Changing spectrum of Budd-Chiari syndrome in India with special reference to non-surgical treatment

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Abstract

AIM: To evaluate patterns of obstruction, etiological spectrum and non-surgical treatment in patients with Budd-Chiari syndrome in India.

METHODS: Forty-nine consecutive cases of Budd-Chiari syndrome (BCS) were prospectively evaluated. All patients with refractory ascites or deteriorating liver function were, depending on morphology of inferior vena cava (IVC) and/or hepatic vein (HV) obstruction, triaged for radiological intervention, in addition to anticoagulation therapy. Asymptomatic patients, patients with diuretic-responsive ascites and stable liver function were, depending on morphology of inferior vena cava (IVC) to the junction of the IVC and right atrium [1-3]. This includes both hepatic vein thrombosis and IVC thrombosis or obliterator hepatocavopathy [4-8].

RESULTS: Mean duration of symptoms was 41.5 ± 11.2 (range = 1-240) mo. HV thrombosis (HVT) was present in 29 (59.1%), IVC thrombosis in eight (16.3%), membranous obstruction of IVC in two (4%) and both IVC-HV thrombosis in 10 (20.4%) cases. Of 35 cases tested for hypercoagulability, 27 (77.1%) were positive for one or more hypercoagulable states. Radiological intervention was technically successful in 37/38 (97.3%): IVC stenting in seven (18.9%), IVC balloon angioplasty in two (5.4%), combined IVC-HV stenting in two (5.4%), HV stenting in 11 (29.7%), transjugular intrahepatic portosystemic shunt (TIPS) in 13 (35.1%) and combined TIPS-IVC stenting in two (5.4%). Complications encountered in follow-up: death in five, re-stenosis of the stent in five (17.1%), hepatic encephalopathy in two and hepatocellular carcinoma in one patient. Of nine patients treated medically, two showed complete resolution of HVT.

CONCLUSION: In our series, HVT was the predominant cause of BCS. In the last five years with the availability of sophisticated tests for hypercoagulability, etiologies were defined in 85.7% of cases. Non-surgical management was successful in most cases.

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Key words: Budd-Chiari syndrome; Interventional radiology; Ascites; Hepatic vein thrombosis; Percutaneous transluminal angioplasty; Stent; Transjugular intrahepatic portosystemic shunt; Thrombophilia

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INTRODUCTION

Budd-Chiari syndrome (BCS) refers to hepatic venous outflow tract obstruction (HVOTO) starting from the level of small hepatic veins (HV) through large HV and inferior vena cava (IVC) to the junction of the IVC and right atrium [1-3]. This includes both hepatic vein thrombosis and IVC thrombosis or obliterator hepatocavopathy [4-8].

Clinical studies on BCS in India date back to the 1970s [6-10], following which, there are many case reports and case studies from India, concentrating on clinical spectrum, on underlying etiology, on diagnostic modalities and/or on various treatment strategies [11-47]. In contrast to the western world, in the Indian series, there is a striking predominance of IVC obstruction (mainly from membrane or web) or combined IVC-HV obstruction rather than HV obstruction alone [12-14]. Tumors, pregnancy, oral contraceptive pills (OCP) and infections were proposed as predominant underlying etiologies, hypercoagulable states were uncommon, and idiopathic cases were the most common [9,12,21,42]. In the series of cases during the last 10 years, various hypercoagulable states are being increasingly described as etiologies of BCS [24,26,28,30,46,47].

Obstruction of the IVC, either thrombotic or non-thrombotic, was considered to be a major cause of BCS in Asia [15]. Two-thirds of IVC obstruction cases leading to BCS are due to membranous obstruction [11]. Datta et al. [48] reported 40 cases of membranous obstruction of IVC (MOVC) while Victor et al. [11] reported 17 cases
of membranous obstruction. Though MOVCl and membranous obstruction of HV was initially thought to be congenital, Okuda demonstrated these lesions to be an after-effect of thrombosis in the IVC or HV which were organised over a period of time. Similar cases of have been reported from Nepal. Originally, it was perceived that MOVCl and membranous obstruction of HV are important causes of BCS which is different from the West. Over the years, many prothrombotic states leading to BCS have been described in India. In an elegant review, Valla has described the level of HVOTO, the nature of obstructive lesions, presentation, course of disease and causes that are comparable in Indian and western literature. A few differences in etiologies were noticed between India and the West i.e. peripartum occurrence of BCS was common in India while oral contraceptive use was commonly implicated in the West.

