

Research progress and clinical applications of SERPINE1 in liver diseases: a critical review

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Abstract

SERPINE1 encodes plasminogen activator inhibitor-1 (PAI-1), a central inhibitor of tissue-type and urokinase-type plasminogen activators. By limiting plasmin generation, modulating extracellular-matrix turnover, and participating in inflammatory, metabolic, vascular, and tumor-microenvironmental processes, SERPINE1 is increasingly recognized as a context-dependent mediator in liver disease. Earlier versions of the literature often presented SERPINE1 as a uniformly pathogenic factor. A more balanced synthesis indicates that its effects depend on disease stage, cellular source, and biological context: hepatocyte- and adipose-associated PAI-1 may link metabolic stress to steatosis and insulin resistance; activated hepatic stellate cell-derived PAI-1 appears more directly related to fibrogenesis; endothelial and platelet-related PAI-1 may contribute to hypofibrinolysis and portal-vein thrombosis; and tumor- or stromal-derived PAI-1 may shape invasion, epithelial-mesenchymal transition, angiogenesis, and immune-cell recruitment in hepatocellular carcinoma. Clinical studies support an association between circulating PAI-1 and metabolic dysfunction-associated steatotic liver disease (MASLD), but most data are cross-sectional, heterogeneous, or derived from biomarker-discovery cohorts rather than definitive prospective validation. Therapeutically, PAI-1 inhibition has shown promise in cell, organoid, and animal models, particularly in steatosis and fibrotic remodeling; however, there is insufficient evidence to regard SERPINE1-targeted therapy as clinically established for liver diseases. This review critically summarizes the mechanistic, epidemiological, diagnostic, and therapeutic evidence for SERPINE1 in liver diseases, highlights unresolved controversies, and proposes a translational framework for future research.

Keywords: SERPINE1, PAI-1, MASLD, MASH, liver fibrosis, hepatocellular carcinoma, biomarker, targeted therapy

Introduction

SERPINE1, the gene encoding PAI-1, has attracted at-

tention in hepatology because it connects several processes that are central to liver disease progression: fibrinolysis, extracellular-matrix remodeling, inflammation,

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metabolic dysfunction, vascular thrombosis, and tumor progression ^[1,2]. The liver is both a metabolic organ and a hemostatic organ. Therefore, a molecule such as PAI-1 cannot be interpreted only as a fibrosis marker or only as a coagulation factor; its biological meaning changes depending on whether the dominant process is steatosis, inflammatory injury, fibrogenesis, cirrhosis-associated hemostatic imbalance, or tumor remodeling.

The terminology of steatotic liver disease has recently changed. In accordance with the 2023 multisociety Delphi consensus, the term metabolic dysfunction-associated steatotic liver disease (MASLD) is used in this review, and metabolic dysfunction-associated steatohepatitis (MASH) is used for the inflammatory and fibrosing phenotype previously referred to as NASH ^[3]. When describing older studies, NAFLD/NASH is retained only when it appears in the original study design or title. This approach avoids both historical confusion and unnecessary inconsistency.

The purpose of this revised review is not simply to list studies. Instead, it organizes the evidence around three questions. First, in which cells and disease stages is SERPINE1 most likely to be mechanistically relevant? Second, which clinical claims are supported by human evidence, and which remain preclinical or exploratory? Third, how can SERPINE1 be integrated into biomarker panels, imaging strategies, and therapeutic development without overstating the current evidence?

Biological Basis of SERPINE1/PAI-1 in Liver Disease

Core fibrinolytic and extracellular-matrix functions

PAI-1 is the major physiological inhibitor of tissue-

type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). By suppressing tPA/uPA activity, PAI-1 reduces conversion of plasminogen to plasmin, thereby limiting fibrinolysis and pericellular proteolysis ^[1]. In liver injury, this function has two competing consequences. On one side, reduced plasmin activity can impair extracellular-matrix degradation and favor fibrotic remodeling. On the other side, in acute injury or advanced cirrhosis, excessive fibrinolysis can contribute to bleeding risk; in such settings, PAI-1 may have a compensatory or protective function.

