










Comparison of plasminogen activator inhibitor-1 levels in chronic hepatitis B patients with hepatic cirrhosis and without hepatic cirrhosis

Andhika Kusuma Hamdany^{1*}, Muhammad Luthfi Parewangi¹, Sahyuddin Saleh¹, Syakib Bakri¹, Fardah Akil¹, Satriawan Abadi¹, Arifin Seweng²

¹Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; ²Department of Biostatistics, Faculty of Public Health, Hasanuddin University, Makassar, Indonesia

Abstract

Edited by: Ksenija Bogoeva-Kostovska
Citation: Hamdany AK, Parewangi ML, Saleh S, Bakri S, Akil F, Abadi S, Seweng A. Comparison of plasminogen activator inhibitor-1 levels in chronic hepatitis B patients with hepatic cirrhosis and without hepatic cirrhosis. Open Access Maced J Med Sci. 2022 Sep 01; 10(B):2023-2028. https://doi.org/10.3889/oamjms.2022.10439

Keywords: Chronic hepatitis B; Hepatic cirrhosis; Plasminogen activator inhibitor-1

***Correspondence:** Andhika Kusuma Hamdany, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. E-mail: andhika.hamdany@gmail.com

Received: 16-Jun-2022

Revised: 26-Aug-2022

Accepted: 29-Aug-2022

Copyright: © 2022 Andhika Kusuma Hamdany, Muhammad Luthfi Parewangi, Sahyuddin Saleh, Syakib Bakri, Fardah Akil, Satriawan Abadi, Arifin Seweng

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Open Access: This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

BACKGROUND: Chronic Hepatitis B infection is one of the most common causes of hepatic cirrhosis. Among all the substance that plays a pivotal role in maintaining the balance between thrombosis and thrombolysis is plasminogen activator inhibitor-1 (PAI-1), synthesized by hepatocytes. The increase and decrease of PAI-1 are a natural response to the ongoing hepatic cirrhosis caused by chronic hepatitis B infection, but may not be seen in non-hepatic cirrhosis. PAI-1 level also depend on the stage of fibrosis. Several conditions may interfere with PAI-1 levels including age, body mass index, and gender.

AIM: This study aims to find out the comparison of PAI-1 levels in hepatitis B patients with hepatic cirrhosis and without hepatic cirrhosis and to compare it with every stage of hepatic cirrhosis.

PATIENTS AND METHODS: This study is an observational analytical study with a cross-sectional approach conducted at Wahidin Sudirohusodo hospitals, Makassar. Subjects are chronic hepatitis B patients with and without hepatic cirrhosis which meet inclusion criteria. Serum PAI-1 levels were measured by using Bender MedSystems human PAI-1 enzyme-linked immunosorbent assay (ELISA) kit (BMS2033) and using ELISA technique. Statistical analysis was performed using Kolmogorov-Smirnov normality test as well as Mann-Whitney method. Statistical results are considered significant if $p < 0.05$.

RESULTS: The research was conducted on 60 subjects who meet inclusion criteria, consisted of 33 men and 27 women. There were 16 patients with hepatic cirrhosis. Levels of PAI-1 in hepatic cirrhosis were significantly different which lower than non-hepatic cirrhosis patient (0.43 ng/mL vs. 1.11 ng/mL, $p = 0.024$). Based on staging of hepatic fibrosis, stage F2 hepatic fibrosis had highest levels of PAI-1, in contrast with end-stage hepatic fibrosis which had the lowest levels.

CONCLUSION: Levels of PAI-1 fluctuates through different stages of hepatic fibrosis. The significant difference of PAI-1 levels in hepatic cirrhosis and non-hepatic cirrhosis demonstrates correlation between PAI-1 and hepatic cirrhosis

Introduction

Hepatitis B virus (HBV) infection is an infectious disease that has an impact on global health. Chronic HBV infection causes increased morbidity and mortality. The main cause of death in hepatitis B is fatal damage to the liver [1].

Globally, it is estimated that around 2 billion people have been infected with HBV and 248 million of them are chronically infected. In Indonesia alone, the prevalence of hepatitis B is around 7.1%. About 15–25% with chronic hepatitis B die from liver cancer and liver cirrhosis. Based on data from The Global Burden of Disease Study, around 686,000 people died in 2013 due to hepatitis B with a mortality rate of 5.9/100,000 population. Of total cases, 300,000 deaths occurred due to liver cancer and 317,400 due to liver cirrhosis [2].

