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Angiotensin II as a Diagnostic Tool for Liver Fibrosis in Patients with Diabetes Mellitus

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ABSTRACT

Background: Liver fibrosis is a common complication of diabetes mellitus (DM) that may progress to cirrhosis and hepatocellular carcinoma. Angiotensin II plays an important role in hepatic fibrogenesis and has been proposed as a potential biomarker for early detection of liver fibrosis. This study aimed to evaluate the diagnostic performance of serum angiotensin II for detecting liver fibrosis using the Fibrosis-4 (FIB-4) index as the reference standard. Methods: A cross-sectional study was conducted in Purwokerto, Indonesia, between February and March 2021 involving 61 patients with DM. Liver fibrosis was defined as a FIB-4 score ≥1.43. Serum angiotensin II levels were measured by ELISA, and diagnostic performance was evaluated using receiver operating characteristic (ROC) analysis to determine the optimal cut-off value, area under the ROC curve (AUROC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios. Results: The participants had a mean age of 60.3 ± 6.2 years, and 32.8% were classified as having liver fibrosis based on the FIB-4 index. The optimal cut-off value of serum angiotensin II was 728.83 pg/mL. The AUROC was 0.60 (95% CI: 0.45–0.76; p = 0.186), with a sensitivity of 60%, specificity of 61%, PPV of 42.9%, NPV of 75.8%, positive likelihood ratio of 1.54, and negative likelihood ratio of 0.66, indicating limited diagnostic performance. Conclusions: Serum angiotensin II demonstrated limited diagnostic accuracy for detecting liver fibrosis in patients with DM. Although it may have potential as an adjunctive non-invasive screening biomarker, its clinical utility requires further validation in larger prospective studies using validated reference standards

1. INTRODUCTION

Diabetes Mellitus (DM) manifests as a metabolic disorder featuring hyperglycemia due to irregular insulin secretion, impaired insulin function, or a combination of both.1,2 According to the International Diabetes Federation (IDF), approximately 589 million adults were living with diabetes worldwide in 2025, and this number is projected to increase substantially over the coming decades, making diabetes one of the leading contributors to chronic liver disease and premature mortality (IDF, 2025). DM complications, including retinopathy, neuropathy, nephropathy, and coronary artery disease, increase health risks (Karuranga et al., 2017). DM patients are also prone to metabolic dysfunction-associated steatotic liver disease (MASLD), previously referred to as non-alcoholic fatty liver disease (NAFLD) (Chen et al., 2020) and liver fibrosis (Ciardullo et al., 2020) with 78.72% of type 2 DM patients developing NAFLD (Atan et al., 2017) and 18.1% to 21% developing fibrosis (Huang et al., 2021). These conditions can lead to cirrhosis and hepatocellular carcinoma (HCC), with cirrhosis found in 6.4% and HCC in 15.3% of NAFLD patients (Pinyopornpanish et al., 2021). The incidence of HCC is higher in patients with fibrosis (0.5 per 100 person-years) and cirrhosis (about 2.1 per 100 person-years) (Lockart et al., 2022), with 80–90% of HCC cases linked to fibrosis (Baglieri et al., 2019). Importantly, liver fibrosis in patients with DM frequently progresses silently during its early stages and is often diagnosed only after irreversible complications, such as cirrhosis or HCC, have developed,

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highlighting the importance of early identification in this high-risk population (Younossi et al., 2024).

The development of liver fibrosis in DM is driven by multiple interconnected mechanisms. Persistent insulin resistance promotes hepatic lipid accumulation and lipotoxicity, leading to oxidative stress, mitochondrial dysfunction, and chronic low-grade inflammation. These processes stimulate the production of pro-inflammatory cytokines and profibrotic mediators, resulting in activation of hepatic stellate cells (HSCs), excessive extracellular matrix deposition, and progressive hepatic fibrosis (Friedman, 2008; Younossi et al., 2024). Among these pathways, activation of the renin–angiotensin system has emerged as an important contributor to hepatic fibrogenesis.

Angiotensin II is a key element in liver fibrosis progression in DM, acting in insulin resistance and fibrogenesis within the liver (Silva et al., 2017; Wael et al., 2025). Biologically, Angiotensin II promotes fibrosis through activation of the angiotensin II type 1 receptor (AT1R), which stimulates transforming growth factor-β1 (TGF-β1), activates hepatic stellate cells, enhances collagen synthesis, increases oxidative stress, and amplifies inflammatory signaling pathways, including NF-κB, thereby accelerating hepatic fibrogenesis. These molecular mechanisms provide a strong biological rationale for evaluating Angiotensin II as a potential biomarker of liver fibrosis in patients with DM.

