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Liver function tests in hypertension: a literature review

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Abstract

Background. Individuals with hypertension tend to have higher liver function test (LFT) levels and an increased risk of hypertension when abnormal LFT levels are present. The dysfunction of the liver is identified as a significant contributor to the development of hypertension. **Objective.** The article specifically focuses on review of various LFT markers such as albumin, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase, gamma-glutamyl transferase (GGT), serum bilirubin, lactate dehydrogenase, prothrombin time (PT) and their role in hypertension. **Results.** The increase in albumin concentration from approximately 40 to 50 g/l within the physiological range correlated with a rise in systolic blood pressure ranging from 5 to 11 mmHg in males and from 6 to 17 mmHg in females. Also, there is a negative correlation between serum ALP and indices of artery anatomy and function in hypertensive African men. Moreover, an inverse correlation between elevated ALT levels and hypertension in Chinese adults, suggesting that elevated ALT may precede the onset of hypertension. The overall prevalence of elevated ALT and AST among freshmen was 6,8 % and 2,3 %, respectively, suggesting a strong correlation between ALT levels and hypertension in both males and females. Another study indicated that higher GGT levels were associated with an increased risk of hypertension. In men with pre-hypertension, but not in normotensive individuals, serum bilirubin levels negatively correlated with arterial stiffness. No significant relationship between arterial stiffness and bilirubin levels was observed in women. An increase in serum LDH level is linked to the severity of pregnancy-induced hypertension and complications for both mother and fetus. Systolic blood pressure and diastolic blood pressure showed a positive correlation with activated partial thromboplastin time (APPT) in hypertensive patients. These findings suggest that PT and APTT measurements could be used as indicators to assess hemostatic abnormalities in individuals with hypertension and guide antihypertensive medication. The exact mechanisms by which the liver function panel influences hypertension were not reported.

Keywords: liver function tests, hypertension, albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, serum bilirubin, prothrombin time

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Резюме

Актуальность. У лиц с артериальной гипертензией (АГ) регистрируются более высокие маркеры функции печени, а также при повышенных показателях функции печени отмечается повышенный риск АГ. Нарушение функции печени рассматривается как фактор, способствующий развитию АГ. **Цель исследования.** В статье особое внимание уделено таким показателям функции печени, как альбумин, щелочная фосфатаза (ЩФ), аланинаминотрансфераза (АЛТ), аспартатаминотрансфераза (АСТ), гамма-глутамилтранспептидаза (ГГТП), сывороточный билирубин, лактатдегидрогеназа (ЛДГ), протромбиновое время (ПВ), и их роли при АГ. **Результаты.** Повышение уровня альбумина от 40 до 50 г/л в пределах физиологических колебаний коррелирует с повышением систолического артериального давления на 5–11 мм рт. ст. у мужчин и на 6–17 мм рт. ст. у женщин. Также показана отрицательная связь между сывороточным уровнем ЩФ и показателями анатомии и функции артерий и африканцев. Обратная связь выявлены между уровнем АЛТ и АГ во взрослой китайской когорте, что дает основания предположить, что повышение уровня АЛТ может предшествовать развитию АГ. В целом встречаемость повышенного уровня АЛТ и АСТ среди первокурсников составила 6,8 % и 2,3 % соответственно. Повышение уровня ГГТП ассоциировано с увеличением риска АГ. У мужчин с предгипертензией (но не у нормотензивных лиц) уровень билирубина в сыворотке крови отрицательно коррелировал с показателями жесткости артерий. У женщин такой связи выявлено не было. Повышение уровня ЛДГ в сыворотке крови было ассоциировано с АГ беременных и развитием осложнений как со стороны матери, так и со стороны плода. Систолическое и диастолическое артериальное давление положительно коррелировало с активированным частичным тромбопластиновым временем (АЧТВ) у лиц с АГ. Можно предположить, что ПВ и АЧТВ могут использоваться как показатели нарушений в системе свертывания крови у лиц с АГ для коррекции терапии. Конкретные механизмы, через которые печеночные маркеры влияют на уровень артериального давления и риск АГ, до конца неясны.

Ключевые слова: показатели функции печени, артериальная гипертензия, альбумин, щелочная фосфатаза, аланинаминотрансфераза, аспартатаминотрансфераза, гамма-глутамилтранспептидаза, лактатдегидрогеназа, сывороточный билирубин, протромбиновое время

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Introduction

The prevalence of hypertension is rapidly increasing worldwide and is a major cause of illness and death. Various factors such as obesity, lifestyle choices, age, gender, environment, and genetics significantly contribute to the development of hypertension. Hypertension often leads to complications such as myocardial infarction (heart attack) and cerebral haemorrhage (bleeding in the brain) [1, 2]. Hypertension is a leading cause of death globally and a major contributor to cardiovascular disease (CVD) [3, 4]. In the year 2000, approximately 26% of the global population had hypertension, and it is expected to rise to 29,2% by the year 2025 [5].