This duality explains why SERPINE1 should not be interpreted as a uniformly harmful gene. A practical example is useful: in chronic MASH fibrosis, persistently high PAI-1 from activated hepatic stellate cells (HSCs) may act like a “brake” on matrix clearance, allowing scar tissue to accumulate. In acute liver injury with hemorrhagic tendency, the same brake may prevent uncontrolled fibrinolysis and protect vascular integrity. The biological direction therefore depends on the dominant pathological process rather than on SERPINE1 expression alone.

Metabolic and hepatocellular axis

Metabolic stress can induce SERPINE1 expression through insulin, glucose, free fatty acids, inflammatory cytokines, and adipose-liver crosstalk ^[1,4,5]. Experimental work indicates that PAI-1 is not merely associated with metabolic dysfunction but may also influence lipid-related transcriptional programs in the liver ^[4]. In this context, SERPINE1 may link obesity, insulin resistance, dyslipidemia, and hepatic steatosis.

Evidence from mouse models supports a relationship between PAI-1 inhibition and reduced hepatic steatosis. However, an important study of the PAI-1 inhibitor

TM5441 showed attenuation of hepatic steatosis without prevention of progressive MASH-related fibrosis [6]. This distinction is critical. It suggests that SERPINE1 may contribute to lipid accumulation and metabolic stress while not being sufficient, by itself, to determine all downstream inflammatory and fibrotic outcomes.

Hepatic stellate cell and fibrogenic axis

Activated HSCs are a major source of extracellular matrix during liver fibrosis. Recent single-nucleus transcriptomic and chromatin-accessibility analyses of human MASLD and MASH livers identified SERPINE1 among activated HSC-enriched genes with increased expression and accessibility [7]. Importantly, this work linked activated HSC-derived PAI-1 to fibrogenic programs and tested genetic or pharmacological targeting approaches in experimental systems. These data strengthen the mechanistic argument that the HSC-specific source of SERPINE1 matters.

The TGF- β /Smad pathway provides a plausible molecular bridge between HSC activation and SERPINE1 expression. TGF- β can induce SERPINE1 transcription, and increased PAI-1 may reduce matrix degradation by limiting plasmin-mediated proteolysis. Nevertheless, this should be described as a disease-promoting loop in experimental and fibrotic contexts, not as an established universal mechanism across all liver diseases.

Immunometabolism and coagulation-inflammation crosstalk

SERPINE1 also participates in the interface between inflammation and coagulation. Inflammatory mediators such as TNF- α , IL-6, LPS, and NF- κ B-related signaling can increase PAI-1 expression [1,5]. In MASLD,

this creates a plausible link between adipose inflammation, hepatic steatosis, systemic insulin resistance, and a prothrombotic state. In cirrhosis, however, hemostasis is rebalanced rather than simply procoagulant or anticoagulant, so single biomarkers must be interpreted cautiously.

Newer work has begun to connect SERPINE1 with neutrophil extracellular traps, HSC-neutrophil communication, and early fibrosis prediction in MASLD [8]. These studies are valuable because they move beyond the older “PAI-1 equals fibrosis” model and instead position SERPINE1 within an immunothrombotic network. However, most NET-related data remain discovery-stage and require prospective validation before routine clinical use (Figure1).

Tumor microenvironment in HCC

In hepatocellular carcinoma (HCC), SERPINE1 should be discussed as a tumor-microenvironment and invasion-related molecule rather than as a simple diagnostic marker. Experimental and bioinformatic studies suggest that PAI-1 may influence epithelial-mesenchymal transition, migration, invasion, angiogenesis, and immune-cell recruitment [9,10]. For example, CAF-derived miR-642a-3p has been reported to modulate HCC cell migration, invasion, and EMT through SERPINE1-related mechanisms [9].

Because several SERPINE1 studies are cancer-type specific, citation accuracy is essential. Evidence from gastric cancer, colorectal cancer, or pan-cancer analyses cannot be used as direct proof for HCC unless it is clearly labeled as indirect or hypothesis-generating. In this revised manuscript, HCC statements are supported by HCC-specific literature or are explicitly described as extrapolations requiring validation.