While non-invasive liver health assessments like FLI, FLS, fibrosis score, and FIB-4 are in use, their diagnostic performance may be influenced by age, obesity, metabolic abnormalities, and biochemical variability, reducing their accuracy in some patients with DM. Therefore, identification of additional biomarkers that directly reflect fibrogenic activity may improve early detection of liver fibrosis. Previous studies investigating Angiotensin II have largely focused on experimental models or explored its biological role in liver fibrogenesis without comprehensively evaluating its diagnostic performance in patients with diabetes mellitus. Moreover, evidence regarding the optimal cut-off value, sensitivity, specificity, and overall diagnostic accuracy of Angiotensin II for detecting liver fibrosis in this population remains limited.

If Angiotensin II demonstrates adequate diagnostic performance, it may serve as a promising non-invasive screening biomarker for identifying liver fibrosis at an earlier stage, enabling timely intervention before progression to cirrhosis or hepatocellular carcinoma. Therefore, this study aimed to evaluate the diagnostic performance of Angiotensin II using receiver operating characteristic (ROC) analysis by determining its optimal cut-off value, sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve (AUC) for detecting liver fibrosis in patients with diabetes mellitus. This study is expected to provide new evidence regarding the clinical utility of Angiotensin II as a biomarker for early detection of liver fibrosis in patients with DM.

2. METHOD

A cross-sectional study was conducted at Prof. Dr. Margono Soekarjo Hospital, 668-bed hospital owned by the Central Java provincial government located in Banyumas District. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Jenderal Soedirman University (approval number 178/KEPK/VIII/2020) and was conducted in accordance with the Declaration of Helsinki of 2008. All participants were provided with detailed explanations regarding the study objectives, potential risks, and anticipated benefits associated with participation. Written informed consent was obtained from all participants prior to enrollment after having the opportunity to receive pertinent details and have any questions answered.

The study included 61 patients with DM who attended the Diabetes Mellitus Clinic at Prof. Dr. Margono Soekarjo Hospital from February to March 2021. Inclusion criteria were patients aged 20-79 years, diagnosed with DM for over five years, and consent to participate. Exclusion criteria included incomplete data, having history of cardiovascular or chronic kidney diseases, or alcohol use. Blood samples (6 mL) were collected, half with EDTA anticoagulant and half without. Samples were analyzed for angiotensin II, thrombocytes, ALT, and AST levels.

In addition to blood analysis, demographic and anthropometric data, including age, sex, height, weight, and Body Mass Index (BMI), were gathered from the participants. Angiotensin II levels were measured using the ELISA competitive method with the Human Ang-II (Angiotensin II) ELISA Kit (Catalog No. E-EL-H0326). Thrombocyte counts were examined using a hematology analyzer (Sysmex KX-21), and AST and ALT levels were measured through a standard method employing a spectrophotometer (IUBIO iMagix-M7). The FIB-4 index was calculated using the formula [age (years) x AST (IU/L)] / [PLT (10^9/L) x ALT^1/2 (IU/L)]. Liver fibrosis diagnosis was based on a FIB-4 score ≥ 1.43. Statistical analysis used mean, SD, independent t-tests, Mann-Whitney test, and AUROC for angiotensin II CoV determination.

3. RESULT AND DISCUSSION

Result

Table 1 illustrates the characteristics of the 61 participants in the study, including 50.8% females, an average age of 60.31 years, and a BMI of 22.7 kg/m2. The average Angiotensin II level was 723.38 pg/mL, and the mean FIB-4 score was 1.35. FIB-4, with a cut-off point of ≥1.43 for liver fibrosis diagnosis (Siddiqui et al., 2017), identified 32.78% of participants with liver fibrosis. Pre-study screening confirmed no participant had a history of alcohol consumption, hypertension, cardiovascular diseases, or chronic kidney diseases.

Table 1. Characteristics of study's samples.

Characteristic	Min	Max	Mean (±SD)	Median
Sex:	-	-	-	
Male (49.2%)				
Female (50.8%)				
Age (year)	49.00	73.00	60.31 (6.17)	62.00
Height (cm)	148.00	172.00	165.50 (6.09)	168.00
Weight (kg)	44.00	78.00	61.11 (8.59)	57.00
BMI (kg/m^2)	17.16	33.32	22.37 (3.41)	22.30
AST (IU/L)	16.00	77.00	32.06 (12.63)	29.00
ALT (IU/L)	6.00	90.00	27.08 (15.61)	22.00
AST/ALT Ratio	0.50	4.00	1.36 (0.59)	1.32
Thrombocyte (10^3/ μL)	64.00	589.00	329.06 (97.11)	323.00
Angiotensin II (pg/mL)	261.76	1284.28	723.38 (237.92)	720.41
FIB-4	0.59	8.17	1.35 (1.01)	1.15
≥1.43 (32.78%)				
<1.43 (67.21%)				

In Table 2, we compared the AST/ALT ratio and the angiotensin II levels of the subjects between the fibrosis group and the non-fibrosis group using the FIB-4 cut-off value of 1.43. The mean AST/ALT ratio was significantly higher in the fibrosis group compared to the non-fibrosis group (1.78 vs 1.15, p=0.000). However, there were no significant differences in the mean levels of angiotensin II between the fibrosis group and the non-fibrosis group (767.48 vs 701.87 pg/mL, p=0.316).