Liver cirrhosis, which is the leading cause of death in chronic hepatitis B, is a pathological condition that describes the end stage of progressive hepatic fibrosis characterized by distortion of the liver architecture and the formation of regenerative nodules [3]. Definition of cirrhosis according to the World Health Organization is a diffuse process characterized by fibrosis and alteration of normal liver architecture to abnormal nodular structures that lack normal lobular organization [4].

From the results of a 2014 Centers for Disease Control and Prevention survey, cirrhosis itself is one of the 15 highest causes of death in the world. Liver cirrhosis was ranked 12th with total mortality of 12%. This is an increase of 0.5% from the 2013 survey results which had 11.5% results. Liver disease itself is considered the second cause of mortality among all digestive diseases in the United States [5]. There

are no significant data for Southeast Asia, but more than 70% of the population is infected with the HBV and about 20% develop liver cirrhosis [6]. In Indonesia, the prevalence data of liver cirrhosis is unclear. At DR. Sarjito Hospital, Yogyakarta, the number of patients with liver cirrhosis was around 4.1% within 1 year. In Medan, within 4 years, liver cirrhosis patients were found (4%) of all patients in the internal medicine department [4].

Hemostasis is a physiological process that stops bleeding at the site of injury while maintaining normal blood flow elsewhere in the circulation. Blood loss is stopped by the formation of a hemostatic plug. There are three processes in the occurrence of hemostasis balance, namely primary, secondary, and tertiary hemostasis. Primary hemostasis is related to the formation of a platelet plug, secondary hemostasis is related to the formation of fibrin threads through the coagulation cascade, and tertiary hemostasis, which plays a role in the formation of plasmin, has a function to break down fibrin through the process of fibrinolysis. The liver plays an important role in the hemostasis system by synthesizing blood clotting factors or fibrinolytic factors. In consequence, the occurrence of liver disease can cause complex changes in the three phases of hemostasis [7].

One of the proteins that have a role in the hemostasis process, especially in the tertiary hemostasis process, is the plasminogen activator inhibitor-1 (PAI-1) protein. PAI-1 is a unique structure and is a specific and fast-acting inhibitor of Plasminogen Activator that plays a role in the fibrinolysis process. Other kinds of plasminogen activators (PAs) are tissue plasminogen activator (t-PA) and urokinogen plasminogen activator (u-PA) which are the primary regulator of activation of plasminogen. PAI-1 can inhibit plasmin and trypsin as well as thrombin to form fibrin [8].

PAI-1 is an acute-phase protein known to correlate with liver fibrosis and is also expressed in hepatocytes. PAI-1 levels are also elevated in the plasma of patients with liver disease. Low PAI-1 levels have also been shown to protect against all three stages of liver disease (early phase [steatosis], middle phase [inflammation/necrosis], and late phase [fibrosis]). A later study by Wang *et al.* [9], also showed that PAI-1-deficient mice had a reduced incidence of liver fibrosis, and increased tPA and matrix metalloproteinase [9] activity compared to normal mice. Liver is hepatitis B infection [9].

Research conducted by Linda Pasta [10] (2015) shows that there are 3 types of genotypes of PAI-1, namely the 4G 4G, 4G 5G, and 5G 5G alleles. Of the three alleles, the PAI-1 4G/4G gene polymorphism had the highest PAI-1 level compared to the other PAI-1 gene polymorphisms. Regarding PAI-1 4G-4G, there are many studies showing the role

of these thrombophilic genetic factors associated with the highest serum PAI-1 activity in the process of liver fibrosis. PAI-1 has an active role in liver fibrosis in mice through a pathogenic mechanism that leads to hepatic stellate cell activation [10].

Research on PAI-1 in hepatitis B has not been widely studied. In one of the results of a study proposed by Divella *et al.* [10], it shows that there was an increase in PAI-1 in patients with hepatocellular carcinoma due to hepatitis B. However, we have not found any studies regarding the relationship between PAI-1 levels in chronic hepatitis B stage [11].

Based on this background, the authors wanted to evaluate the differences in PAI-1 levels in chronic hepatitis B patients with and without liver cirrhosis.

