



Plasma Fibrinogen Level as Prognostic Factor for Hepatocellular Carcinoma

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ABSTRACT

Introduction: This article aims to determine the role of plasma fibrinogen level as a prognostic factor for hepatocellular carcinoma patients. **Method:** A structured literature review will be conducted through PubMed, Google Scholar, and ScienceDirect, according to the selected clinical questions. Literature selection was based on inclusion and exclusion criteria. The three selected literature were then critically appraised using criteria that included validity, importance, and applicability. **Discussion:** The three kinds of literature in this article all state that high plasma fibrinogen levels correlate with poor overall survival in hepatocellular carcinoma patients. **Conclusion:** Plasma fibrinogen levels may act as a prognostic factor for overall survival in hepatocellular carcinoma patients.

Keywords: Fibrinogen, hepatocellular carcinoma, prognosis.

ABSTRAK

Pendahuluan: Artikel ini bertujuan untuk mengetahui peran kadar fibrinogen plasma sebagai salah satu faktor prognostik penderita karsinoma hepatoseluler. **Metode:** Pencarian literatur terstruktur melalui PubMed, Google Scholar, dan ScienceDirect sesuai pertanyaan klinis. Pemilihan artikel berdasarkan kriteria inklusi dan eksklusi. Tiga literatur yang terpilih menjalani penilaian kritis berdasarkan kriteria validitas, *importance*, dan *applicability*. **Pembahasan:** Tiga literatur yang ditelaah menyatakan bahwa kadar fibrinogen plasma tinggi berkorelasi dengan buruknya *overall survival* penderita karsinoma hepatoseluler. **Simpulan:** Kadar fibrinogen plasma dapat berperan sebagai faktor prognostik *overall survival* penderita karsinoma hepatoseluler. **Abdul Jafar Sidik, Wandy Ridayanto. Kadar Plasma Fibrinogen sebagai Faktor Prognostik Karsinoma Hepatoseluler.**

Kata Kunci: Fibrinogen, karsinoma hepatoseluler, prognosis.



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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world. Globally, the incidence reaches one million cases, with a male-to-female patient ratio of 4:1. HCC generally affects patients aged 50-60 years. New incidences of HCC are almost the same as the mortality rate, which indicates high mortality once patients are diagnosed. HCC can present with abdominal pain, anemia, weight loss, weakness, cold sweat, itching, gastrointestinal bleeding, jaundice, etc. The risks of HCC include hepatitis B infection, hepatitis C infection, alcoholic cirrhosis, non-alcoholic steatohepatitis, alpha-antitrypsin deficiency, obstructive cirrhosis, and autoimmune hepatitis.¹

Similar to malignancies in general, HCC arises due to activation of cellular oncogene

pathways accompanied by a decrease in tumor suppressor pathways. Chronic liver damage from viruses, alcohol, metabolism, or autoimmune causes repeated cycles of liver cell death, accompanied by regeneration and repair. The cycle causes a progressive decrease in telomere area on chromosomes which causes genetic instability. This situation causes cells to become susceptible to mutations and epigenetic changes, resulting in a cancer phenotype in the form of uncontrolled proliferation, resistance to apoptosis, cellular invasion, and activation of angiogenesis.²

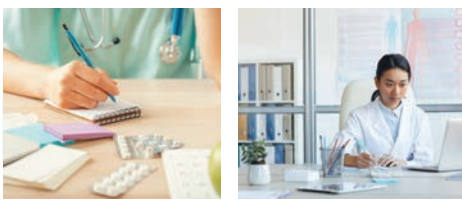
Approximately 80%-90% of HCC occur in liver cirrhosis, so early diagnosis of HCC can be achieved by monitoring cirrhotic patients with ultrasound. The diagnostic modality that can be used to diagnose HCC is radiology with contrast to obtain a washout

image.² Patients diagnosed with HCC can be planned for hepatectomy (resection), local ablation (thermal, radio-frequency ablation, or microwave ablation), liver transplantation, radiation, or chemotherapy.¹

Cancer in general can cause a prothrombotic state or a hypercoagulable state. This can occur due to disruption of the coagulation and fibrinolytic systems, which can be related to long-term prognosis and treatment. The hypercoagulable state indicates the activation of hemostasis components. Tumor cells can activate the coagulation cascade through the production of coagulation factors or by stimulating prothrombotic components such as fibrinogen.³

Fibrinogen is a glycoprotein synthesized by hepatocytes and is an important protein in the

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coagulation pathway, which involves platelet aggregation, plug formation, and wound healing and plays a role in the final stages of the coagulation cascade.⁴ In this article, the authors examine the potential of fibrinogen as a prognostic factor in hepatocellular carcinoma patients.

Method

A literature search was conducted on 17 May 2024 on three online scientific databases, PubMed, Google Scholar, and Science Direct. The keywords used in this search are “hepatocellular carcinoma”, “fibrinogen”, and “prognosis”. The inclusion criteria used in this literature were cohort research and studies within ten years. The exclusion criteria are research that uses animal subjects.