Table 2. Comparison of AST/ALT Ratio and Angiotensin II based on FIB-4 level.

Variable (Mean)	FIB-4 ≥1.43	FIB-4 <1.43	p
AST/ALT Ratio	1.78	1.15	0.000[a]
Angiotensin II (pg/mL)	767.48	701.87	0.316[b]

a: Mann Whitney Test; b: independent t-test

The study determined the optimal cut-off value (CoV) for angiotensin II to be 728.83 pg/mL, achieving the best sensitivity (60%) and specificity (61%) measures. The corresponding Area Under the Receiver Operating Characteristic Curve (AUROC) was calculated as 0.60 (95%CI: 0.45 – 0.76), with a p-value of 0.186, indicating a fair predictive ability. For a visual representation, Figure 1 displays the AUROC of angiotensin II with the determined CoV of 728.83 pg/mL, providing a clear insight into the diagnostic performance of this marker.

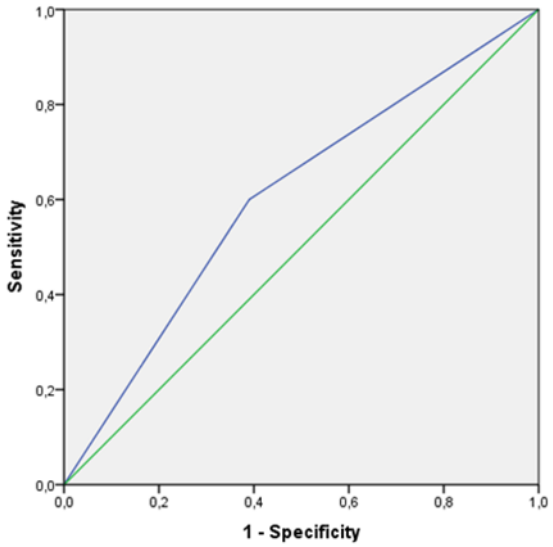

Figure 1. AUROC of Angiotensin II Curve with CoV of 728.83 pg/mL

The study's results elucidate the diagnostic potential of angiotensin II at a threshold of 728.83 pg/mL. The evaluation showcased a sensitivity of 60% and specificity of 61%, accompanied by a positive predictive value (PPV) of 42.9% and a negative predictive value (NPV) of 75.8%. The positive likelihood ratio (PLR) stood at 1.54, while the negative likelihood ratio (NLR) was 0.66. Furthermore, the odds ratio (OR) was calculated at 2.34, as outlined in Table 3.

Table 3. Diagnostic values of Angiotensin II

Diagnostic values	Values	95%CI
Sensitivity	60%	36.1 – 80.9%
Specificity	61%	44.5 – 75.8%
Positive Predictive Value	42.9%	24.5% - 62.8%
Negative Predictive Value	75.8%	57.7% - 88.9%
Positive Likelihood Ratio	1.54	0.91 – 2.6
Negative Likelihood Ratio	0.66	0.36 – 1.18
Odds Ratio	2.34	0.8 – 6.86

Discussion

The study aimed to determine the cut-off value and diagnostic value of angiotensin II for liver fibrosis in DM patients, using FIB-4 as a benchmark. The prevalence of liver fibrosis by FIB-4 was 32.78%, with an angiotensin II cut-off value of 728.23 pg/mL, sensitivity of 60%, and specificity of 61%. FIB-4, with a score ≥1.43, showed a 92.9% specificity, 95.4% PPV, and an AUROC of 0.821, but lower sensitivity (60.2%) and NPV (48.6%) (Siddiqui et al., 2017). Other studies, also validated the use of FIB-4 to predict liver fibrosis prevalence (Sumida et al., 2012).

The variance in liver fibrosis prevalence in this study compared to others is attributed to different gold standards used. A study found a 78.72% prevalence of NAFLD in type 2 diabetes patients using fibro Scan, while the others., using liver biopsy, reported NAFLD liver fibrosis rates at 23% and 31%, respectively . The choice of gold standard diagnosis in liver fibrosis can impact reported prevalence rates and should be carefully considered in future studies.

