Case Control Study

Correlation analysis of collagen proportionate area in Budd-Chiari syndrome: A preliminary clinicopathological study

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Abstract

BACKGROUND
Collagen proportionate area (CPA) is an important index for assessing the severity of liver fibrosis. Budd-Chiari syndrome can frequently progress to liver fibrosis and cirrhosis. CPA might play an important role in the pathological progress of Budd-Chiari syndrome.

AIM
To explore the role of CPA in predicting the outcomes of patients with Budd-Chiari syndrome.

METHODS
Nine patients with Budd-Chiari syndrome undergoing transjugular intrahepatic portosystemic shunt (TIPS) were included. The median CPA level and correlation of CPA and prognosis of TIPS were determined.

RESULTS
Median CPA was 23.07% (range: 0%-40.20%). Pearson’s χ² test demonstrated a significant correlation of CPA with history of gastrointestinal bleeding (Pearson’s coefficient: 0.832, \( P = 0.005 \)), alanine aminotransferase (Pearson’s coefficient: -0.694, \( P = 0.038 \)), and prothrombin time (Pearson’s coefficient: 0.68, \( P = 0.044 \)). Although CPA was not significantly correlated with shunt dysfunction or hepatic encephalopathy after TIPS, the absolute CPA was relatively larger in patients who developed shunt dysfunction or hepatic encephalopathy after TIPS.

CONCLUSION
INTRODUCTION

Liver histology represents a clinically important tool for assessing the severity of liver fibrosis and the presence of liver cirrhosis in chronic liver diseases[1]. The conventional liver histological assessment systems, such as Knodell, Metavir, and Ishak scores, are semi-quantitative[2-4]. Recently, collagen proportionate area (CPA), a novel parameter that is fully quantitative for assessing the fibrotic area in liver tissues, has been developed and widely explored. CPA refers to the ratio of the area of collagen to the area of tissue. Early studies found that CPA was significantly correlated with Ishak stage, and that CPA, but not Ishak stage, was independently associated with hepatic venous pressure gradient[5]. Additionally, CPA can predict the risk of decompensation in liver transplant recipients with hepatitis C virus infection[6] and compensated cirrhotic patients with hepatitis C virus infection[7]. Evidence also suggests that CPA, rather than Laennec, Kumar, and Nagula semi-quantitative sub-classification parameters, septal thickness, and nodular size, predicts the risk of further decompensation in cirrhotic patients[8].

Budd-Chiari syndrome refers to the obstruction of hepatic venous outflow from hepatic veins to supra-hepatic inferior vena cava[9-11] and is classified as acute, subacute, and chronic according to the rapidity and extension of occlusion and clinical presentations[9]. Patients with acute and subacute forms of Budd-Chiari syndrome can present with acute hepatic failure due to extensive necrosis of hepatic tissues[9,11,12]. Most patients with the chronic form of Budd-Chiari syndrome progress to liver fibrosis and cirrhosis because of long-term hepatic congestion, and they often present with portal hypertension-related gastrointestinal hemorrhage as well as leg ulcers and abdominal varices[10].

Severity of liver fibrosis and cirrhosis may reflect the disease status of Budd-Chiari syndrome. Until now, the role of CPA has not been analyzed in patients with Budd-Chiari syndrome. We conducted a preliminary clinicopathological study to analyze the correlation between CPA and clinical and laboratory variables and clinical outcomes in such patients.

MATERIALS AND METHODS

We retrospectively reviewed patients with Budd-Chiari syndrome who were admitted to the Beijing Shijitan Hospital of the Capital Medical University who underwent transjugular intrahepatic portosystemic shunt (TIPS) between August 2016 and July 2017. Budd-Chiari syndrome was diagnosed according to the current consensus and practice guideline[10,11]. All eligible patients underwent contrast-enhanced computed tomography (CT) before TIPS and had liver biopsy specimens collected during TIPS procedures. Computer-assisted digital image analyses of picroSirius red stained liver histological sections were performed to calculate the CPA.

We collected data regarding demographic profile, history of other liver diseases,
location of the obstruction, clinical presentations and signs, CT findings, and major laboratory test results. We recorded shunt dysfunction, hepatic encephalopathy and death events, time of shunt dysfunction and hepatic encephalopathy development, and time of death during follow-up. The patients were followed until February 2018, the last visit, or death.

Continuous data are presented as means with standard deviation and median with range. The categorical data are presented as frequency with percentage. Pearson’s χ² test was performed to explore the correlation of CPA with other variables. Pearson’s coefficient with P value was calculated. A two-side P value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics version 19.0.0 software (Armonk, NY, United States).