Literature was identified in an electronic database search. Literature screening was based on the suitability of the title and abstract and eliminating all duplicate literatures. Nine literatures passed the screening, five from PubMed, three from Google Scholar, and one from Science Direct. Four screened literature are purchased versions; they could not be opened in full text. The final five full-text literatures were read for critical appraisal and eligibility. The flowchart of the literature selection can be seen in **Scheme .**

The literature was critically appraised in terms of validity, importance, and applicability, based on the Centre for Evidence-Based Medicine (CEBM), the University of Oxford 2010 guidance.⁵

Based on the results of this critical appraisal, three pieces of literature are valid, clinically important, and can be applied to patients with a diagnosis of HCC. These three kinds of literature analyze the relationship between plasma fibrinogen and the outcome in the form of overall survival, and the authors took data in the form of HR/hazard ratio.

Discussion

Several studies have recently found a relationship between hypercoagulation and the stage of cancer. Fibrinogen is a 340-kDa glycoprotein that is synthesized by the liver and converted into fibrin by active thrombin.⁶ Fibrinogen is known to be associated with tumor stage and poor prognosis in several types of cancer, such as lung cancer,⁷ breast

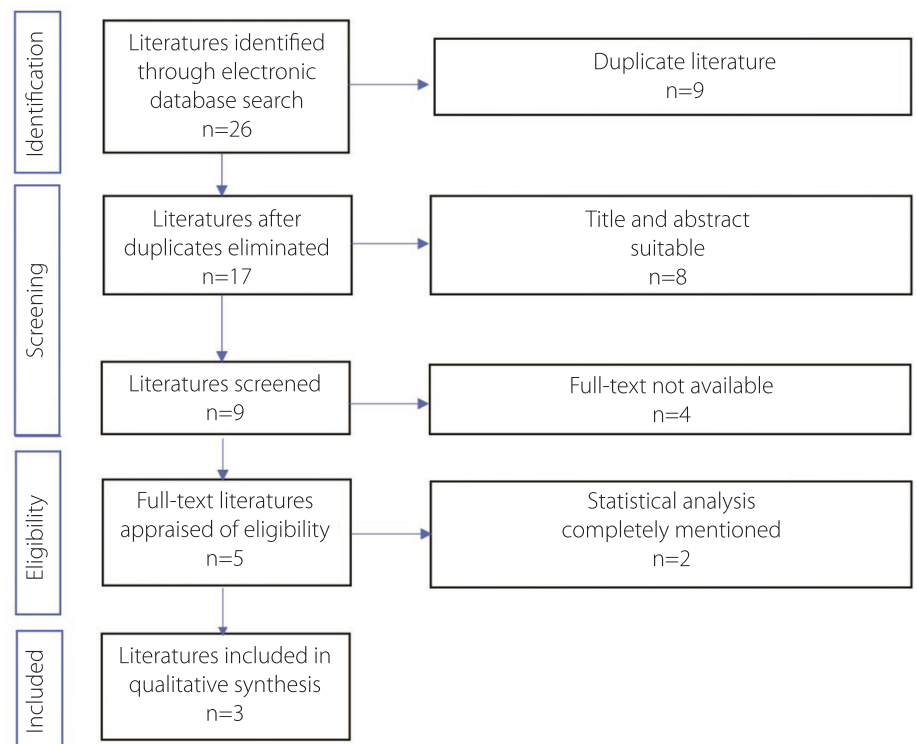
cancer,⁸ gastric cancer,⁹ and biliary tract cancer.¹⁰

Hepatocellular carcinoma (HCC) is one of the cancers with the highest prevalence in the world.¹¹ Patients with HCC have a life expectancy of 6-20 years. HCC is the third largest cause of mortality.¹² Several prognostic factors available in HCC include the presence of portal vein thrombosis, advanced cirrhosis, and the Child-Pugh score.¹³ In this article, plasma fibrinogen levels are examined in relation to patient prognosis in the form of mortality through three kinds of literature selected through a structured literature search.

The first literature by Kinoshita, *et al*, presented data regarding a retrospective cohort study of 113 HCC patients. The sample was patients diagnosed with HCC at Jikei University Daisan Hospital with the exclusion criteria of incomplete data, infectious conditions, and thromboembolic disease. This study sought the relationship between plasma fibrinogen levels, clinicopathological parameters, and overall survival. In this study, the mean plasma fibrinogen in HCC patients was 279 mg/dL. An increase in plasma fibrinogen levels is associated with increasing tumor size,

tumor vascular invasion, and an increase in the Cancer of the Liver Italian Program (CLIP) score. The CLIP score is a prognostic system for HCC that describes both liver function and tumor characteristics and is calculated by assigning a score (0, 1, or 2) to each of four clinical factors: a) Child-Pugh stage; b) number of tumor nodules and whether the tumor extends through $\leq 50\%$ or $> 50\%$ of the liver; c) AFP level; and d) portal vein thrombosis.² This study also showed that plasma fibrinogen was associated with overall survival with a hazard ratio of 1.236 ($p=0.046$, CI 95%).⁶