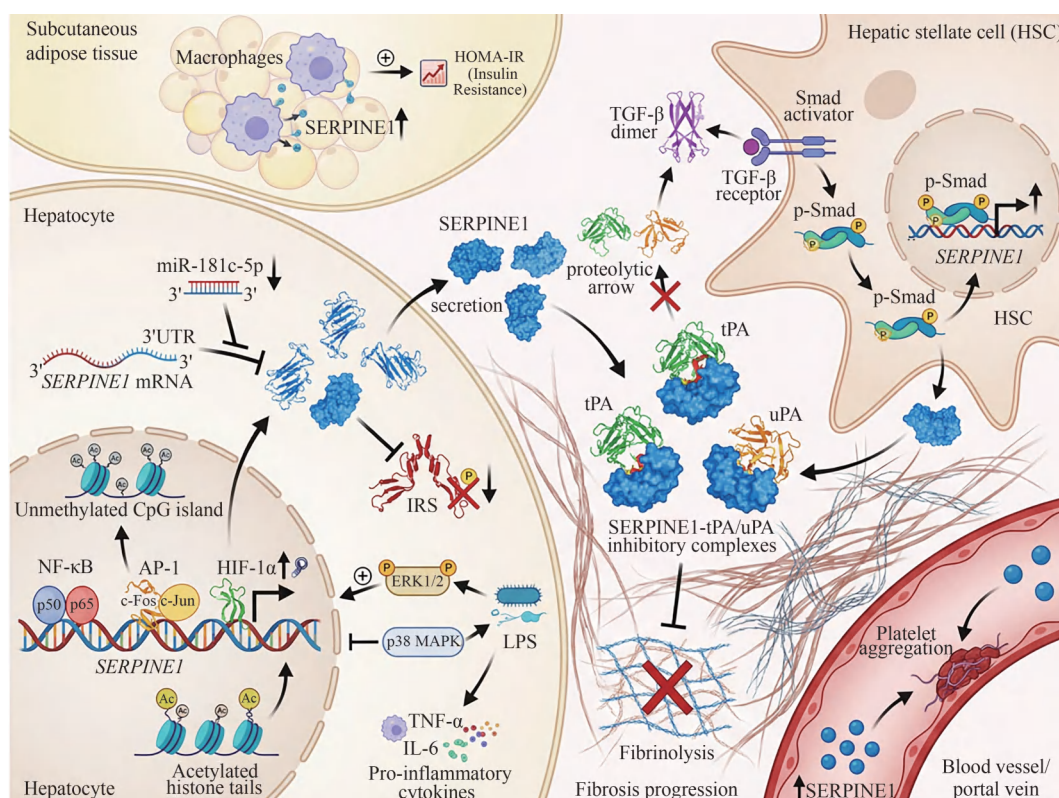


Figure 1. Fundamental theoretical basis of SERPINE1 in the field of liver diseases.

Evidence across major liver disease categories

MASLD and MASH

Among liver diseases, MASLD/MASH provides the strongest rationale for studying SERPINE1 because metabolic dysfunction, adipose inflammation, steatosis, fibrogenesis, and vascular risk converge in this condition. Human studies generally show higher circulating PAI-1 levels in individuals with steatotic liver disease, particularly in populations with obesity or insulin resistance^[5,11,12]. However, the magnitude and interpretation of this association vary by diagnostic method, population characteristics, and adjustment for adiposity and metabolic risk factors.

A recent FibroScan-based cross-sectional study in apparently healthy individuals with overweight or obesity found that circulating PAI-1 correlated with liver steatosis and, to a lesser extent, fibrosis^[11]. The au-

thors emphasized the need for longitudinal trials to clarify causality. This is a useful model for cautious writing: PAI-1 may be associated with steatosis and metabolic risk, but cross-sectional data cannot prove that SERPINE1 independently drives disease progression in humans.

In MASH fibrosis, the strongest mechanistic evidence now comes from multi-omics and single-cell approaches that localize SERPINE1 to activated HSC programs^[7]. This shifts the review from a descriptive biomarker narrative to a source-specific model: circulating PAI-1 may reflect combined hepatic, adipose, endothelial, and inflammatory inputs, whereas HSC-derived PAI-1 may be more directly relevant to fibrogenesis.