RESULTS

Nine patients (four males and five females) with Budd-Chiari syndrome were included. Median age was 29 years (range: 12-60 years). Patient characteristics are shown in Table 1. Among them, six patients had obstruction of all major hepatic veins, two patients had obstruction of inferior vena cava, three patients had a history of gastrointestinal bleeding, and seven patients had hepatic patchy enhancement on CT. Median CPA was 23.07% (range: 0%-40.20%). Two patients developed shunt dysfunction after TIPS and had a CPA of 32.5% and 23.07%, respectively. One patient developed hepatic encephalopathy after TIPS and had the largest CPA (40.2%). No patient died during follow-up.

CPA was significantly correlated with prior history of gastrointestinal bleeding (Pearson’s coefficient: 0.832, P = 0.005), alanine aminotransferase (Pearson’s coefficient: -0.694, P = 0.038), and prothrombin time (Pearson’s coefficient: 0.68, P = 0.044) (Table 2). There was, however, no significant correlation between CPA and shunt dysfunction (Pearson’s coefficient: -0.168, P = 0.665) and hepatic encephalopathy (Pearson’s coefficient: -0.453, P = 0.221) after TIPS.

DISCUSSION

Budd-Chiari syndrome is a rare vascular liver disease, which can progress into liver cirrhosis. Currently, TIPS is the mainstay treatment option for Budd-Chiari syndrome[14]. Despite favorable survival of patients with Budd-Chiari syndrome[15], a majority of patients treated with TIPS will experience adverse events, such as shunt dysfunction and/or hepatic encephalopathy. Common risk factors for the development of shunt dysfunction include type of stent and inferior vena cava obstruction. Risk factors for the development of hepatic encephalopathy include age, prior hepatic encephalopathy, and type of stent[1]. The present study for the first time explored whether CPA can predict the outcomes of Budd-Chiari syndrome patients after TIPS. However, we did not find any significant association of CPA with shunt dysfunction or hepatic encephalopathy. This unexpected phenomenon might be mainly attributed to the fact that this disease is so rare, and only nine patients were included. Additional explanation for this phenomenon could be the small proportion of patients who developed shunt dysfunction (n = 2/9) and hepatic encephalopathy (n = 1/9) in the present study. Indeed, it should be noted that only one patient developed hepatic encephalopathy, and this patient had the largest CPA (40.2%) among the included patients. Two patients developed shunt dysfunction and had a CPA equal to or beyond the median value (32.5% and 23.07%). This preliminary result encourages us to enlarge the sample size and confirm the predictive role of CPA.

Our study also found that CPA was positively associated with prior history of gastrointestinal bleeding and prothrombin time at baseline but negatively associated with alanine aminotransferase. These findings can be explained by the following fact. First, in patients with Budd Chiari syndrome, gastrointestinal bleeding is mainly attributed to the development of portal hypertension and secondary variceal bleeding, which is closely associated with progression of liver fibrosis. Second, prothrombin time is an important component of Child-Pugh and model for end-stage liver disease (commonly known as MELD) scores for assessing the outcomes of liver cirrhosis[16,17]. Third, a higher level of alanine aminotransferase reflects less frequent liver fibrosis but more frequent liver cell necrosis in patients with Budd Chiari syndrome[18].