Liver function tests (LFTs or LFs) are blood tests that provide information about the liver's health. These tests include a number of measurements, such as prothrombin time (PT/INR), partial thromboplastin time (PTT), albumin, bilirubin (both direct and indirect), and other related assays. Elevated levels of liver transaminases, specifically aspartate aminotransferase (AST or SGOT) and alanine transaminase (ALT or SGPT), are indicative of liver damage [6–8]. There is growing evidence of the relationship between hypertension and the functional integrity of the liver. Clinical and experimental evidence has shown that liver disease is not directly associated with the development of hypertension [9, 10].

Similarly, individuals with hypertension exhibit higher levels of LFTs and are at an increased risk of disease associated with abnormal LFT levels. Studies showed abnormalities in liver enzymes such as serum ALT, total bilirubin, and serum AST in hypertensive individuals [11]. Additionally, S. Rahman and colleagues (2020) concluded that the prevalence of elevated liver enzymes was greater among individuals with hypertension [12]. At the Glasgow Blood Pressure Clinic, 15–8% of men and 6% of women with hypertension had abnormal liver function tests [13]. In both genders, a dose-response relationship was observed between abnormal blood pressure and levels of ALT, AST, gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) [14].

Design and methods

Numerous studies have indicated the significant role of liver dysfunction in the development of hypertension. Therefore, the purpose of this paper is to provide an overview of the role of liver function tests or liver panels, including albumin, ALP, ALT, AST, GGT, lactate dehydrogenase, serum bilirubin, and PT in hypertension (Fig. 1). To conduct the literature review, various databases such as Google Scholar, PubMed, and Science Direct were utilized (Table 1). The search was completed on November 20, 2022. Keywords such as "Liver Function Tests", "Hypertension", "Albumin", "Alkaline phosphatase", "Alanine transaminase", "Aspartate aminotransferase", "Gamma-glutamyl transferase", "Lactate dehydrogenase", "Serum Bilirubin", and "Prothrombin time" were used. The search was limited to papers published in English. Although more recent studies were prioritized, no specific time limit was set. The references of relevant articles were also examined and appropriate articles were extracted.

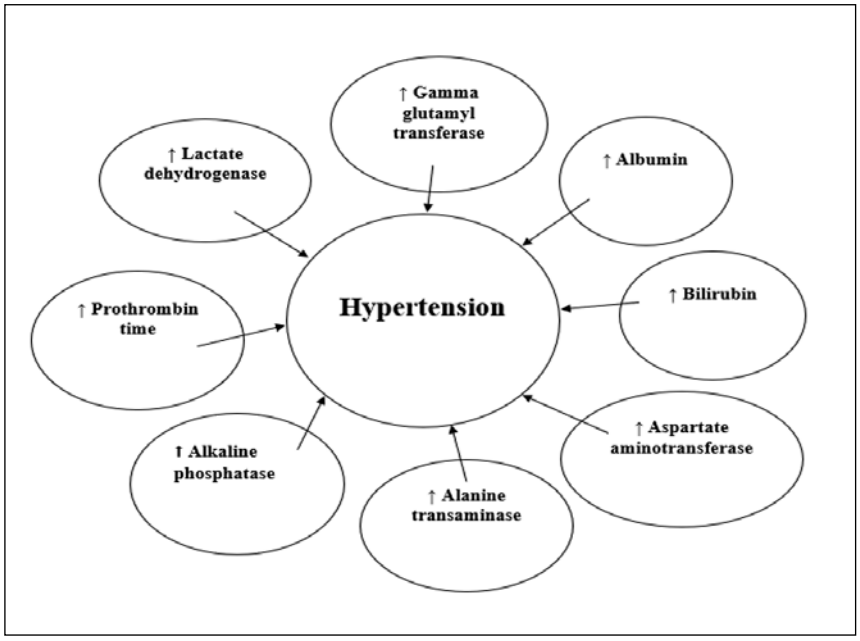

Figure 1. Circulating levels of major liver function tests in hypertension

Source: (↑) elevated and (↓) reduced levels.

Table 1

FULL SEARCH STRATEGY OF THE DATABASES

PubMed	For biomedical and life sciences research, including medicine, biology, and health-related topics https://pubmed.ncbi.nlm.nih.gov/
ScienceDirect	A platform offering access to a wide range of scientific, technical, and medical research articles https://www.sciencedirect.com/
Google Scholar	A free search engine that indices scholarly articles, theses, books, conference papers, and patents across various disciplines https://scholar.google.com/

Role of major liver function tests in hypertension

This review specifically focuses on a subset of liver function tests in the context of hypertension. While there are various liver function tests available, the tests highlighted in this review include albumin, ALP, ALT, AST, GGT, lactate dehydrogenase, serum bilirubin, and PT (Table 2).