Alcohol-related liver disease, viral hepatitis, and cirrhosis

Alcohol-related liver disease shares several pathological

features with MASLD, including steatosis, inflammation, oxidative stress, and fibrosis. Experimental models and older mechanistic work suggest that PAI-1 may participate in alcohol-induced steatosis and fibrin deposition ^[13,14]. Nevertheless, the clinical evidence base is less mature than in MASLD, and the role of PAI-1 may differ across early steatosis, alcoholic hepatitis, advanced cirrhosis, and hyperfibrinolytic states.

In viral hepatitis and cirrhosis, SERPINE1 should be considered within a broader hemostatic and fibrotic network. Studies of the PAI-1 4G/5G polymorphism in HCV-related cirrhosis or HCC have produced inconsistent results ^[15,16]. Some populations show associations with thrombosis or disease risk, whereas others show no significant relationship. Therefore, SERPINE1 polymorphisms should be described as candidate modifiers rather than validated clinical predictors.

Portal-vein thrombosis (PVT) is particularly relevant because MASLD-related cirrhosis is associated with a prothrombotic phenotype, and PAI-1 contributes to hypofibrinolysis ^[16–18]. However, PVT is multifactorial, involving portal-flow reduction, endothelial dysfunc-

tion, inflammation, platelet activation, inherited thrombophilia, and cirrhosis severity. PAI-1 should therefore be framed as one component of thromboinflammatory risk, not as a standalone determinant.

HCC

In HCC, SERPINE1 is relevant to tumor biology, but the clinical role remains unsettled. HCC-specific studies suggest that PAI-1 can be linked with tumor grade, immune microenvironment features, invasion, and EMT-related programs ^[9,10]. These observations support further investigation of SERPINE1 as part of molecular or immunohistochemical panels (Table 1).

At the same time, HCC biomarker development is a demanding clinical field. A marker must improve diagnosis, risk stratification, or treatment selection beyond established clinical variables, imaging, alpha-fetoprotein, and current molecular models. Most SERPINE1-HCC studies are retrospective, bioinformatic, or mechanistic. Thus, the evidence supports hypothesis generation and panel development, but not the conclusion that SERPINE1 alone is ready for routine HCC diagnosis or therapeutic decision-making.

Table 1. Context-specific interpretation of SERPINE1 in liver diseases.

Context	Likely dominant source	Major biological link	Current evidence level	Clinical caution
MASLD / early steatosis	Hepatocytes, adipose tissue, endothelium	Lipid metabolism, insulin resistance, systemic inflammation	Human association plus animal models	Cross-sectional data do not prove causality
MASH fibrosis	Activated hepatic stellate cells	TGF- β -related activation, ECM deposition, reduced matrix degradation	Single-cell/multi-omics plus experimental validation	Needs prospective human validation
Cirrhosis and PVT	Endothelium, platelets, injured liver, inflammatory cells	Hypofibrinolysis and thromboinflammation	Clinical association and mechanistic plausibility	PVT is multifactorial; PAI-1 alone is insufficient
Acute liver injury	Endothelium, inflammatory and parenchymal cells	Limitation of excessive fibrinolysis and bleeding	Experimental evidence	Potential protective role must be acknowledged
HCC	Tumor cells, CAFs, stromal and immune cells	EMT, invasion, angiogenesis, immune crosstalk	HCC-specific studies plus bioinformatic evidence	Not a standalone diagnostic marker

Diagnostic and risk-assessment applications

Circulating PAI-1 as a biomarker

Circulating PAI-1 has potential value as a biomarker because it captures information from several disease-relevant compartments: adipose tissue, hepatocytes, HSCs, endothelium, platelets, and inflammatory cells. This broad origin is both an advantage and a limitation. It may help detect systemic metabolic and thromboinflammatory stress, but it also reduces organ specificity.

Meta-analytic and clinical studies indicate that serum or plasma PAI-1 is often elevated in adult NAFLD/MASLD, especially in biopsy-proven or imaging-confirmed disease ^[11,12]. However, diagnostic performance varies across cohorts, and PAI-1 is influenced by age, sex, obesity, diabetes, circadian rhythm, inflammation, and medications. Therefore, PAI-1 should be evaluated as part of multi-marker panels rather than promoted as a single definitive diagnostic test.

Biomarker claims should also distinguish diagnosis, staging, prognosis, and monitoring. An association with steatosis does not automatically imply reliable staging of fibrosis; a correlation with fibrosis does not prove prediction of future decompensation; and a decrease after intervention does not necessarily mean PAI-1 is a causal therapeutic target. Clear separation of these endpoints improves scientific rigor.