In conclusion, this preliminary clinicopathological study found a marginal effect of CPA on the outcomes of Budd-Chiari syndrome patients treated with TIPS. Further study with a larger sample size should be carried out to confirm the present findings.
| Variable                          | n  | Frequency [n (%), or mean ± SD] | Median (range) |
|----------------------------------|----|---------------------------------|----------------|
| Age                              | 9  | 30.00 ± 15.75                   | 29.00 (12.00-60.00) |
| Gender (male/female)             | 9  | 4 (44.4)/5 (55.6)               |                |
| Hepatitis B virus                | 9  | 0 (0)                           |                |
| Hepatitis C virus                | 9  | 0 (0)                           |                |
| Alcohol abuse                    | 9  | 0 (0)                           |                |
| Vascular obstruction             |    |                                 |                |
| IVC obstruction                  | 9  | 2 (22.2)                        |                |
| RHV obstruction                  | 9  | 8 (88.9)                        |                |
| MHV obstruction                  | 9  | 7 (77.8)                        |                |
| LHV obstruction                  | 9  | 9 (100.0)                       |                |
| All HVs obstruction              | 9  | 6 (66.7)                        |                |
| Portal vein thrombosis           | 9  | 0 (0)                           |                |
| Clinical presentations and signs  |    |                                 |                |
| Hepatic encephalopathy before TIPS | 9 | 0 (0)                           |                |
| Gastrointestinal bleeding        | 9  | 3 (33.3)                        |                |
| Abdominal pain                   | 9  | 2 (22.2)                        |                |
| Abdominal distension             | 9  | 7 (77.8)                        |                |
| Abdominal varices                | 9  | 1 (11.1)                        |                |
| Limb swelling                    | 9  | 1 (11.1)                        |                |
| Pigmentation                     | 9  | 1 (11.1)                        |                |
| Limb ulcer                       | 9  | 1 (11.1)                        |                |
| CT signs                         |    |                                 |                |
| Hydrothorax on CT                | 9  | 5 (33.3)                        |                |
| Ascites on CT                    | 9  | 4 (44.4)                        |                |
| Splenomegaly on CT               | 9  | 8 (88.9)                        |                |
| Hepatic patchy enhancement on CT  | 9 | 7 (77.8)                        |                |
| Gastroesophageal varices on CT    | 9 | 7 (77.8)                        |                |
| Paraesophageal varices on CT      | 9 | 1 (11.1)                        |                |
| Laboratory tests                 |    |                                 |                |
| Hemoglobin (g/L)                 | 9  | 122.67 ± 34.81                  | 127.00 (82.00-171.00) |
| White blood cell (10^9/L)        | 9  | 6.86 ± 2.85                     | 6.67 (2.99-12.48) |
| Platelet count (10^9/L)          | 9  | 122.22 ± 69.32                  | 109.00 (42.00-270.00) |
| Alanine aminotransferase (U/L)   | 9  | 29.22 ± 17.56                   | 23.00 (13.00-71.00) |
| Aspartate aminotransferase (U/L) | 9 | 47.22 ± 20.97                   | 39.00 (18.00-71.00) |
| Alkaline phosphatase (U/L)       | 9  | 178.33 ± 69.20                  | 148.00 (96.00-288.00) |
| Gamma glutamyl transferase (U/L) | 9 | 93.44 ± 42.21                   | 84.00 (19.00-161.00) |
| Total bilirubin (mmol/L)         | 9  | 86.98 ± 91.81                   | 42.80 (18.90-262.40) |
| Direct bilirubin (mmol/L)        | 9  | 57.71 ± 68.42                   | 17.30 (6.20-180.00) |
| Albumin (g/L)                    | 9  | 36.19 ± 7.08                    | 39.60 (22.20-44.10) |
| Prothrombin time (s)             | 9  | 55.67 ± 15.33                   | 56.00 (25.00-78.00) |
| International normalized ratio   | 9  | 1.48 ± 0.43                     | 1.37 (1.12-2.55) |
| Serum creatinine (mmol/L)        | 9  | 51.00 ± 14.65                   | 50.00 (29.00-76.00) |
| Blood urea nitrogen (mmol/L)     | 9  | 5.06 ± 1.51                     | 5.15 (2.94-8.27) |
| Sodium (mmol/L)                  | 9  | 134.78 ± 8.56                   | 138.00 (120.00-143.00) |
| Potassium (mmol/L)               | 9  | 4.33 ± 0.64                     | 4.17 (3.77-5.77) |
| Collagen proportionate area      | 9  | 23.44 ± 13.88                   | 23.07 (0-40.20) |
| Shunt dysfunction after TIPS     | 9  | 2 (22.2)                        |                |
| Hepatic encephalopathy after TIPS| 9 | 1 (11.1)                        |                |

CT: Computer tomography; HV: Hepatic vein; IVC: Inferior vena cava; LHV: Left hepatic vein; MHV: Middle hepatic vein; RHV: Right hepatic vein; TIPS: Transjugular intrahepatic portosystemic shunt.
## Table 2 Correlation analysis of collagen proportionate area