Objectives

To find out the comparison of PAI-1 levels in hepatitis B patients with hepatic cirrhosis and without hepatic cirrhosis, PAI-1 levels in each hepatic fibrosis stage, and to discover the correlation of PAI-1 levels with the severity of hepatic fibrosis.

Patients and Methods

Study design

This study was designed with an observational analytical study with a cross-sectional approach. Subjects were recruited in the outpatient and inpatient department of Wahidin Sudirohusodo hospital with the diagnosis of chronic hepatitis B at RSWS since October 2021. The inclusion criteria are people with and without hepatic cirrhosis who have not received antiviral therapy. Intact serum PAI-1 levels were measured using an enzyme immunoassay kit.

Laboratory analysis

Sampling is done by consecutive sampling. Blood is taken from the mediana cubiti vein with a volume of 3 ccs and inserted into the citrate tube. The blood sample was examined by calculating PAI-1 plasma levels using the Bender MedSystems human PAI-1 enzyme-linked immunosorbent assay (ELISA) kit (BMS2033) and using the ELISA technique with units of ng/mL size.

Blood samples that have been collected are centrifuged at a speed of 4000× g for 10 min. The plasma sample will then be retrieved and then we examine it with a BMS2033 human PAI-1 ELISA kit.

Operational definition

Hepatic fibrosis is defined by the result of fibroscan from chronic hepatitis B patient. By its severity, from mild to severe, hepatic fibrosis is divided by F0–F4.

Hepatic cirrhosis is defined as a late-stage hepatic fibrosis with a slow decline in function due to chronic inflammation over a long period of time. Diagnosis of hepatic cirrhosis if it meets any of the following criteria:

- Fibroscan results F4 (cirrhosis) or,
- Abdominal ultrasound shows the results of hepatic cirrhosis or,
- Multi slice computed tomography abdomen shows the result of hepatic cirrhosis.

PAI-1 levels are the value of PAI-1 using the ELISA procedure. PAI-1 levels are measured in ng/ml units.

Statistical analysis

The analysis method consists of descriptive analysis methods and statistical tests. Variables are performed normality tests using Kolmogorov–Smirnov analysis tests.

- Differences in PAI-1 levels between hepatitis patients with hepatic cirrhosis and without hepatic cirrhosis use unpaired t-tests if the distribution is normal. If the distribution is abnormal, then the Mann–Whitney test is performed as an alternative test.
- The difference in PAI-1 levels between four groups of chronic hepatitis B patients with cirrhosis based on fibrosis degree (F0–F1, F2, F3, and F4) is analyzed by the One-Way ANOVA test if the distribution is normal. If the distribution is not normal, then the Kruskal–Wallis test is performed as an alternative test.

Statistical test results are considered significant if the test $p < 0.05$. The results obtained will be displayed in the form of narration, equipped with tables and figures.

Ethical issues

The research was conducted following the tenets of the Declaration of Helsinki. The Ethics Committee For Clinical Research of Faculty of Medicine Hasanuddin University and Dr. Wahidin Sudirohusodo Hospital Makassar approved this study. The institutional ethical committee at the Faculty of Medicine Hasanuddin University accepted all study protocols. Accordingly, written informed consent was taken from all participants.

Results

Characteristics of research subjects

In this study, subjects met the criteria of 60 subjects consisting of 33 (55.0%) men and 27 (45.0%) women. Based on the age category, the subjects involved in the <60-year-old category were 52 people (86.7%) compared to 8 for >60-year-old subjects (13.3%). Based on BMI, subjects were divided into obese and non-obese subjects, of which there were 44 people (73.3%) obese subjects compared to 16 (26.7%) non-obese subjects. Of the 60 subjects, there were 44 (73.3%) subjects who did not have cirrhosis and 16 (26.7%) subjects who had cirrhosis (Table 1).

Table 1: Characteristics of research subjects

| Category | n (60) | % |
|-----------|--------|------|
| Gender | | |
| Man | 33 | 55.0 |
| Woman | 27 | 45.0 |
| Age | | |
| <60 years | 52 | 86.7 |
| ≥60 years | 8 | 13.3 |
| IMT | | |
| Non-obese | 44 | 73.3 |
| Obese | 16 | 26.7 |
| Cirrhosis | | |
| Not | 44 | 73.3 |
| Yes | 16 | 26.7 |

PAI-1 levels in its relation to cirrhosis

PAI-1 levels were found to be significantly lower in subjects who had cirrhosis (0.43) than in non-cirrhosis subjects (1.11). This suggests a significant association between PAI-1 levels and cirrhosis ($p = 0.024$) (Table 2 and Figure 1).