Albumin

Albumin, a vital serum protein, plays various roles such as transporting chemicals, maintaining plasma colloid osmotic pressure, and exhibiting antioxidant activity. Its levels are tightly regulated by physiological systems [15]. The liver ability to produce substances, known as biosynthetic capacity, or how well a patient's liver is functioning can be evaluated by analyzing serum albumin levels. To gain a more comprehensive understanding of liver biosynthesis, serum albumin is often examined together with prothrombin time and/or international normalized ratio. However, it is worth noting that normal serum albumin levels can be observed in cases of chronic liver disease, while abnormal levels may be present even in individuals with normal liver function. A study focusing on patients being assessed for gastric bypass found a weak correlation between liver pathology and liver function tests. Additionally, low levels of serum albumin, known as hypoalbuminemia, may indicate reduced albumin production or a dilution effect due to increased free fluid in the body [16]. Generally, albumin levels tend to be higher in men compared to women and in younger individuals compared to older ones. Within the normal range, an increase in albumin content was associated with elevated systolic and diastolic blood pressure in both sexes and across different age groups. The increase in albumin concentration from approximately 40 to 50 g/l within the physiological range correlated with the rise in systolic blood pressure ranging from 5 to 11 mmHg in males and 6 to 17 mmHg in females. Corresponding increases in diastolic blood pressure ranged from 3 to 7 mmHg in men and from 4 to 9 mmHg in women. Each standard deviation increase in albumin concentration was associated with a 1–3 mmHg increase in blood pressure [17].

In a separate study, lower serum albumin levels in Chinese hypertensive adults were associated with a higher prevalence of peripheral arterial disease (PAD) in men but not in women [18]. Another study highlighted a correlation between serum albumin levels and disruption of the circadian blood pressure rhythm, with more than two-thirds of patients exhibiting a non-dipper pattern. This finding was particularly significant for non-diabetic essential hypertension patients with mild proteinuria. The study emphasized the importance of serum albumin levels as an independent predictor of nocturnal systolic dipping, in contrast to urine albumin excretion [19]. Even within the normal range, below the threshold for microalbuminuria, urinary albumin was found to be an independent predictor of hypertension and elevated blood pressure in the general population [20]. According to the findings of G.W. Choi and colleagues (2021), significant predictors for the development of hypertension included serum albumin levels, along with polymorphisms of rs2894536 in *LOC107986598* and rs10972486 in *ATP8B5P*. Higher albumin concentrations, as indicated by two hypoalbuminemia-related genetic variants (rs2894536 and rs10972486), were associated with reduced hazard ratios (HRs) for the development of hypertension. Genetically determined hypoalbuminemia significantly predicted the onset of hypertension [21].

Alkaline phosphatase

Alkaline phosphatase (ALP) is present in various tissues such as the liver, bone, kidney, intestine, and placenta. Consequently, serum ALP consists of multiple ALP isoenzymes, which can be separated through electrophoresis. Normal serum ALP comprises liver and bone components, with bone ALP being heated labile. Liver ALP increases in situations

Table 2

SUMMARY OF MAJOR LIVER FUNCTION TESTS IN HYPERTENSION

First author	Year of publication	LFTs	The main finding of LFTs in hypertension	ref
Ding et al.	2020	Serum albumin	Lower serum albumin levels among Chinese hypertensive adults were only associated with a higher frequency of peripheral arterial disease (PAD) in men and not in women.	[18]
Ahbap et al.	2016	Urine albumin	The paper highlights the significance of serum albumin levels as an independent predictor of nocturnal systolic dipping, at least in non-diabetic essential hypertension patients with mild proteinuria, as opposed to urine albumin excretion.	[19]
Takase et al.	2015	Urinary albumin	Urinary albumin was an independent predictor of hypertension and elevations in blood pressure in the general population.	[20]
Choi et al.	2021	Serum albumin	Significant predictors of the development of hypertension included serum albumin (HR = 0,654, 95% CI 0,521–0,820), polymorphisms of rs2894536 in *LOC107986598* (HR = 1,176, 95% CI 1,015–1,361), and rs10972486 in *ATP8B5P* (HR = 1,152, 95% CI 1,009–1,316).	[21]
Shimizu et al.	2013	Serum ALP	ALP was associated with hypertension for both male and female non-drinkers, but not for drinkers.	[25]
Zhang et al.	2021	Serum ALP	Chinese hypertensive people had a considerably greater risk of having their first stroke even when serum ALP levels were within the normal range.	[26]
Khalili et al.	2022	Serum ALP	Males and females both had an elevated risk of hypertension when their serum ALP activity was higher. Increased ALP may therefore be a precursor of hypertension.	[14]
Schutte et al.	2013	Serum ALP	In hypertensive African men, serum ALP negatively correlated with indices of artery anatomy and function.	[27]
Aliyu et al.	2006	Serum ALP	The severity of hypertension strongly correlated with the serum heat-stable ALP activity in patients with pre-eclampsia/eclampsia.	[28]
Jia J et al.	2021	Serum ALT	The linear relationship between serum ALT and hypertension or blood pressure, suggests that aberrant liver metabolism, as evidenced by high serum ALT, may contribute to hypertension or elevated blood pressure.	[31]
Wu et al.	2017	Serum ALT	In elderly Chinese rural population, ALT levels substantially correlated with hypertension only in women.	[32]
Rahman et al.	2020	Serum ALT, GGT activity	In Bangladeshi individuals, elevated serum ALT and GGT activity positively correlated with hypertension.	[12]

