Diagnostic and Predictive Recurrence Value of Plasma Fibrinogen in Patients With Adrenocortical Carcinoma

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ABSTRACT

BACKGROUND: The correlation between fibrinogen levels and adrenocortical carcinoma (ACC) remains unclear. This study aimed to explore the value of preoperative plasma fibrinogen as a biomarker for ACC.

METHODS: We identified 40 patients with ACC and 170 patients with adrenal adenoma (AA) who underwent surgery at our institution between 2015 and 2022. Plasma fibrinogen levels and postoperative tumor recurrence information of the patients were also recorded. For intergroup comparisons, data obtained from the AA and ACC groups were evaluated using a *t*-test. The cutoff value of fibrinogen level was determined using a receiver operating characteristic (ROC) curve.

RESULTS: Mean fibrinogen levels in the AA and ACC groups were 2.81 ± 0.59 g/L and 3.88 ± 1.75 g/L, respectively ($P < .001$). Fibrinogen level, which can help distinguish between AA and ACC, was evaluated using the ROC curve. The cutoff fibrinogen level was estimated as 3.87 g/L according to the Youden index. With this value, the sensitivity was 62.5%, specificity was 95.7%, and the area under the ROC curve (AUC) was 0.74 ($P < .001$). Fibrinogen level, which can help distinguish between recurrence and non-recurrence, was evaluated using the ROC curve. The cutoff fibrinogen level was estimated as 3.96 g/L according to the Youden index. The sensitivity, specificity, and AUC were 90%, 71.4%, and 0.85, respectively ($P < .001$).

CONCLUSION: According to the data in this study, plasma fibrinogen could be used to distinguish ACC from AA. Most importantly, plasma fibrinogen may be used to identify recurrence of postoperative ACC.

KEYWORDS: Fibrinogen, adrenocortical carcinoma, adrenal adenoma, recurrence, ROC curve

Introduction

Adrenocortical carcinoma (ACC) is a rare malignancy with a poor prognosis and an incidence rate of 0.5 to 2 per million per year.[1] Owing to the insidious onset of ACC, the disease usually does not cause any clinical symptoms until it advances to progressive stages. Therefore, there is an urgent need for the early detection and diagnosis of early diagnostic markers for clinical use. Most patients with ACC have poor prognosis; the expected 5-year survival rate of stage I patients is 80%, whereas that of stage IV patients is only 13%.[2] Even patients with stage I to III tumors still have a high risk of recurrence after surgical treatment, and approximately 40% of them can develop recurrence and metastasis within 2 years.[3] Surgery is the main treatment for most early-stage patients, and mitotane can be used as an initial treatment for patients with ACC who have no surgical opportunity or cannot completely remove the tumor. Mitotane alone may delay or prevent recurrence.[4] However, Glenn et al[5] conducted a retrospective review of 576 patients with ACC who underwent resection of stage I to III ACC and found that 70% of the patients developed disease recurrence.

Activation of the coagulation system is closely related to the occurrence, development, and metastasis of tumors. Fibrinogen is a key glycoprotein produced by the liver that functions as a nonspecific acute-phase reactant and is involved in inflammatory responses, clotting pathways, and tumor formation. Fibrinogen is involved in the proliferation and metastasis of malignant tumors by participating in the composition of the extracellular matrix in the tumor microenvironment, which is recognized by various integrins, activating the coagulation system, and promoting the metastasis of circulating tumor cells.[6] A large number of studies have suggested fibrinogen as a valuable marker for detecting cancers, informing prognoses, and monitoring treatment responses.[7-9] Patients with malignant tumors often exhibit varying degrees of blood hypercoagulability. Ma et al[10] conducted a retrospective analysis of penile cancer and found that preoperative fibrinogen level can be used as an independent prognostic marker to predict the survival outcome of patients. Masaaki Yamamoto et al[11] found that preoperative plasma fibrinogen level had the highest predictive value for recurrence among seven known prognostic markers (C-reactive protein, platelet count, platelet/lymphocyte ratio,

and neutrophil/lymphocyte ratio), which would be useful for predicting prognosis after gastric cancer surgery. However, the correlation between fibrinogen levels and ACC remains unclear. In this study, we investigated the correlation between fibrinogen levels and ACC.