Table 2: Analysis of PAI-1 levels (ng/mL) in relation with cirrhosis

| Cirrhosis | n | Mean | SD | p* |
|-----------|----|------|------|-------|
| No | 44 | 1.11 | 1.64 | 0.024 |
| Yes | 16 | 0.43 | 0.78 | |

*Mann–Whitney test.

Our further analysis shows that PAI-1 levels in the F2 fibrosis stage have the highest concentration compared to other stages while stage F4 (Cirrhosis) is a stage with the lowest PAI-1 rate. High PAI-1 levels in F2 fibrosis differ significantly from PAI-1 levels in

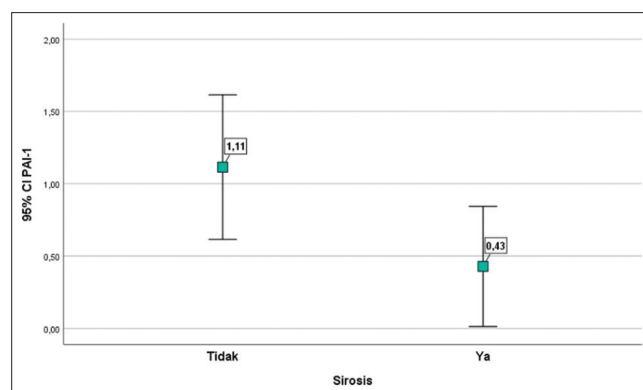


Figure 1: PAI-1 levels in relation with cirrhosis

stage F4 ($p = 0.020$), but do not differ significantly from stages F0–F1 ($p = 0.061$) and F3 ($p = 0.071$) (Table 3 and Figure 2).

Table 3: PAI-1 levels according to degrees of fibrosis

| Degree of fibrosis | Degree of fibrosis | PAI-1 Average value difference | 95% CI | | p |
|--------------------|--------------------|--------------------------------|-------------|-------------|-------|
| | | | Lower bound | Upper bound | |
| F0–F1 | F2 | -1.47 | -3.0045 | 0.0711 | 0.061 |
| | F3 | 0.21 | -0.9923 | 1.4203 | 0.724 |
| | F4 | 0.5 | -0.4095 | 1.4332 | 0.271 |
| F2 | F0–F1 | 1.47 | -0.711 | 3.0045 | 0.061 |
| | F3 | 1.68 | -0.1455 | 3.5069 | 0.071 |
| | F4 | 1.98 | 0.3267 | 3.6304 | 0.020 |
| F3 | F0–F1 | -0.21 | -1.4203 | 0.9923 | 0.724 |
| | F2 | -1.68 | -3.5069 | 0.1455 | 0.071 |
| | F4 | 0.29 | -1.0509 | 1.6466 | 0.660 |
| F4 | F0–F1 | -0.51 | -1.4332 | 0.4095 | 0.271 |
| | F2 | -1.97 | -3.6304 | -0.3267 | 0.020 |
| | F3 | -0.29 | -1.6466 | 1.0509 | 0.660 |

Correlation between PAI-1 in correlation with confounding factors

PAI-1 levels were found to be lower in women (0.82 ng/mL) compared to men (1.02 ng/mL), but were not statistically significant

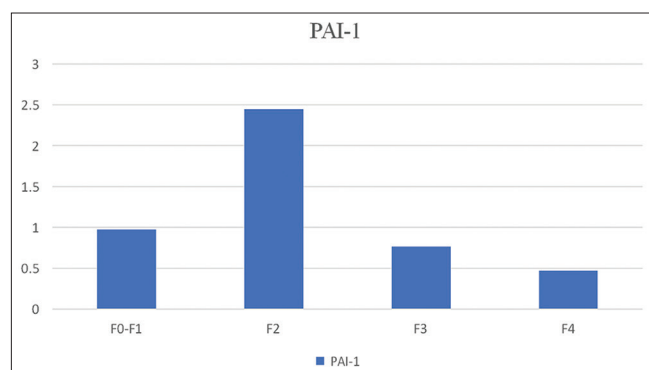


Figure 2: PAI-1 levels according to degrees of cirrhosis

($p = 0.672$). Based on age, PAI-1 levels were found to be higher at 60 years of age (1.53 ng/mL) than at < age 60 years (0.84 ng/mL), but obtained were not statistically significant ($p = 0.957$). Based on BMI, PAI-1 levels were found to be higher in obese subjects (1.09 ng/mL) than in non-obese subjects (0.87 ng/mL), but were not statistically significant ($p = 0.927$) (Table 4).

