmacy (Tajiri and Shimizu, 2013). The most common abnormalities observed are elevated levels of aspartate aminotransferase, alkaline phosphatase and bilirubin, and increased mean corpuscular volume (Frith et al, 2008). Mortality in over 60-year-olds is 34%, management is supportive, and abstinence from alcohol is the mainstay of treatment (Frith et al, 2008).

Non-alcoholic fatty liver disease

Ageing is associated with an increase in central obesity, excessive visceral fat, and increased blood levels of cholesterol and high-density lipoprotein, resulting in enhanced insulin resistance, which is a major pathophysiological trigger for metabolic liver disease (Kim et al, 2015). The overall prevalence of non-alcoholic fatty liver disease is as high as 35% in people older than 65 years and is significantly higher than in younger counterparts (Kim et al, 2015). The current mainstay of treatment is lifestyle modification, including exercise and Mediterranean diets, which improves non-alcoholic fatty liver disease outcomes and those of other metabolic diseases (Kim et al, 2015).

Drug-induced liver injury

Drug-induced liver injury is on the rise among the general population and more so in older people; the precise prevalence in older population is unknown but estimates range from 23% to 45% (Danjuma et al, 2020). Multimorbidity along with polypharmacy make older people more vulnerable to drug-induced liver injury (Kullak-Ublick et al, 2017). A prospective study looking at polypharmacy in old age (mean age 82 years) showed 73% took at least four or more prescription medications (Tajiri and Shimizu, 2013). This makes it challenging to establish causality and identify a single culprit drug; a test system called MetaHeps can be useful in this scenario (Kullak-Ublick et al, 2017). The international expert group for drug-induced liver injury proposed the following thresholds for diagnosis: alanine

aminotransferase value ≥5 × upper limit normal, alkaline phosphatase value ≥2 × upper limit normal or alanine aminotransferase value ≥3 × upper limit normal and bilirubin ≥2 × upper limit normal. Danjuma et al (2020) found that over 30% of drug-induced liver injury in old age is avoidable with rational decision making, avoiding medications and interactions associated with increased risk of drug-induced liver injury. Management involves prompt recognition and discontinuation of the offending drug, close monitoring and, in cases of drug-induced liver injury with autoimmune features, consideration of corticosteroids after liver specialist advice (Kullak-Ublick et al, 2017).

Autoimmune hepatitis

Autoimmune hepatitis is an immune-mediated inflammatory condition of the liver and can present as acute hepatitis, liver failure or chronic liver disease. Although it is typically considered a disease of younger age, the incidence is rising in older people (Durazzo et al, 2019). The clinical presentation largely remains the same in all age groups, but above the age of 60 years can be with a relatively higher alkaline phosphatase and gamma-glutamyl transferase level than younger patients (Peng et al, 2014). The workup includes testing for the presence of liver autoantibodies and serum immunoglobulins, specifically IgG, with liver biopsy to confirm the diagnosis (Newsome et al, 2018). It is worth noting that seronegative autoimmune hepatitis is more common in older patients. Other comorbidities, polypharmacy and increased risk of side effects make management particularly challenging in this age group. Treatment with steroids alone or in combination with azathioprine is the most commonly used and well-tolerated immunosuppressive regimen (Durazzo et al, 2019).

Viral hepatitis (A, B, C, E)

Hepatitis E virus infection is significantly ($P \leq 0.05$) more common in older people (median age 64 years) than hepatitis A, hepatitis B and hepatitis C virus (Kokki et al, 2016). The typical route of hepatitis B virus and hepatitis C virus transmission in the older generation is blood transfusion or surgery before the 1990s (Kim et al, 2015), whereas hepatitis E virus and hepatitis A virus are mainly transmitted via the faeco-oral route. All people with acute and chronic elevated levels of liver transaminases should be risk assessed and tested for viral hepatitis. Hepatitis A virus is usually self-limiting but can cause significant hepatocellular dysfunction and rise in liver enzyme levels, with mortality demonstrably higher in people age 75 years or over (Tajiri and Shimizu, 2013). A vaccine is available for hepatitis A virus and hepatitis B virus worldwide.

Conclusions

The prevalence of chronic liver disease in the ageing population is rising in proportion with advancing life expectancy. Deranged liver function test results are commonly reported in older patients, both in community and hospital settings. Although liver function testing is part of routine clinical practice and is a frequently requested blood test, a significant proportion of patients continue to be diagnosed at an advanced stage of liver disease whereby the scope of any intervention is minimal. Normal liver function test results do not exclude liver disease, and at the same time, impaired liver function test results are not always indicative of liver disease. A targeted history to identify liver disease-specific risk factors and the integration of recently available non-invasive liver disease diagnostic investigations in clinical practice can enhance early diagnosis of liver disease and thus help to reduce the morbidity and mortality associated with advanced disease. Further research is needed to establish the true prevalence and natural history of impaired liver function in the older population.

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Key points

- Deranged liver function test results are a common finding in older people.
- Common causes include non-alcoholic fatty liver disease, alcohol-related liver disease and drug-induced liver injury.
- Deranged liver function test results do not always indicate liver disease, nor does normal liver function test results exclude liver disease.
- Clinicians need to consider individual patient risk factors during the assessment and request further investigation to establish aetiology with caution and only where indicated.
- Assessment of patients with abnormal liver function tests should include non-invasive tests to stage liver disease.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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