Continuation of table 2

First author	Year of publication	LFTs	The main finding of LFTs in hypertension	ref
Huang et al.	2021	Serum ALT	Elevated ALT and hypertension inversely correlated in Chinese adults, and elevated ALT likely precedes the onset of hypertension.	[33]
Zhu et al.	2021	ALT, AST	The overall prevalence of elevated ALT and AST were 6,8 % and 2,3 % among freshmen. ALT level was related to both male and female freshmen's hypertension.	[35]
Yoon et al.	2021	(AST/ALT) ratio	In Korean people with hypertension, the high pulse pressure inversely correlated with ALT but favorably correlated with AST and AST/ALT ratio.	[36]
Dan et al.	2012	GGT	GGT levels were higher in hypertension patients when compared to their age- and sex-matched normotensive peers, pointing to a possible causal relationship.	[38]
Ortakoyluoglu et al.	2016	GGT	The non-dipper group had greater GGT levels, which were associated with the nighttime decline in diurnal blood pressure. The non-dipper group had higher levels of uric acid and C-reactive protein.	[39]
Liu et al.	2012	GGT	The development of hypertension correlated with GGT levels.	[40]
Lee et al.	2015	GGT	Serum GGT levels significantly correlated with significant cardiovascular risks factors such as MetS, DM, and urine albumin excretion in hypertensive patients.	[41]
Baduwal et al.	2020	GGT	GGT levels might be utilized as indicators of prehypertension and hypertension.	[42]
Ermis et al.	2012	GGT	One of the causes of the cardiovascular problems associated with non-dipper pattern might be increased GGT activity, which has been reported to be connected with CRP levels.	[43]
Karakurt et al.	2011	GGT	Higher serum GGT levels were linked to increased blood pressure and the development of hypertension	[44]
Lee et al.	2003	GGT	The physiologically normal range for serum GGT was linked to the incidence of DM and hypertension.	[45]
Wang et al.	2015	Bilirubin	The prevention and management of hypertension, as well as coronary heart disease, could be greatly influenced by methods to increase the bioavailability of tissue and circulating bilirubin or to imitate bilirubin antioxidant qualities.	[48]
Tang et al.	2022	Bilirubin	Higher levels of total and unconjugated bilirubin were risk factors for hypertension while higher levels of conjugated bilirubin had the inverse effect.	[49]
Kunutsor et al.	2017	Bilirubin	Circulating total bilirubin weakened an inverse relationship to the risk of developing hypertension may be the result of biases such as unmeasured confounding and/or reverse causation.	[50]