Table 4: Comparison of PAI-1 levels (ng/mL) by gender, age, and BMI

| Gender | n | Mean | SD | p* |
|--------------|----|------|------|-------|
| Man | 33 | 1.02 | 1.62 | 0.672 |
| Woman | 27 | 0.82 | 1.33 | |
| Age category | | | | |
| <60 years | 52 | 0.84 | 1.29 | 0.957 |
| ≥60 years | 8 | 1.53 | 2.48 | |
| BMI | | | | |
| Non-Obese | 44 | 0.87 | 1.32 | 0.927 |
| Obese | 16 | 1.09 | 1.93 | |

Discussion

In this study, PAI-1 levels in cirrhosis subjects were lower (0.43 ng/mL) compared to non-cirrhosis

subjects (1.11 ng/mL) ($p < 0.05$). PAI-1 is one of the main fibrinolysis inhibitors that work to inhibit the activity of t-PA and u-PA in activating plasminogen into plasminogen. PAI-1 will be attached to the fibrin threads, inhibiting t-PA and u-PA so that the fibrinolysis process will stop working.

Research which was conducted by Lisman *et al.*[11] shows that PAI-1 levels, together with plasminogen, $\alpha 2$ antiplasmin, TAFI, and factor XIII will be reduced due to the presence of endothelial injury. PAI-1 levels vary and may be normal or increased because fibrinolytic interactivity varies between individuals. Hyperfibrinolysis is the result of an imbalance between activators and fibrinolysis inhibitors. TPA levels increase due to reduced liver clearance, while PAI-1 levels do not respond well to changes in tPA, resulting in imbalance through the excessive activity of tPA in patients with severe hepatic cirrhosis. Ascites fluid in cirrhosis of the liver has fibrinolytic activity, in some cases; the reabsorption of ascites fluid into the systemic circulation may contribute to an increase in the degree of fibrinolysis [11].

The hemostasis process is important in the incidence of hepatic fibrosis. The hemostasis process needs to run optimally to prevent the worsening of hepatic fibrosis. It is reported that there is a connection between PAs and PAI-1 in different stages of hepatic fibrosis [12]. In the early stages of hepatic fibrosis, PAs and their receptors are more predominantly expressed, in addition, an increase from PAI-1 inhibits the activity of PAs which leads to the hindrance of excessive degradation of the extracellular matrix, leads to accumulation of extracellular matrix that triggers fibrogenesis [13]. Supporting this statement, Kareem WA also explained in his study that PAI-1 levels were significantly lower in patients with hepatic cirrhosis than in non-hepatic cirrhosis patients [14]. Different things obtained in our study where the lowest PAI-1 levels were obtained in the cirrhosis stage.

While in other publications, hyperfibrinolysis (high PAs/PAI-1 ratio) is a common condition in hepatic cirrhosis patients and is a predictor of patient severity [15]. Hyperfibrinolysis conditions that occur due to increased PA and/or decreased PAI-1 so that the risk of bleeding will be higher in patients with hepatic cirrhosis so mortality will increase as well [16], [17], [18], [19], [20].

In this study, PAI-1 levels in male subjects were higher (1.02 ng/mL) than in female subjects (0.82 ng/mL), but not statistically significant ($p > 0.05$). Yousuf *et al.* [21] found that higher amounts of PAI-1 levels were found in male sufferers compared to women. In men, testosterone levels are associated with decreased PAI-1 levels in plasma. The state of hypogonadism will increase the expression of PAI-1, while the use of androgen drugs will lower PAI-1 levels. In women, estrogen levels are associated with low levels of PAI-1 in women [21].