Methods

We retrospectively evaluated the data of 40 patients with ACC and 170 patients with adrenal adenoma (AA) who underwent resection at Tianjin Medical University General Hospital and Peking Union Medical College Hospital between January 1, 2015 and May 1, 2022. Tumors were graded according to the Union for International Cancer Control TNM 2004 staging system. All pertinent laboratory and pathological results and medical data were obtained from hospital databases. Data obtained from the patients' routine preoperative test results included plasma fibrinogen levels, age, sex, body mass index (BMI), type of surgery, marginal condition, mitotane-based specific chemotherapy, and radiotherapy. The time points for blood collection to assess fibrinogen levels was 1 day before surgery. Fibrinogen levels were measured by enzyme-linked immunosorbent assay (ELISA) using the assay kits "KA0475" from Abnova. Patients with coexisting hematologic diseases and those in the inflammatory phase were excluded from this study. The cutoff value of fibrinogen level was determined using a receiver operating characteristic (ROC) curve to distinguish between AA and ACC. Patients with ACC were divided into recurrence and non-recurrence groups according to whether they experienced recurrence 1 year after surgery. Preoperative plasma fibrinogen levels were used to distinguish postoperative recurrence of ACC, and the cutoff value of the ROC curve was obtained.

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 22.0; IBM Corp., Armonk, NY, USA). For data comparison within the inter-group comparison (AA and ACC groups), data obtained from patients were evaluated using Student's t-test. Statistical significance was set at $P < .05$.

Results

The data of the 210 cases are presented in Table 1 (including fibrinogen levels, sex, age, BMI, stage, and recurrence information). ACC consisted of 40 patients (there were 46 patients, 6 of whom were excluded), with the diameter from 3.5 to 19.0 cm and an average diameter of 6.67 ± 3.70 cm; whereas AA consisted of 170 patients (there were 204 patients, 34 of whom were excluded), with the diameter from 0.7 to 5.0 cm and an average diameter of 2.11 ± 0.60 cm. The mean fibrinogen of the AA and ACC groups were 2.81 ± 0.59 g/L and 3.88 ± 1.75 g/L, respectively ($P < .001$; see Figure 1).

Fibrinogen level, which can help distinguish between AA and ACC, was evaluated using the ROC curve. The cutoff value of fibrinogen level was estimated as 3.87 g/L according to the

Table 1. Basic characteristic of patients.

GROUPS	ACC	AA
Number of cases	40	170
Gender		
M	21	79
F	19	91
Age (mean years)	62.93 ± 5.37	55.97 ± 11.36
BMI (mean)	24.68 ± 2.26	25.74 ± 4.99
Fibrinogen (mean, g/L)	3.88 ± 1.75	2.81 ± 0.59
Marginal condition (positive/negative)	6/34	—
Mitotane-based specific chemotherapy (Yes vs No)	31/9	—
Stage (cases)		
I-II	26	—
III-IV	14	—
Postoperative recurrence (1 year)		
Yes	24	—
No	16	—

Abbreviations: AA, adrenal adenoma; ACC, adrenocortical carcinoma.

Youden index (see Figure 2). With this value, the sensitivity was 62.5%, specificity was 95.7%, and the area under the ROC curve (AUC) was 0.74 ($P < .001$, confidence interval = 0.628-0.857).

In ACC tumors, the fibrinogen level can help distinguish between postoperative recurrence and no recurrence, which was evaluated using the ROC curve. The cutoff value of fibrinogen level was estimated as 3.96 g/L according to the Youden index (see Figure 3). The sensitivity, specificity, and AUC were 90%, 71.4%, and 0.85 (confidence interval = 0.690-1.0), respectively ($P < .001$)