In this study, the fibrosis group exhibited a higher AST/ALT ratio, indicating more prolonged liver cell damage, as a higher AST relative to ALT often signifies chronic liver damage. While both AST and ALT levels usually increase in liver damage, they are moderately elevated in fibrosis. It's important to note that ALT enzyme is primarily located in the cytoplasm, while most AST is found in the liver cells' mitochondria (Connell et al., 2012). Liver damage is associated with an increased AST/ALT ratio, which is higher in the fibrosis group compared to the non-fibrosis group. A higher AST level relative to ALT indicates chronic and prolonged liver cell damage. While both AST and ALT levels generally rise in liver damage, liver fibrosis typically shows moderately elevated levels, with ALT primarily in the cytoplasm and AST in liver cell mitochondria (Shetty et al., 2021).

The study also found higher mean angiotensin II levels in the fibrosis group, aligning with Shim previous findings (Shim et al., 2018). However, these levels differ from Hartl et al., who reported average levels of 46.2 pmol/L in the cACLD group and 343.7 pmol/L in the dACLD group (Hartl et al., 2023) who found 36.69 pg/mL in controls and 42.18 pg/mL in the NAFLD group (Li et al., 2019). The discrepancies may stem from different study populations, as Li et al. focused on non-DM patients, while our study involved DM patients, potentially influencing angiotensin II levels.

Angiotensin II, a primary component of the renin-angiotensin system (RAS), plays a crucial role in liver fibrosis through classical and alternative pathways. It is synthesized in the liver as an α2-globulin glycoprotein and transformed into angiotensin I by renin and prorenin. Angiotensin I is then converted into angiotensin II by ACE. Binding of angiotensin II to the angiotensin type 1 receptor (AT1) triggers inflammatory, proliferative, and vascular processes within the liver, leading to cell proliferation and promoting fibrogenesis. The regulation of angiotensin within the RAS is observed in patients with type II diabetes mellitus (DM). ACE inhibitor administration has shown beneficial effects in repairing liver damage, reinforcing the role of angiotensin in liver injury 27–29.

Angiotensin II impairs insulin sensitivity by hindering insulin-stimulated tyrosine phosphorylation, affecting the phosphatidylinositol-3-kinase (PI3K) and insulin receptor substrate (IRS-1) interaction (Gutierrez-rodelo et al., 2022). PI3K is responsible for the activation of downstream signaling pathways that lead to glucose uptake and utilization in various tissues, including the liver, muscle, and adipose tissue. However, when angiotensin II reduces insulin-stimulated tyrosine phosphorylation, it impairs the interaction between PI3K and IRS-1, leading to a downregulation of insulin receptor signaling (Gutierrez-rodelo et al., 2022). This impairment disrupts insulin receptor signaling, leading to increased liver glucose production and higher blood glucose levels, potentially causing hyperglycemia and type 2 diabetes (Chait et al., 2020). This contributes to increased blood glucose levels, which can lead to hyperglycemia and the development of type 2 diabetes. Furthermore, angiotensin II reduces adipose tissue's fat storage capacity, causing triglyceride accumulation in the liver and exacerbating insulin resistance, thus contributing to non-alcoholic fatty liver disease (NAFLD) (Marusic et al., 2021).

With a cut-off value of 728.83 pg/mL, angiotensin II shows a 60% sensitivity and 61% specificity in detecting liver fibrosis (Leeflang et al., 2019). Based on the result of sensitivity, specificity, PPV, NPV, as well as LR positive and negative values, angiotensin II still cannot be used to establish the liver fibrosis diagnosis, yet it is more appropriate if utilized as a screening test. Despite its limitations, this study presents valuable insights into the role of angiotensin II as a potential biomarker for early liver fibrosis screening in DM patients within the Indonesian population. The research contributes to the limited body of literature in this area and serves as a reference point for future investigations aiming to validate Angiotensin II's significance as a biomarker for liver fibrosis in individuals with DM.

4. CONCLUSION

This study demonstrated that serum angiotensin II, at an optimal cut-off value of 728.83 pg/mL, showed limited diagnostic performance for detecting liver fibrosis in patients with diabetes mellitus, with an AUROC of 0.60 (95% CI: 0.45–0.76; p=0.186), 60% sensitivity, and 61%

specificity. These findings indicate that angiotensin II alone is insufficient as a reliable diagnostic biomarker for establishing liver fibrosis. Nevertheless, given its biological role in hepatic fibrogenesis and its moderate negative predictive value, angiotensin II may still have potential as an adjunctive biomarker or an initial non-invasive screening tool when used in combination with established clinical scoring systems or other fibrosis biomarkers, rather than as a standalone diagnostic test. This study is limited by its cross-sectional design, relatively small sample size, single-center setting, and the use of the FIB-4 index instead of FibroScan or liver biopsy as the reference standard. Therefore, larger prospective multicenter studies using validated reference standards, such as FibroScan or liver biopsy, are warranted to further validate the diagnostic utility and clinical applicability of angiotensin II in detecting liver fibrosis among patients with diabetes mellitus.

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