Integration with imaging and clinical scores

The most realistic clinical application is integration

with existing noninvasive tools such as FIB-4, transient elastography, controlled attenuation parameter, magnetic resonance-based fat quantification, or inflammatory-metabolic panels. SERPINE1-related markers may improve performance when they add biological information not captured by aminotransferases, platelet count, age, body mass index, glycemic indices, or imaging.

Recent biomarker-discovery studies combining transcriptomics, single-cell analysis, serum validation, and clinical variables suggest that SERPINE1 may contribute to early fibrosis prediction in MASLD ^[8]. Such work is promising because it combines mechanism with clinical measurement. Nonetheless, before clinical adoption, external validation, calibration, decision-curve analysis, cost-effectiveness, and threshold reproducibility are required.

Genetic polymorphisms

The SERPINE1 promoter 4G/5G variant is biologically plausible because it can influence PAI-1 expression. However, liver-disease association studies have produced inconsistent results across ethnic groups, disease etiologies, and control definitions ^[15,16,19]. These inconsistencies likely reflect modest effect sizes, small samples, population stratification, environmental modification, and interaction with metabolic or viral risk factors.

Accordingly, polymorphism data should not be overinterpreted. It is appropriate to state that SERPINE1 genetic variants may modify susceptibility or thrombotic phenotype in selected populations, but current evidence does not support routine SERPINE1 genotyping for MASLD, fibrosis, cirrhosis, or HCC risk assessment.

Therapeutic implications

Preclinical PAI-1 inhibition

PAI-1 inhibitors such as TM5441, TM5275, TM5614, and related compounds have been used to test whether PAI-1 is a modifiable contributor to metabolic and fibrotic liver injury ^[4,6,20]. In preclinical models, PAI-1 inhibition can improve steatosis, metabolic parameters, or fibrotic readouts. TM5275, for example, attenuated hepatic fibrosis in rat models of metabolic syndrome-associated fibrosis through suppression of activated HSCs ^[20].

However, the evidence is not uniformly positive. TM5441 attenuated hepatic steatosis but did not prevent progressive MASH-related fibrosis in mice ^[6]. This finding should be highlighted rather than minimized because it demonstrates that SERPINE1 biology is disease-stage and endpoint dependent. It also prevents overstatement of therapeutic potential.

Translational gap and safety considerations

The current therapeutic literature should be described as preclinical and translational, not as established clinical therapy for liver diseases. Claims of phase II efficacy or routine clinical benefit should be removed unless supported by a verified liver-disease trial. At present, the most defensible conclusion is that PAI-1 inhibition is a promising strategy requiring rigorous clinical testing.

Safety is a central issue. Because PAI-1 regulates fibrinolysis, systemic inhibition could theoretically increase bleeding risk, especially in patients with advanced cirrhosis, thrombocytopenia, portal hypertension, varices, or altered coagulation balance. Liver-directed delivery, cell-specific targeting, partial inhibi-

tion, or patient selection may be required to widen the therapeutic window.

Combination and precision strategies

Combination therapy should be framed as a research direction rather than a proven clinical strategy. In MASLD/MASH, SERPINE1-targeted approaches could theoretically complement interventions that reduce metabolic stress, such as weight loss, incretin-based therapies, lipid-lowering strategies, or anti-inflammatory approaches. In fibrosis, PAI-1 inhibition may need to be paired with therapies targeting HSC activation, TGF- β signaling, matrix cross-linking, or immune-cell recruitment.

In HCC, SERPINE1 may be more relevant as a tumor-microenvironment marker than as a direct single-drug target. Its association with EMT, CAF signaling, angiogenesis, and immune infiltration suggests potential value in stratifying tumor biology or identifying combinations with anti-angiogenic therapy and immunotherapy. These possibilities remain exploratory and require HCC-specific validation.

Controversies and future directions

Reconciling pathogenic and protective roles

The most important controversy is the apparent contradiction between pathogenic and protective roles of PAI-1. This contradiction can be resolved by using a context model. In chronic metabolic injury, high SERPINE1 may amplify steatosis, HSC activation, and matrix persistence. In acute injury or hyperfibrinolytic states, PAI-1 may reduce bleeding and preserve tissue integrity. In cancer, PAI-1 may support invasion and immune remodeling, but effects can vary with tumor stage and stromal composition.