Discussion

Patients with tumors are often in a hypercoagulable state.[12,13] Some studies have shown that fibrinogen levels are higher in patients with tumors than in patients without tumors.[14-16] To the best of our knowledge, this is the first study to examine the correlation between fibrinogen levels and ACC. This study confirmed these findings. First, the mean fibrinogen of ACC was significantly higher than AA (3.88 ± 1.75 g/L vs 2.81 ± 0.59 g/L, respectively; $P < .001$). Fibrinogen levels can help distinguish between AA and ACC using an ROC curve. The cutoff fibrinogen level was estimated as 3.87 g/L. Second, fibrinogen level can help distinguish between postoperative recurrence and non-recurrence. The cutoff fibrinogen level was estimated as 3.96 g/L.
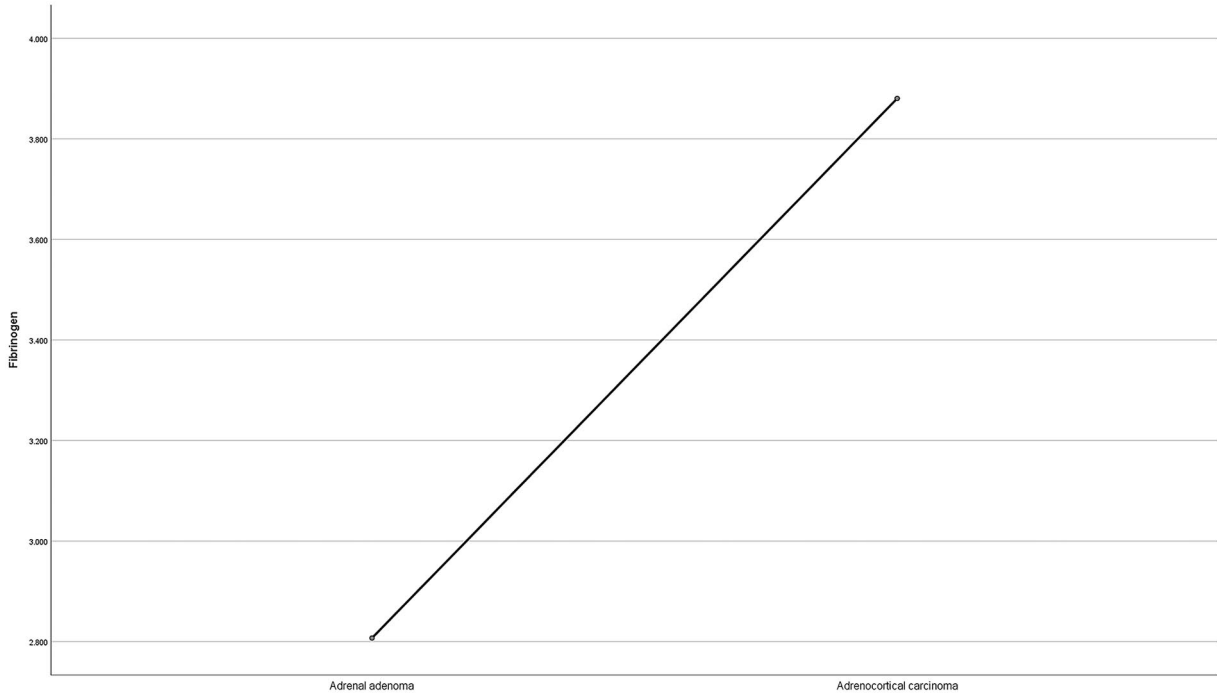
Figure 1. The mean fibrinogen value of the AA and ACC groups. The fibrinogen levels are higher in patients with ACC than in patients with AA. AA indicates adrenal adenoma; ACC, adrenocortical carcinoma.
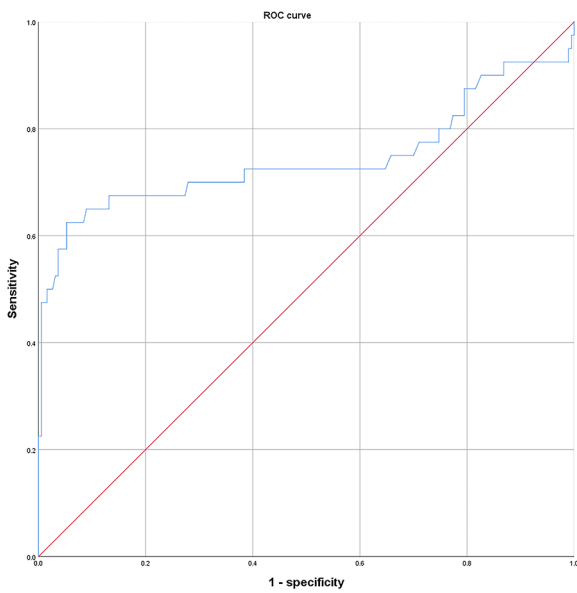