Continuation of table 2

First author	Year of publication	LFTs	The main finding of LFTs in hypertension	ref
Huang et al.	2016	Bilirubin	In men with pre-hypertension but not normotension, serum bilirubin negatively correlated with an increase in arterial stiffness. In women, there was no evidence of a significant relationship between arterial stiffness and bilirubin levels.	[51]
Yu et al.	2019	Bilirubin	In preterm newborns, neonatal serum bilirubin levels positively correlated with childhood hypertension and blood pressure. Research may help clarify how bilirubin contributes to the prevention of hypertension.	[52]
McCallum et al.	2015	Bilirubin	The findings encourage more research to clarify the processes by which bilirubin and liver enzymes may influence blood pressure and cardiovascular risk, but there was insufficient evidence to justify their use in risk stratification.	[53]
Cai et al.	2021	LDH	The conclusion is that to confirm LDH as an early marker for the risk of renal involvement in hypertensives, more research is required.	[56]
Vazquez-Alaniz et al.	2019	LDH	Serum LDH was an indicator of severity, diagnosis and unfavourable maternal outcomes in hypertensive disorders in pregnancy.	[57]
Khidri et al.	2020	LDH	Serum LDH indicated the severity and development of pre-eclampsia.	[58]
Talwar et al.	2017	LDH	Poor maternal and perinatal outcomes as well as higher LDH levels were related to high blood pressure.	[59]
Prajapati et al.	2021	LDH	An increase in serum LDH level correlated with the severity of pregnancy-induced hypertension and maternal and fetal complications.	[60]
Jiskani et al.	2017	PT, APTT, INR	The examination of coagulation markers in newly diagnosed hypertension patients showed a considerable increase, indicating their propensity for hemostatic problems and coagulopathy.	[62]
Nnenna Adaeze et al.	2014	PT, APTT	PT and APTT measurements could be used as indicators to assess hemostatic abnormalities in hypertension individuals and serve as a guide for antihypertensive medication.	[63]
Eledo et al.	2018	PT	Hypertension patients had significantly higher platelet counts, PT, and APTT than healthy controls.	[64]
Nwovu et al.	2018	PT	There was no statistically significant difference between the PT and platelet count ($p > 0,05$). Can be an indicator of haemostatic abnormalities in patients with hypertension.	[65]

of biliary obstruction, observed on canalicular surfaces (intrahepatic and extrahepatic). In hepatocyte damage, ALP is often within the normal range or only mildly elevated. Alkaline phosphatases, a type of phosphomonoesterases, hydrolyze phosphate esters with optimal activity at a pH of 10. Enzyme activity is measured in international units (IU), representing the amount of enzyme required to catalyze the conversion of 1 mol of substrate per minute. The commonly used approach yields a reference range of 35 to 125 IU per litre in the adult population, although reference ranges vary depending on the methodology used. This characteristic helps differentiate between biliary dysfunction and liver parenchymal disease [22, 23]. Elevated hepatic enzyme activity consistently corresponds to an increase in serum ALP activity. This is mainly attributed to a rise in the translation of ALP mRNA, which is facilitated by the higher concentration of bile acids. Additionally, there is an augmented secretion of ALP into the bloodstream through canalicular leakage into the hepatic sinusoid. However, the specific mechanism triggering its release into circulation has not been fully understood [24].

Despite ALP being an enzyme affected by alcohol use and its association with hypertension, there is currently no research on the correlation between serum ALP levels and the risk of hypertension from alcohol use. The odds ratio and 95% confidence interval (CI) of hypertension per 1-log increment of ALP were 0,95 for men and 1,57 for women, after adjusting for multiple variables. ALP was associated with hypertension in non-drinking males and females, but not in drinkers. Therefore, alcohol consumption should be considered a potential confounding factor when analyzing the associations between ALP and blood pressure [25]. In a study by Y. Zhang and colleagues (2021), Chinese hypertensive individuals had a significantly higher risk of experiencing their first stroke, even when serum ALP levels were within the normal range [26].

In participants with normal levels of ALT, AST, GGT, and ALP, there were dose-response increases in abnormal blood pressure for both sexes. Both males and females exhibited an elevated risk of hypertension with higher serum ALP activity, indicating that increased ALP may be a precursor of hypertension [14]. Similarly, R. Schutte and colleagues (2013) found a negative correlation between serum ALP and indices of artery anatomy and function in hypertensive African men [27]. In patients with pre-eclampsia/eclampsia, the severity of hypertension showed a strong correlation with serum heat-stable ALP activity, suggesting its potential use in the early detection of complications [28].

Alanine transaminase

Alanine transaminase also known as alanine aminotransferase (ALT or ALAT), is an enzyme of the transaminase class (EC 2.6.1.2). In the past, it was referred to as serum glutamate-pyruvate transaminase or serum glutamic-pyruvic transaminase (SGPT). Arthur Karmen and his colleagues were the first to characterize this enzyme in the mid-1950s. ALT is present in plasma and various body tissues but is predominantly found in the liver. Its primary role is to facilitate the two parts of the alanine cycle. Clinically, the levels of serum ALT, serum AST (aspartate transaminase), and their ratio (AST/ALT ratio) are commonly measured as biomarkers of liver health. These tests are included in blood panels. ALT has a half-life of approximately 47 hours in the bloodstream and is removed from circulation by sinusoidal cells in the liver [29, 30]. A study by J. Jia and colleagues (2021) conducted cross-sectional research and established a linear relationship between serum ALT levels and hypertension or blood pressure. This suggests that abnormal liver metabolism, as indicated by high serum ALT, may contribute to the development of hypertension or elevated blood pressure conditions [31]. In elderly Chinese rural population, a significant correlation between ALT levels and hypertension was observed only in women [32].