In this study, PAI-1 levels in subjects age 60 years were higher (1.53 ng/mL) than subjects with < age 60 years (0.84 ng/mL), but not statistically

significant ($p > 0.05$). Eren *et al.* [22] stated in their study that in general PAI-1 levels will increase in old age because it is associated with the incidence of metabolic diseases such as cardiovascular disease and diabetes mellitus. In older people without comorbidities, PAI-1 levels may still increase. This has to do with PAI-1 being synthesized and secreted in senescent cells and contributing directly to the aging process through mechanisms of decreased p53 levels and increased insulin-like growth factor binding protein 3 [22].

In this study, PAI-1 levels were found higher in obese subjects (1.09 ng/mL) compared to non-obese subjects (0.87 ng/mL), but not statistically significant ($p > 0.05$). Deveraj *et al.* [23] in his research showed that endothelial dysfunction in the obese state will trigger PAI-1 secretion. Cytokine excretion of IL-6 and TNF- α by fat cells where cytokines IL-6 and TNF- α are one of the factors that play a role in the mechanism of vascular endothelial dysfunction, where endothelial dysfunction will increase PAI-1 expression. In addition, obesity is also associated with insulin resistance which will also spur endothelial dysfunction. There is evidence that a combination of hyperinsulinemia, hyperglycemia, and hypertriglyceridemia will increase PAI-1 levels in healthy humans. PAI-1 mRNA can be found in adipose cells in obese people. Weight loss will significantly lower PAI-1 levels in obese people [23].

Limitations of the study

More research is needed to determine PAI-1 levels at various severity of cirrhosis based on its clinical presentation and its relation to hyperfibrinolysis.

Authors' Contribution

AKH, MLP, and SS were the principal investigators of the study and drafted the manuscript; AKH and AS collected and analyzed the data; AKH and AS contributed to the concept and design of the study; MLP and SS revisited the manuscript and critically evaluated the intellectual contents. All authors participated in the final draft preparation, manuscript revision, and critical evaluation of the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Ethical Considerations

The authors have observed all ethical issues (including plagiarism, data fabrication, and double publication).

References

- Allison MG, Shanholtz CB, Sachdeva A. Hematological issues in liver disease. *Crit Care Clin.* 2016;32(3):385-96. <https://doi.org/10.1016/j.ccc.2016.03.004>
PMid:27339678
- Arteel GE. New role of plasminogen activator inhibitor-1 in alcohol-induced liver injury. *J Gastroenterol Hepatol.* 2008;23(Suppl 1):S54-9. <https://doi.org/10.1111/j.1440-1746.2007.05285.x>
PMid:18336665
- Flevaris P, Vaughan D. The role of plasminogen activator inhibitor Type-1 in fibrosis. *Semin Thromb Hemost.* 2017;43(2):169-77. <https://doi.org/10.1055/s-0036-1586228>
PMid:27556351
- Lamontagne RJ, Bagga S, Bouchard MJ. Hepatitis B virus molecular biology and pathogenesis. *Hepatoma Res.* 2016;2(7):163-86. <https://doi.org/10.20517/2394-5079.2016.05>
PMid:28042609
- MacLachlan JH, Cowie BC. Hepatitis B virus epidemiology. *Cold Spring Harb Perspect Med.* 2015;5(5):a021410. <https://doi.org/10.1101/cshperspect.a021410>
PMid:25934461
- Chu CM, Liaw YF. Hepatitis B virus-related cirrhosis: Natural history and treatment. *Semin Liver Dis.* 2006;26(2):142-52. <https://doi.org/10.1055/s-2006-939752>
PMid:16673292
- Smith A, Baumgartner K, Bositis C. Cirrhosis: Diagnosis and management. *Am Fam Physician.* 2019;100(12):759-70.
PMid:31845776
- Wiegand J, Berg T. The etiology, diagnosis, and prevention of liver cirrhosis. *Dtsch Arztebl Int.* 2013;110(6):85-91. <https://doi.org/10.3238/arztebl.2013.0085>
PMid:23451000
- AbdulHameed MD, Tawa GJ, Kumar K, Ippolito DL, Lewis JA, Stallings JD, *et al.* Systems level analysis and identification of pathways and networks associated with liver fibrosis. *PLoS One.* 2014;9(11):e112193. <https://doi.org/10.1371/journal.pone.0112193>
PMid:25380136
- Divella R, Mazzocca A, Gadaleta C, Simone G, Paradiso A, Quaranta M, *et al.* Influence of plasminogen activator inhibitor-1 (SERPINE1) 4G/5G polymorphism on circulating SERPINE-1 antigen expression in HCC associated with viral infection. *Cancer Genomics Proteomics.* 2012;9(4):193-8.
PMid:22798504
- Lisman T, Leebeek FW, Mosnier LO, Bouma BN, Meijers JC, Janssen HL, *et al.* Thrombin-activatable fibrinolysis inhibitor deficiency in cirrhosis is not associated with increased plasma fibrinolysis. *Gastroenterology.* 2001;121(1):131-9. <https://doi.org/10.1053/gast.2001.25481>
PMid:11438502
- Yildiz SY, Kuru P, Oner ET, Agirbasli M. Functional stability of plasminogen activator inhibitor-1. *ScientificWorldJournal.* 2014;2014:8582983. <https://doi.org/10.1155/2014/858293>
PMid:25386620
- Noguchi R, Kaji K, Namisaki T, Moriya K, Kawaratani H, Kitade M, *et al.* Novel oral plasminogen activator inhibitor.1 inhibitor TM5275 attenuates hepatic fibrosis under metabolic syndrome via suppression of activated hepatic stellate cells in rats. *Mol Med Rep.* 2020;22(4):2948-56. <https://doi.org/10.3892/mmr.2020.11360>
PMid:32945412