Figure 2. ROC curves of fibrinogen for distinguishing between AA and ACC. According to the cutoff value of fibrinogen, sensitivity was found to be 62.5%, specificity was 95.7%, and area under ROC curve (AUC) was 0.74 ($P < .001$, confidence interval = 0.628-0.857).
AA indicates adrenal adenoma; ACC, adrenocortical carcinoma; ROC, receiver operating characteristic.
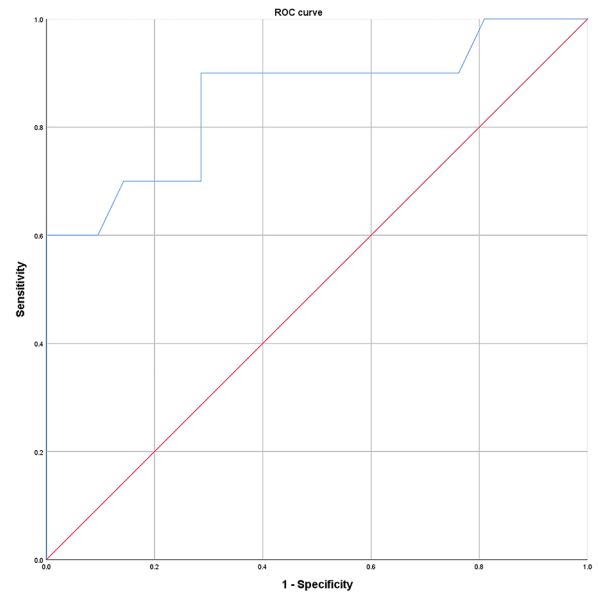

Figure 3. ROC curves of fibrinogen for distinguishing between postoperative tumor recurrence and no-recurrence. According to the cutoff value of fibrinogen, sensitivity was found as 90%, specificity was 71.4%, and AUC was 0.85 ($P < .001$, confidence interval = 0.690-1.0).
AUC indicates area under the ROC curve; ROC, receiver operating characteristic.

One of the major clinical features of ACC is its low rate of early diagnosis, and it is difficult to distinguish ACC from benign adenomas using preoperative computed tomography (CT) or magnetic resonance imaging (MRI). Approximately half of the patients were initially treated for metastatic symptoms. Another characteristic of patients with ACC is poor

prognosis. Postoperative in situ recurrence of ACC is mainly related to late tumor stage and surgical technique. Surgical resection of patients with locally advanced ACC can be performed according to the R0 resection principles. If necessary, the adjacent organs that may be involved should be excised, which may reduce the risk of local recurrence. Misperception of

benign adrenal tumors before surgery and failure to observe the principle of no tumor during surgery increases the risk of local recurrence after surgery. These guidelines are not the preferred recommendations for minimally invasive surgery of ACC. Because ACC could not be accurately judged before surgery, minimally invasive surgical treatment was adopted, and intra-operative tumor rupture or R0 resection could not be achieved, which is an important cause of local recurrence.[17] The reasons about ACC patients the high risk of recurrence in patients with ACC include a ruptured capsule, large-size or high-grade histology.[18] Telomerase reverse transcriptase (TERT) has recently been shown to immortalize cells via telomerase activation and is associated with the recurrence of ACC.[19] Based on microarray analysis of lncRNA expression profiles, Glover et al[20] speculated that three genes, *BUB1B*, *IGFL2*, and *IGFBP5*, were significantly correlated with differentially expressed lncRNAs. In patients without recurrence who tolerate mitotane therapy, it is recommended that the drug be administered for at least 2 years[21] and up to 5 years.[22] It is difficult to determine whether therapeutic benefits result from mitotane alone. In a meta-analysis including six retrospective studies, mitotane therapy resulted in improved mortality but not in decreased recurrence.[22]