Similarly, S. Rahman and colleagues (2020) concluded that elevated levels of liver enzymes were more prevalent in individuals with hypertension. Among Bangladeshi individuals, increased serum ALT and GGT activity showed a positive correlation with hypertension [12]. In contrast, G. Huang and colleagues (2021) found an inverse correlation between elevated ALT levels and hypertension in Chinese adults, suggesting that elevated ALT may precede the onset of hypertension [33].

Aspartate aminotransferase

Aspartate aminotransferase (AST) is an enzyme of the transaminase class responsible for facilitating the conversion of aspartate and alpha-ketoglutarate into oxaloacetate and glutamate. This enzyme was formerly referred to as serum glutamate oxalate transaminase (SGOT) and is present in all tissues except for bone, with the highest levels found in the liver and skeletal muscle. The concentration of AST increases in response to conditions such as bruising, trauma, necrosis, infection, or neoplasia affecting the liver or muscle. In cases of cellular damage, AST is detected in cerebrospinal fluid, exudates, and transudates, with the level corresponding to the extent of the damage. While low levels of AST can also be found in urine, they are not useful for diagnosing renal damage [34]. High blood pressure is increasingly prevalent among

young individuals and is a well-known risk factor for cardiovascular events. L. Zhu and colleagues (2021) examined the association between ALT and AST levels and hypertension in Chinese freshmen. The overall prevalence of elevated ALT and AST among freshmen was 6,8 % and 2,3 %, respectively, suggesting a strong correlation between ALT levels and hypertension in both male and female freshmen [35]. Additionally, H. Yoon (2021) discussed the relationship between the AST/ALT ratio and pulse pressure in Korean individuals with hypertension. Among Korean individuals with hypertension, higher pulse pressure was inversely correlated with ALT but positively correlated with AST and the AST/ALT ratio [36].

Gamma-glutamyl transferase

Gamma-glutamyl transferase (GGT) is a group of enzymes that play role in transferring amino acids from one peptide to another or an amino acid. Although it is classified as an amino acid transferase, it is sometimes referred to as a "transpeptidase" due to its function in transferring a gamma-glutamyl group to a different acceptor. The reference range for GGT activity is typically 0 to 50 IU/L for males and 0 to 30 IU/L for females, with higher activity in males likely due to its presence in prostatic tissue [22]. In mammalian cells, GGT initiates the breakdown of extracellular glutathione. Serum GGT has been widely utilized as an indicator of liver dysfunction and as a marker of alcohol consumption. In recent years, significant progress has been made in these fields, shedding light on its physiological role in combating oxidative stress. This is achieved by breaking down extracellular glutathione and providing its constituent amino acids to the cells. Conditions that elevate serum GGT levels, such as obstructive liver disease, excessive alcohol intake, and the use of enzyme-inducing drugs, can lead to an increase in free radical production and pose a risk of glutathione depletion. Interestingly, the products resulting from the GGT reaction may themselves contribute to elevated free radical production, especially when the iron is present [37].

However, there is limited research exploring the relationship between GGT and hypertension. S. Dan and colleagues (2012) found that GGT levels were higher in hypertensive patients compared to age- and sex-matched normotensive individuals, suggesting a potential causal relationship [38].

Hypertension is a significant contributor to illness and death. Serum GGT, a biomarker of oxidative stress, has been associated with an increased risk of diabetes and hypertension. A. Ortakoyluoglu and colleagues (2016) conducted a study to examine the relationship between serum GGT levels, an early indicator of endothelial dysfunction and inflammation, and the disruption of the diurnal blood pressure rhythm. The non-dipper group had higher GGT levels [39]. Several prospective observational studies have suggested a positive correlation between GGT levels and the risk of hypertension. To determine the precise relationship between GGT levels and the development of hypertension, a systematic review and meta-analysis were conducted. The results strongly indicated that higher GGT levels were associated with an increased risk of hypertension. However, additional research is required to confirm these findings and elucidate the underlying mechanisms connecting GGT levels with hypertension prevalence [40].

Previous research has shown a correlation between serum GGT levels and CVD risk factors in the general population, including hypertension, diabetes mellitus (DM), and metabolic syndrome (MetS). In Korean hypertensive patients, serum GGT levels were significantly associated with major cardiovascular risk factors such as MetS, DM, and urine albumin excretion. Even after adjusting for age and gender, there was a strong correlation between serum GGT levels and prehypertension and hypertension, suggesting that GGT levels could serve as indicators of these conditions [41, 42]. Non-dipper pattern, characterized by the absence of nighttime blood pressure decline, has been linked to increased cardiovascular morbidity and mortality. This condition is associated with higher levels of serum GGT, which indicates oxidative stress, as well as elevated C-reactive protein (CRP) levels. Increased GGT activity, which is connected to CRP levels, may contribute to the cardiovascular problems associated with non-dipper pattern [43].