The majority of patients with BCS present with a chronic course, while only a small number of patients present with acute or fulminant forms. BCS is mostly encountered in the adult population and considered uncommon in children; when seen in children, the clinical presentation is similar. Anti-thrombotic drugs and anticoagulants form the mainstay in the treatment of acute and chronic BCS. Percutaneous balloon angioplasty for membranous obstruction of the IVC and hepatic vein has also been used successfully in the treatment of BCS. Although TIPS has gained popularity in the treatment of BCS, it has rarely been performed in India, with only one case being reported. Furthermore, there are only a few reports on the use of covered TIPS in BCS. In this report, we evaluated patterns of obstruction, aetiological spectrum and non-surgical treatment of BCS in patients.

MATERIALS AND METHODS

In last seven years (during the study period of 1999 to 2005), all the consecutive cases of BCS were prospectively evaluated. Diagnosis of BCS was based on angiographic evidence of HVOTO (i.e. obstruction of IVC and/or HV) and/or histological evidence of BCS (sinusoidal dilation with centrilobular congestion with variable amount of pericentral hepatocytic necrosis and pericentral fibrosis).

The protocol for evaluation of BCS in our unit is shown in Figure 1. BCS was suspected in the following situations: patients with ascites of high serum-ascitic fluid albumin gradient (> 1.1) and with low cell count (< 250 cells/cm³); patients with ascites and/or back veins in the presence of hepatomegaly and/or right upper quadrant pain; patients with refractory ascites, patients with acute liver failure with hepatomegaly and/or ascites; patients with a known hypercoagulable state who showed evidence of liver involvement (on clinical examination, biochemistry or imaging); and patients with unexplained chronic liver disease (when work-up for alcoholic, drug-induced, viral, metabolic or autoimmune liver disease were negative). All such patients (suspected BCS) were subjected to ultrasonography of the abdomen and Doppler studies with special emphasis on IVC, HV and splanchnic venous system. If HVOTO was confirmed, patients were subjected to inferior vena cavo gram and hepatic venogram (via transfemoral, transjugular and/or transhepatic route) to define the site and morphology of the obstruction. However, if ultrasonography/Doppler was negative or ambiguous for HVOTO, computerised tomography (CT) angiography or magnetic resonance (MR) angiography (if CT angiography was contraindicated) was performed. If CT angiography or MR angiography showed HVOTO, these patients were subjected to catheter venography. If computerised tomography with angiography or magnetic resonance angiography was negative, these patients were subjected to liver biopsy (either via percutaneous or transjugular route depending on clinical status) to define BCS and rule out other diseases like veno-occlusive disease. All patients with suspected BCS were subjected to chest x-ray, electrocardiogram and 2-dimensional echo of the heart to rule out cardiac etiology. Liver histology was performed whenever possible to confirm the diagnosis and to define the presence of cirrhosis. Upper gastrointestinal endoscopy was performed in all cases of BCS to determine the presence of varices.

All the patients with BCS were subjected to tests available for hypercoagulable state before starting any treatment. In the initial two years of the study period, tests for protein C, protein S and antithrombin III levels in addition to work-up for myeloproliferative disease and paroxysmal nocturnal haemoglobinuria (PNH) were performed. During the last five years of the study period, tests for protein C, protein S and antithrombin III levels (corrections for liver dysfunction were done), serum homocysteine levels, factor V Leiden, prothrombin gene 20210 and MTHFR gene mutations, lupus anticoagulant, anticardiolipin and antiphospholipid antibodies, tests for PNH (Sucrose lysis and Ham tests), complete blood counts and bone marrow histopathology/cytogenetic studies (whenever feasible) for myeloproliferative disorder were performed. Imaging (ultrasonography, computerised tomography and/or magnetic resonance imaging of abdomen), serological markers (including tumor markers and tests for amoebiasis or echinococcosis) and/or histology were done to identify underlying etiology for BCS as and when required. All the female patients were subjected to a urine test for pregnancy and were questioned regarding use of oral contraceptive pills.