| Variable                                                  | n  | Pearson coefficient | P value |
|-----------------------------------------------------------|----|---------------------|---------|
| Age                                                       | 9  | 0.360               | 0.342   |
| Gender (male/female)                                      | 9  | 0.038               | 0.922   |
| Hepatitis B virus                                         | 9  | NA                  | NA      |
| Hepatitis C virus                                         | 9  | NA                  | NA      |
| Alcohol abuse                                             | 9  | NA                  | NA      |
| Vascular obstruction                                      |    |                     |         |
| IVC obstruction                                           | 9  | -0.390              | 0.300   |
| RHV obstruction                                           | 9  | -0.502              | 0.168   |
| MHV obstruction                                           | 9  | -0.136              | 0.726   |
| LHV obstruction                                           | 9  | NA                  | NA      |
| All HVs obstruction                                       | 9  | -0.455              | 0.218   |
| Portal vein thrombosis                                    | 9  | NA                  | NA      |
| Clinical presentations and signs                          |    |                     |         |
| Hepatic encephalopathy before TIPS                       | 9  | NA                  | NA      |
| Gastrointestinal bleeding                                 | 9  | 0.832               | 0.005   |
| Abdominal pain                                            | 9  | -0.257              | 0.504   |
| Abdominal distension                                      | 9  | -0.093              | 0.813   |
| Abdominal varices                                         | 9  | -0.342              | 0.367   |
| Limb swelling                                             | 9  | -0.233              | 0.547   |
| Pigmentation                                              | 9  | -0.342              | 0.367   |
| Limb ulcer                                                | 9  | NA                  | NA      |
| CT signs                                                  |    |                     |         |
| Hydrothorax on CT                                         | 9  | 0.142               | 0.716   |
| Ascites on CT                                             | 9  | -0.012              | 0.975   |
| Splenomegaly on CT                                        | 9  | -0.502              | 0.168   |
| Hepatic patchy enhancement on CT                          | 9  | -0.037              | 0.924   |
| Gastroesophageal varices on CT                            | 9  | 0.219               | 0.572   |
| Paraesophageal varices on CT                              | 9  | 0.633               | 0.067   |
| Laboratory tests                                          |    |                     |         |
| Hemoglobin (g/L)                                          | 9  | 0.157               | 0.687   |
| White blood cell (10⁹/L)                                  | 9  | -0.25               | 0.949   |
| Platelet count (10⁹/L)                                    | 9  | 0.242               | 0.530   |
| Alanine aminotransferase (U/L)                            | 9  | -0.694              | 0.038   |
| Aspartate aminotransferase (U/L)                          | 9  | -0.642              | 0.062   |
| Alkaline phosphatase (U/L)                                | 9  | -0.358              | 0.344   |
| Gamma glutamyl transferase (U/L)                          | 9  | 0.080               | 0.837   |
| Total bilirubin (μmol/L)                                  | 9  | -0.338              | 0.373   |
| Direct bilirubin (μmol/L)                                 | 9  | -0.415              | 0.267   |
| Albumin (g/L)                                             | 9  | 0.348               | 0.358   |
| Prothrombin time (seconds)                                | 9  | 0.68                | 0.044   |
| International normalized ratio                            | 9  | -0.638              | 0.065   |
| Serum creatinine (μmol/L)                                 | 9  | 0.019               | 0.962   |
| Blood urea nitrogen (mmol/L)                              | 9  | -0.411              | 0.272   |
| Sodium (mmol/L)                                           | 9  | 0.272               | 0.478   |
| Potassium (mmol/L)                                        | 9  | -0.376              | 0.319   |
| Shunt dysfunction after TIPS                              | 9  | -0.168              | 0.665   |
| Hepatic encephalopathy after TIPS                         | 9  | -0.453              | 0.221   |

CT: Computed tomography; HV: Hepatic vein; IVC: Inferior vena cava; LHV: Left hepatic vein; MHV: Middle hepatic vein; RHV: Right hepatic vein; TIPS: Transjugular intrahepatic portosystemic shunt; NA: Not available.
Collagen proportionate area (CPA) is an important index for assessing the severity of liver fibrosis. Budd-Chiari syndrome can frequently progress to liver fibrosis and cirrhosis. Clinically, we found that CPA might play an important role in the pathological progress of Budd-Chiari syndrome. We designed the study to investigate this hypothesis.

Nine patients with Budd-Chiari syndrome undergoing transjugular intrahepatic portosystemic shunt (TIPS) were included. The median CPA level, correlation of CPA and patients’ history, and correlation of CPA and prognosis of TIPS were conducted.

The median CPA was 23.07% (range: 0%-40.20%). Pearson’s $\chi^2$ test demonstrated a significant correlation of CPA with a history of gastrointestinal bleeding (Pearson’s coefficient: 0.832, $P = 0.005$), alanine aminotransferase (Pearson’s coefficient: -0.694, $P = 0.038$), and prothrombin time (Pearson’s coefficient: 0.68, $P = 0.048$). Although CPA was not significantly correlated with shunt dysfunction or hepatic encephalopathy after TIPS, the absolute CPA was relatively larger in patients who developed shunt dysfunction or hepatic encephalopathy after TIPS.

This preliminary clinicopathological study found a marginal effect of CPA on the outcomes of Budd-Chiari syndrome. We conducted a preliminary clinicopathological study to explore the role of CPA in predicting the outcomes of patients with Budd-Chiari syndrome.

In the future, more patients could be recruited in the study.

In the future studies of Budd-Chiari syndrome and portal hypertension, emphasis should be placed on the correlation of pathological changes and outcomes of TIPS.
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