Future studies should therefore report not only PAI-1 expression but also the disease stage, cellular source, compartment measured, and endpoint. For example, serum PAI-1 in an obese patient with early MASLD is not biologically equivalent to HSC-specific SERPINE1 in MASH fibrosis or stromal PAI-1 in HCC.

Multi-omics, single-cell technologies, and spatial biology

Emerging technologies can address several weaknesses in the existing literature. Single-cell and single-nucleus sequencing can identify which cell populations express SERPINE1 in different disease stages. Chromatin-accessibility data can reveal regulatory programs that activate SERPINE1. Spatial transcriptomics and multiplex immunohistochemistry can show whether SERPINE1-expressing cells are located near fibrotic septa, inflammatory aggregates, vascular structures, or invasive tumor fronts.

These methods are particularly important because circulating PAI-1 is biologically nonspecific. A high plasma level may reflect adipose inflammation, endothelial activation, hepatic production, platelet release, or tumor-associated stroma. Multi-omics approaches

can deconvolute these sources and help determine when SERPINE1 is a driver, a marker, or a compensatory response.

Proposed research priorities

First, prospective cohorts should test whether PAI-1 improves prediction of fibrosis progression, decompensation, PVT, or HCC beyond established clinical and imaging models. Second, disease-stage-specific studies should compare simple steatosis, MASH without advanced fibrosis, advanced fibrosis, cirrhosis, and HCC rather than pooling heterogeneous cases. Third, therapeutic studies should use endpoints that distinguish steatosis improvement from fibrosis regression and vascular safety.

Fourth, HCC studies should avoid borrowing conclusions from non-liver cancers unless clearly labeled as indirect evidence. Fifth, SERPINE1 polymorphism studies should be interpreted with attention to ancestry, metabolic status, viral etiology, sample size, and gene-environment interactions. Finally, clinical trial design should consider bleeding risk, cirrhosis severity, portal-hypertension status, and the possibility that partial or cell-specific inhibition may be safer than systemic blockade (Table 2).

Table 2. Translational evidence and recommended wording.

Topic	Supported statement	Avoid overstating	Recommended wording
MASLD biomarker	PAI-1 is often elevated and associated with steatosis/metabolic risk.	PAI-1 is a validated standalone diagnostic test.	PAI-1 may contribute to multi-marker risk stratification after external validation.
MASH fibrosis	HSC-derived SERPINE1 is implicated in fibrogenic programs.	SERPINE1 alone determines fibrosis progression.	SERPINE1 is a mechanistically plausible component of fibrogenic HSC networks.
PVT/cirrhosis	PAI-1 contributes to hypofibrinolytic tendency.	High PAI-1 alone predicts PVT.	SERPINE1 should be considered within broader thromboinflammatory risk models.
HCC	SERPINE1 relates to EMT, stromal signaling, and immune microenvironment in HCC studies.	Gastric-cancer evidence proves HCC prognosis.	HCC-specific validation is required for diagnostic or prognostic claims.
Therapy	PAI-1 inhibitors show preclinical promise.	Clinical efficacy is established.	PAI-1 inhibition remains experimental for liver disease and requires safety-focused trials.

Conclusion

SERPINE1/PAI-1 is best understood as a context-dependent hub linking fibrinolysis, extracellular-matrix remodeling, metabolic stress, inflammation, vascular dysfunction, and tumor-microenvironmental remodeling in liver diseases. The strongest current evidence supports its association with MASLD/MASH biology, particularly steatosis, metabolic inflammation, activated HSC programs, and fibrogenesis. In cirrhosis and PVT, SERPINE1 belongs to a broader thromboinflammatory network rather than serving as a stand-alone predictor. In HCC, SERPINE1 is a plausible marker of stromal and invasive biology, but its clinical use remains exploratory. Therapeutic targeting of PAI-1 is promising but remains largely preclinical; future studies must define patient selection, disease stage, cellular source, treatment endpoint, and bleeding safety. A critical, source-specific, and evidence-graded approach will be essential for translating SERPINE1 research into clinically useful biomarkers or therapies.

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