The second literature by Liu, *et al*, was a retrospective cohort study on 252 samples; 192 were diagnosed with HCC. The characteristics of the subjects in this study were patients with HCC who were diagnosed histologically with exclusion criteria of a history of arterial thromboembolism in the last 3 months, continuous use of anticoagulants, a history of stroke/thrombosis in the last 6 months, or a history of congenital coagulation disorders. This study analyzed the prognostic value and clinical involvement of plasma fibrinogen levels in HCC patients. The mean plasma fibrinogen in this study was 307 mg/dL. This study shows that increased fibrinogen is associated with tumor size and stage. Elevated



Scheme. Flowchart of literature selection.



Table. Characteristics of studies and results.

No	Author	Sample	Methodology	Fibrinogen	Predictive Factors	Statistic Results
1	Kinoshita, <i>et al</i> , 2013. ⁶	113 HCC	Retrospective cohort	Mean 279 mg/dL	Tumor size Vascular invasion Liver cancer score Overall survival	HR=1.236 p=0.046 CI 95%
2	Liu, <i>et al</i> , 2017. ¹⁴	252 (192 HCC)	Retrospective cohort	Mean 307 mg/dL	Tumor size and stage Systemic inflammation Recurrence within 3 years Survival rate	HR=5.19 p=0.001 CI 95%
3	Zhang, <i>et al</i> , 2017. ¹⁵	308 HCC	Retrospective cohort	Mean 343 mg/dL	Tumor size and stage Portal vein invasion Overall survival	HR=1.61 p=0.001 CI 95%

fibrinogen was also associated with systemic inflammation, increased tumor recurrence within 3 years, and decreased survival rate with a hazard ratio of 5.19 (p=0.001, CI 95%).¹⁴

The third literature by Zhang, *et al*, was a retrospective cohort study of 308 HCC patients. Subjects were patients diagnosed with HCC at the Hospital of Chongqing Medical University who were ≥18 years old, had complete follow-up, had plasma fibrinogen data at diagnosis, and were not diagnosed with cholangiohepatic carcinoma or liver metastases. The mean plasma fibrinogen in this study was 343 mg/dL. It was found that increased fibrinogen was associated with advanced-stage HCC, portal vein invasion, and increased tumor size. Increased plasma fibrinogen was also associated with overall survival with a hazard ratio of 1.61 (P=0.001, CI 95%).¹⁵

These three kinds of literature state that increased fibrinogen is associated with clinicopathological parameters and overall survival of HCC patients with statistically significant results. These three literatures are

also in line with research on other cancers such as lung, breast, gastric, and biliary tract cancers, where high fibrinogen levels are associated with the patient's tumor stage and poor prognosis.¹⁶

Fibrinogen is a multifunctional protein that influences various cellular processes during tumorigenesis and metastasis. Fibrinogen is one of the extracellular matrix components that is often found and is associated with tumor cells. Fibrinogen produces proliferative signals to support the binding of growth factors such as FGF-2 (fibroblast growth factor-2) and VEGF (vascular endothelial growth factor). The binding of these growth factors causes the promotion of cellular adhesion, proliferation, and migration during angiogenesis and tumor cell growth.^{17,18} In addition, fibrinogen deposition around the tumor can increase the interaction between tumor cells and platelets, which then form thrombin. The fibrinogen layer also protects tumor cells against the cytotoxicity of natural killer cells with thrombin.¹⁹ Inflammatory proteins such as interleukin-6 and C-reactive protein (CRP) also increase fibrinogen

secretion. Elevated interleukin-6 and CRP in serum are also associated with malnutrition and poor performance.¹⁶

Conclusion

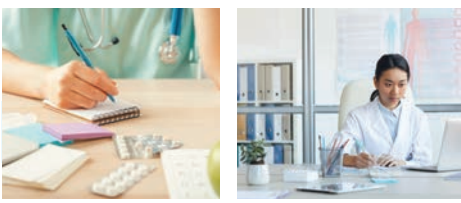
Cancer is generally associated with the patient's hypercoagulable state which is a higher plasma fibrinogen level. Based on the review, increasing plasma fibrinogen levels are correlated with increasing tumor size, tumor stage, presence of tumor vascular invasion, and recurrence of tumor; all affect the overall survival in hepatocellular carcinoma patients. Therefore, plasma fibrinogen level may act as a prognostic factor for overall survival in hepatocellular carcinoma patients.

Suggestion

The author recommends that plasma fibrinogen level examination be performed in hepatocellular carcinoma patients. This is useful for determining how aggressive the management will be applied. A meta-analysis is suggested to obtain a pooled harm ratio for increasing fibrinogen levels.

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