In a nationally representative sample of Turkish individuals, the relationship between prehypertension and serum GGT levels was investigated. GGT is present on most cell surfaces and in serum and serves as a marker for oxidative stress. Higher serum GGT levels were associated with elevated blood pressure and the development of hypertension. Furthermore, GGT may play a role in the aetiology of MetS, DM, obstructive sleep apnea syndrome, and CVD. The elevated GGT levels observed in prehypertensive patients supported the notion that they experience higher oxidative stress. It is crucial to closely monitor cardiovascular risk factors, even during the prehypertensive stage [44]. The enzyme GGT, which helps maintain cellular glutathione levels and can also induce oxidative stress, is a potential indicator of oxidative stress. D. H. Lee and colleagues (2003) conducted a prospective study to investigate whether blood GGT levels could predict the incidence of DM and hypertension. The study found that GGT levels within the physiological range were

associated with an increased risk of developing DM and hypertension, suggesting a role of oxidative stress in the pathogenesis of these conditions [45].

Serum Bilirubin

Bilirubin, the product of erythroid cell destruction and heme-containing protein breakdown, is derived from two main sources. The majority of bilirubin (around 80 %) is produced through the premature destruction of erythroid cells in the bone marrow and the breakdown of haemoglobin in senescent red blood cells. The remaining portion comes from the breakdown of heme-containing proteins in other tissues, particularly the liver and muscles, including proteins like myoglobin, cytochromes, catalase, peroxidase, and tryptophan pyrrolase. On average, the daily production of bilirubin is approximately 4 mg/kg of body weight [46, 47].

Oxidative stress has been implicated in the development of hypertension. Cohort studies have recognized serum bilirubin as an independent cardiovascular risk factor and a significant contributor to the antioxidant capacity of blood plasma. However, there is limited and conflicting data regarding the association between bilirubin and blood pressure. High levels of serum bilirubin may reduce the risk of hypertension by inhibiting the production of reactive oxygen species in vascular cells and preventing their activation. Finding ways to increase the bioavailability of bilirubin in tissues and circulation or replicating its antioxidant properties could have a significant impact on the prevention and management of hypertension and coronary heart disease [48].

C. Tang and colleagues (2022) conducted a study in the Guankou Ageing Cohort to investigate the relationship between bilirubin and hypertension. Their findings showed that total and unconjugated bilirubin was associated with an increased risk of hypertension, while conjugated bilirubin had the opposite effect [49]. The future risk of CVD is inversely and independently correlated with the level of total bilirubin in the blood. However, the association between circulating total bilirubin and incident hypertension remains unclear. To evaluate this relationship, the authors implemented a Mendelian randomization approach. It was suggested that biases such as unmeasured confounding and reverse causation might weaken the inverse association between circulating total bilirubin and the risk of developing hypertension. Further investigation is needed to better understand this relationship [50].

Serum bilirubin levels, a protective biomarker of coronary artery disease, have been inversely associated with coronary atherosclerosis. In males, both with and without a history of hypertension, there is a negative correlation between serum bilirubin levels and brachial-ankle pulse wave velocity (baPWV). However, it is unclear if pre-hypertensive or normotensive individuals experience similar correlations. Y. H. Huang and colleagues (2016) conducted a study to examine the association between arterial stiffness and serum bilirubin levels in pre-hypertensive and normotensive participants of both sexes. In men with pre-hypertension, but not in normotensive individuals, serum bilirubin levels negatively correlated with arterial stiffness. No significant relationship between arterial stiffness and bilirubin levels was observed in women [51].

Moreover, consistent findings have been reported when maximal newborn serum bilirubin levels are considered as an exposure factor. In preterm newborns, neonatal serum bilirubin levels positively correlated with childhood hypertension and blood pressure. This research may provide insights into how bilirubin contributes to the prevention of hypertension [52]. Additionally, mounting evidence from general population studies suggests that serum bilirubin and liver enzymes may affect blood pressure and cardiovascular risk. However, it remains unclear if these factors influence long-term survival or blood pressure control in hypertensive patients. Further research is needed to elucidate the mechanisms by which bilirubin and liver enzymes may influence blood pressure and cardiovascular risk, but currently, there is insufficient evidence to support their use in risk stratification [53].