All patients with refractory ascites (RA) or deteriorating
liver function (presence of hepatic encephalopathy (HE) or jaundice, serum bilirubin > 2 mg/dL, serum albumin < 3 g/dL and/or international standardised ratio of prothrombin time (INR) > 2), depending on morphology of IVC and/or HV obstruction, were triaged for either IVC stenting, HV stenting, TIPS or in combination: (1) For supra-hepatic IVC block with patent HV: IVC balloon angioplasty with self-expandable metallic stent (SEMS) placement; (2) For membranous obstruction of inferior vena cava (MOVC): IVC balloon angioplasty; (3) For juxta-hepatic IVC block with patent HV: IVC balloon angioplasty with SEMS placement; (4) For juxta-hepatic IVC block and short-segment HV block (< 3 cm) involving all three HV or two major HV: IVC balloon angioplasty with SEMS placement and HV balloon angioplasty with SEMS placement; (5) For juxta-hepatic IVC block and long-segment HV block (> 3 cm): IVC balloon angioplasty with SEMS followed by TIPS placement; (6) For short-segment HV block (< 3 cm) involving all three or two major HV: HV balloon angioplasty with SEMS placement; (7) For long-segment HV block (> 3 cm) involving all three or two major HV: TIPS placement. In addition to symptomatic therapy, all these patients were started on anticoagulation following radiological intervention with the aim of keeping INR 2-3. Asymptomatic patients, patients with diuretic-responsive ascites, patients with stable liver function or patients who were not willing to undergo radiological intervention were subjected to anticoagulation to keep INR 2-3 in addition to symptomatic therapy (including low-salt diet, diuretic therapy and/or beta-blockers as needed). Percutaneous-venous shunting was offered to patients with RA who were not candidates for any intervention.

Follow-up was done on the 3rd d, at the end of the 1st mo, every 3rd mo for the 1st year and every 6th mo thereafter. During each follow-up visit, clinical, biochemical and ultrasonography/Doppler evaluations were done.

Patients with TIPS or SEMS dysfunction were managed by repeat radiological interventions.

For patients undergoing TIPS, the following outcome measures were used: (a) technical success: creation of a channel by stent between hepatic vein and portal vein to reduce the portosystemic pressure gradient (PPG) to less than 12 mmHg; (b) TIPS dysfunction: 50% decrease in portal vein blood flow velocity on Doppler, angiographic evidence of stent stenosis (> 50% reduction in diameter) or increase in PPG > 12 mmHg in presence of recurrent ascites/hepatic hydrothorax or gastrointestinal bleeding and (c) primary patency: duration of continuous TIPS patency without re-intervention. Comparison between uncovered TIPS and covered TIPS was done using chi square test. Institutional review board permission was obtained.

RESULTS

During the study period, 49 patients (mean age = 34.3 ± 6.5 years; age range = 1-57 years; male:female ratio = 24:25) were included in the study. In our series there were only two children below the age of 18 years. One child at the age of one year presented with rapidly accumulating ascites, the other child at the age of 11 had refractory ascites for 5 mo.

Clinical presentation and biochemical features of these patients are shown in Tables 1 and 2. Ultrasoundography with Doppler studies was diagnostic in 80% of patients. The remaining 20% of patients required CT/MR angiography for diagnosis. Liver histology was done in 28 (57.1%) cases, of which 14 (50% of 28 cases) were cirrhotic.

