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***Case Control Study***

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

He FL *et al*. Collagen proportionate area in BCS

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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 into 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 conducted.

***RESULTS***

Median CPA was 23.07% (range: 0%-40.20%). Pearson’s Chi-square 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 did not significantly correlate 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***

This preliminary clinicopathological study found a marginal effect of CPA on the outcomes of Budd-Chiari syndrome patients treated with TIPS.

**Key words:** Budd-Chiari syndrome; Hepatic vein; Occlusion; thrombosis; Fibrosis

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**Core tip:** With nine patients recruited in the study, we found a marginal effect of collagen proportionate area on the outcomes of Budd-Chiari syndrome patients treated with transjugular intrahepatic portosystemic shunt.

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**INTRODUCTION**

Liver histology represents a clinically important tool for assessing the severity of liver fibrosis and 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 which is fully quantitative for assessing the fibrotic area in liver tissues, has been developed and widely explored. CPA refers to a ratio of the area of collagen to the area of tissue. Early studies found that CPA 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], which is classified as acute, subacute, and chronic according to the rapidity and extension of occlusion and clinical presentations[12]. Patients with acute and subacute forms of Budd-Chiari syndrome can present with acute hepatic failure due to extensive necrosis of hepatic tissues [10,11]. Most of patients with chronic form of Budd-Chiari syndrome progress to liver fibrosis and cirrhosis because of long-term hepatic congestion, who often present with portal hypertension-related gastrointestinal hemorrhage except for leg ulcer and abdominal varices[13].

Severity of liver fibrosis and cirrhosis may reflect the disease status of Budd-Chiari syndrome. Until now, the role of CPA has never been analyzed in patients with Budd-Chiari syndrome. We conducted a preliminary clinicopathological study to analyze the correlation of CPA with clinical and laboratory variables and clinical outcomes in such patients.

**MATERIALS AND METHODS**

We retrospectively reviewed the patients with Budd-Chiari syndrome who were admitted to the Beijing Shijitan Hospital of the Capital Medical University and 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 of eligible patients should undergo contrast-enhanced computed tomography (CT) before TIPS and have 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 the data regarding demographic profile, history of other liver diseases, location of obstruction, clinical presentations and signs, CT findings, and major laboratory data. We recorded the shunt dysfunction, hepatic encephalopathy and death events, and 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.

The continuous data were presented as means with standard deviation and median with range. The categorical data were presented as frequency with percentage. Pearson’s Chi-square 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.

**RESULTS**

Nine patients (4 males and 5 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, 6 patients had obstruction of all major hepatic veins, 2 patients had obstruction of inferior vena cava, 3 patients had a history of gastrointestinal bleeding, and 7 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 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). But there was no significant correlation of CPA with 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 a 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 was so rare that only 9 patients were included. Additional explanation for this phenomenon should be a 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 had the largest CPA (40.2%) among these included patients, and two patients developed shunt dysfunction and had a CPA equal to or beyond median value (32.5% and 23.07%). This preliminary result might promote us to enlarge the sample size to 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 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.

**ARTICLE HIGHLIGHTS**

***Research background***

Collagen proportionate area (CPA) is an important index for assessing the severity of liver fibrosis. Budd-Chiari syndrome can frequently progress into liver fibrosis and cirrhosis.

***Research motivation***

in clinical work, we found that CPA might play an important role in the pathological progress of Budd-Chiari syndrome. We designed the study to check the hypothesis.

***Research objetctives***

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

***Research methods***

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.

***Research results***

Median CPA was 23.07% (range: 0%-40.20%). Pearson’s Chi-square 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 did not significantly correlate 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.

***Research conclusion***

this preliminary clinicopathological study found a marginal effect of CPA on the outcomes of Budd-Chiari syndrome patients treated with TIPS. This study provided a new perspective of predict the outcome of Budd-Chiari syndrome. In the future, more patients could be recruited in the study.

***Research perspectives***

In the future study of Budd-Chiari syndrome and portal hypertension， more focus could be payed in the correlation of pathological changes and outcomes of transjugular intrahepatic portosystemic shunt.

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**Table 1 Patient characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | ***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 | 3 (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 (109/L) | 9 | 6.86 ± 2.85 | 6.67 (2.99-12.48) |
| Platelets count (109/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 (umol/L) | 9 | 86.98 ± 91.81 | 42.80 (18.90-262.40) |
| Direct bilirubin (umol/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 (umol/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**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | ***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 | -.025 | 0.949 |
| Platelets 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 (umol/L) | 9 | -0.338 | 0.373 |
| Direct bilirubin (umol/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 (umol/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: 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; NA: Not available.