Many studies have focused on using preoperative blood tests (red blood cell distribution width, lymphocyte-to-monocyte ratio, mean platelet volume, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio) to predict outcomes in patients with ACC.[23-25] However, no study has evaluated whether fibrinogen can differentiate AA from ACC and predict postoperative ACC recurrence. Fibrinogen is synthesized in the liver as a 350 kDa glycoprotein, which is converted to insoluble fibrin by activating thrombin. Fibrinogens play an important role in blood coagulation, thrombosis, wound healing, and platelet aggregation. In recent years, the relationship between hypercoagulability and malignant tumor progression has attracted considerable attention. Plasma fibrinogen is the main protein involved in coagulation in humans. The coagulation function of patients with malignant tumors is enhanced, and the body is in a state of hypercoagulation, which can easily lead to thrombosis. Fibrin plays an important role in inflammation and blood agglutination reactions. In addition, recent studies have shown the relationship between fibrinogen and ovarian cancer,[26] breast cancer,[27] renal cell carcinoma,[28,29] cervical cancer,[30] esophageal cancer,[31] colon cancer,[32] prostate cancer,[33] non-small cell lung cancer,[34] and bladder cancer,[35] as potential factors to predict the therapeutic efficacy and prognosis of patients with many types of cancer. In this study, ROC analysis revealed that preoperative plasma fibrinogen level was of great value in the differential diagnosis of ACC and AA and in the identification of postoperative recurrence of ACC. To the best of our knowledge, this is the only study to evaluate the relationship between ACC and fibrinogen levels. In addition, it is unclear whether fibrinogen level is an independent prognostic factor

for survival. Previous studies have described the mechanisms underlying hyperfibrinogenemia in patients with malignant tumors.[36,37] Malignant cells usually have high levels of a fibrinogen receptor called intercellular adhesion molecule 1 (ICAM-1), whereas platelets have a fibrinogen receptor called aIIb3 integrin. Malignant cells bind to platelets via fibrinogen. These clumps form tumor clots that bind to the endothelium at the original site of the adrenal gland, adjacent tissues, and other organs, and hide in the target organ, preventing the immune system from attacking. Through this mechanism, fibrinogen plays a role in tumor progression, recurrence, and metastasis.

This study has some limitations. First, owing to the retrospective nature of this study, the attributable factors suffered from recall bias and could not be analyzed. Second, long-term exposure to elevated glucocorticoid levels leads to alterations in fibrinogen levels and function, possibly similar to tumor-associated inflammatory responses. To some extent, our findings may have been influenced by the functional status of the tumor and resulting glucocorticoid overproduction. Third, the values of systemic coagulation markers are highly influenced by many factors; therefore, small increases or decreases in these values may have affected the assessment. We believe that more comprehensive and extensive patient studies may more clearly reveal the correlation between fibrinogen levels and tumor volume in ACC.

Conclusions

ACC is a rare malignancy with a poor prognosis. Preoperative plasma fibrinogen level had the highest predictive value for recurrence among seven known prognostic markers, which would be useful for predicting prognosis after cancer surgery. However, the correlation between fibrinogen levels and ACC remains unclear. In this study, we investigated the correlation between fibrinogen levels and ACC. According to the data in this study, it reminds us that plasma fibrinogen could be used to distinguish ACC from AA. Most importantly, plasma fibrinogen may be used to identify recurrence of postoperative ACC.

Author Contributions
Study conception and design was done by CM and QM. Data acquisition was done by CM and BY. BY contributed toward software. Data analysis and interpretation of results was done by all authors. Initial drafting of article was done by CM. Critical revision of article was done by CM and QM. All authors read and approved the final article.

Data Availability Statement
The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Ethical Statement

This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Local ethical approval was obtained from the Ethics Committee of the Peking Union Medical College Hospital (2021-022801) and the Ethics Committee of Tianjin Medical University General Hospital (Institutional Review Board 2023-KY-088).

Informed Consent

Written informed consent was obtained from all patients for being included in the study.

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