Lactate dehydrogenase

Lactate dehydrogenase (LDH) is present in almost all tissues of the body. Elevated levels of LDH in the blood can be indicative of various diseases, including liver disease, anaemia, heart attacks, bone fractures, muscle damage, cancer, and more [54]. Furthermore, an increased level of LDH may be associated with arterial stiffness and an elevated 10-year risk of CVD. In populations undergoing health examinations, LDH levels could serve as a novel predictor for arterial stiffness and the risk of CVD over 10 years [55]. In Chinese patients with hypertension, albuminuria was found to correlate with LDH levels, particularly in those with hyperhomocysteinemia. LDH and white blood cell count were better indicators of albuminuria in hypertensive individuals compared to standard renal function tests. However, further research is needed to establish LDH as an early marker for renal involvement risk in hypertensive patients [56].

Serum LDH concentration has been identified as a diagnostic and prognostic indicator for the severity and adverse maternal outcomes of hypertensive disorders in pregnancy. It is particularly relevant

in pre-eclampsia, which is also associated with proteinuria. Early detection of pre-eclampsia through the measurement of LDH levels helps avoiding major complications and adverse consequences. Elevated LDH levels guide effective monitoring and care for pre-eclampsia [57,58]. Women with pre-eclampsia and eclampsia exhibit significantly higher LDH levels and these higher levels are associated with poor maternal and perinatal outcomes. High blood pressure shows a significant correlation with both elevated LDH levels and adverse outcomes [59]. Additionally, S. Prajapati and colleagues (2021) reported that an increase in serum LDH level is linked to the severity of pregnancy-induced hypertension (PIH) and complications for both the mother and fetus [60].

Prothrombin time

The prothrombin time (PT) is frequently monitored in patients with liver impairment due to its affordability, easy accessibility, and perceived ability to indicate the risk of bleeding. The PT becomes prolonged as the liver synthetic capacity declines since it affects the levels of factors produced by the liver, including both pro-coagulant factors and anticoagulant factors like antithrombin, protein C, and protein S. In liver failure, the levels of these anticoagulant factors are reduced [61]. On the other hand, hypertension is a leading factor in CVD. Abnormal coagulation characteristics, predisposing to atherosclerosis, are typically found after unfavourable events such as myocardial infarction or cerebral bleeding. In a hypertensive group, all coagulation parameters, including mean PT of 15,07 ± 1,92 seconds ($p = 0,02$), activated APTT of 37,14 ± 4,06 seconds ($p = 0,001$), and international normalized ratio (INR) of 1,04 ± 0,18 ($p \leq 0,001$), were higher compared to the control group with mean PT of 12,36 ± 0,74 seconds, APTT of 30,4 ± 2,39 seconds, and INR of 0,87 ± 0,07 [62]. Several scientific findings have demonstrated the effects of hypertension on hemostasis and the functions of blood coagulation products in the clinical development of hypertension. Systolic blood pressure and diastolic blood pressure showed a positive correlation with APTT in hypertensive patients. These findings suggest that PT and APTT measurements could be used as indicators to assess hemostatic abnormalities in individuals with hypertension and guide antihypertensive medication [63].

Another study by B. O. Eledo and colleagues (2018) found that hypertension patients had significantly higher platelet counts, PT, and APTT compared to healthy controls. The authors emphasized the importance of early optimal therapy in hypertension patients to prevent coagulation and thrombosis-related complications [64]. In contrast, a study by A. I. Nwovu and colleagues (2018) concluded that there was no statistically significant difference in PT and platelet count ($p > 0,05$) as indices for assessing hemostatic anomalies in patients with hypertension [65].

Conclusions

Albumin, ALP, ALT, AST, GGT, LDH, and serum bilirubin, play a significant role in the development of hypertension. The specific mechanism by which the liver panel affects hypertension was not reported. The therapeutic management of these liver function tests is essential to control major liver diseases in patients with hypertension.

Conflict of interest / Конфликт интересов

The authors declare no conflict of interest. / Авторы заявили об отсутствии конфликта интересов.

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S. Rafaqat — conceptualization, methodology, resources handling, data curation, original draft preparation, revision and editing; A. Arshad — original draft preparation; IN — revision and editing; H. Khurshid — review and editing; S. Rafaqat — review and editing, editing support. All authors reviewed and approved the final version of the manuscript and its submission to the journal.

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С. Рафакат — разработка общей концепции, методологии, сбор данных, составление первичного варианта рукописи, написание рукописи, критическая оценка интеллектуального содержания рукописи, редактирование рукописи; А. Аршад — составление первичного варианта рукописи, написание рукописи; И. Ношар — редактирование рукописи; Х. Куршид — редактирование рукописи; С. Рафакат — критическая оценка интеллектуального содержания рукописи, редактирование рукописи, принятие окончательного решения о готовности рукописи к публикации. Все авторы внесли существенный вклад в подготовку статьи, прочли, одобрили финальную версию и выразили согласие с подачей ее на рассмотрение в журнал.

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