14. Kareem WA, Abdullah BH, Waheed HJ. Estimation of plasminogen activator inhibitor-1 and some biochemical markers in a sample of Iraqi patients with liver cirrhosis. *Syst Rev Pharm.* 2021;12(3):96-9. <https://doi.org/10.31838/srp.2021.3.17>
15. Beier JI, Arteel GE. Alcoholic liver disease and the potential role of plasminogen activator inhibitor-1 and fibrin metabolism. *Exp Biol Med (Maywood).* 2012;237(1):1-9. <https://doi.org/10.1258/ebm.2011.011255>
PMid:22238286
16. Ferro D, Celestini A, Violi F. Hyperfibrinolysis in liver disease. *Clin Liver Dis.* 2009;13(1):21-31. <https://doi.org/10.1016/j.cld.2008.09.008>
PMid:19150306
17. Leebeek FW, Rijken DC. The fibrinolytic status in liver diseases. *Semin Thromb Hemost.* 2015;41(5):474-80. <https://doi.org/10.1055/s-0035-1550437>
PMid:26049070
18. Von Montfort C, Beier JI, Kaiser JP, Guo L, Joshi-Barve S, Pritchard MT, *et al.* PAI-1 plays a protective role in CCl4-induced hepatic fibrosis in mice: Role of hepatocyte division. *Am J Physiol Gastrointest Liver Physiol.* 2010;298(5):657-66. <https://doi.org/10.1152/ajpgi.00107.2009>
PMid:20203062
19. Nam D, Seong HC, Hahn YS. Plasminogen activator inhibitor-1 and oncogenesis in the liver disease. *J Cell Signal.* 2021;2(3):221-7. <https://doi.org/10.33696/signaling.2.054>
PMid:34671766
20. Ghosh AK, Vaughan DE. PAI-1 in tissue fibrosis asish. *J Cell Physiol.* 2012;227(2):493-707. <https://doi.org/10.1002/jcp.22783>
PMid:21465481
21. Yousuf SD, Ganie MA, Jeelani S, Mudassar S, Shah ZA, Zargar MA, *et al.* Effect of six-month use of oral contraceptive pills on plasminogen activator inhibitor-1 and factor VIII among women with polycystic ovary syndrome: An observational pilot study. *Indian J Med Res.* 2018;148(Suppl):S151-5. https://doi.org/10.4103/ijmr.IJMR_1899_17
PMid:30964093
22. Eren M, Boe AE, Kiyachko EA, Vaughan DE. Role of plasminogen activator inhibitor-1 in senescence and aging. *Semin Thromb Hemost.* 2014;40(6):645-51. <https://doi.org/10.1055/s-0034-1387883>
PMid:25173500
23. Devaraj S, Xu DY, Jialal I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells. *Circulation.* 2003;107(3):398-404. <https://doi.org/10.1161/01.CIR.0000052617.91920.FD>
PMid:12551862