Morphology of hepatic venous outflow tract obstruction was short segment hepatic vein thrombosis in 13 patients, long segment in 16 patients, supra hepatic IVC in three, juxta hepatic IVC in five, IVC plus short segment hepatic vein in six and long segment hepatic vein in four. Associated portal vein thrombosis was seen in two (4%) and superior mesenteric vein thrombosis was seen in one (2%) patient. Features of caudate lobe hypertrophy and extrinsic compression of IVC (on imaging and/or HV) was seen in 30 (61.2%) cases. One MOVC case had past imaging (on CTA) evidence of IVC, which was done to rule out intraabdominal malignancy as a cause of femoral vein thrombosis and was negative for the same. At that time, IVCT patient was asymptomatic. Four years later this patient presented with symptomatic MOVC and was found to have factor V Leiden mutation.

Etiological spectrum in 35 patients who had undergone
all tests for thrombophilia work up was Polycythemia vera 3 (8.5%), Protein C deficiency two (6%), Protein S deficiency one (3%), Hyper homocysteinemia two (6%), Anti thrombin III deficiency three (9%), Anti cardiolipin antibodies five (14%), Factor V laden mutation four (11.4), Lupus anti-coagulant two (6%), PNH one (3%), Multiple abnormalities four (11%), Renal Cell Carcinoma one (3%), IVC leiomyoma one (3%), Acute myeloid leukemia one (3%), Idiopathic six (19%). None of the patients was pregnant or taking OCP.

Radiological interventions done in 38 patients were as follows: IVC stenting eight (20%), IVC balloon angiography two (5%), Combined IVC Hepatic Vein stenting two (5%), Hepatic vein stenting 11 (30%), TIPS 15 (40%), and IVC stenting with TIPS two (5%).

In one patient with supra-hepatic IVC block with refractory ascites and deteriorating liver function, attempted IVC stenting failed; he was then lost to follow-up. In the radiological intervention group, technical success was achieved in 97.3% (37/38 cases). One (2.7%) patient had a technical complication of post-TIPS (uncovered TIPS) peritoneal haemorrhage, to which the patient succumbed. Another patient (HV stenting) with acute myeloid leukemia succumbed within 1 mo of follow-up. Complete resolution of ascites or improvement in liver function was seen within 3 mo of follow-up in the remaining 35 cases. During further follow-up (mean period = 24.5 ± 12.5 mo, range = 3-84 mo) of these 35 cases, mortality was 8.5% (3/35 cases): causes of death were liver-related in one case [resistant HE (covered TIPS-related)] and non-liver related in two cases [one with intracranial bleeding (anticoagulation therapy related, one in IVC-HV stenting group) and one with metastatic renal cell carcinoma (one with IVC stenting)]. Details of other complications encountered during follow-up are as follows: (a) Episodes of HE responsive to medical treatment were seen in two post-TIPS (both covered TIPS) cases (5.7%). (b) Re-occlusion of stent was seen in six (17.1%) cases (one at 1-mo, two at 3-mo, two at 6-mo and one at 1-year follow-up) of which one had IVC stent, two had HV stent, two had uncovered TIPS and one had covered TIPS, radiological re-intervention (balloon dilatation) was possible in all cases. During further follow-up, in the event of stent occlusion, one patient with uncovered TIPS was offered covered TIPS and one patient with HV stent underwent balloon angioplasty again. (c) Hepatocellular carcinoma (HCC) was encountered at 2-year follow-up in one (2.8%) patient with MOV, who had undergone IVC balloon angioplasty and was treated three times with trans-arterial chemo-embolisation during further five years follow-up. During follow-up of these 35 cases, only two patients (of HV stenting) were lost to follow-up after 6 mo.

On evaluating the patient subset with TIPS treatment, technical success was achieved in all 15 (100%) patients (five uncovered TIPS and 10 covered TIPS), procedural complication (uncovered TIPS) was seen in one (6.6%) patient, total mortality (one in uncovered TIPS and one in covered TIPS) was 13.3% (two patients), re-occlusion rate was 23% (one with covered and two with uncovered TIPS) in 13 survivors, primary patency rate at 6 mo for uncovered TIPS was 50% and for covered TIPS was 88.9%, and occurrence of new-onset HE was in 20% (3 patients of covered TIPS). There was a statistically significant difference (P < 0.05) in primary patency rate between covered and uncovered TIPS.

Eleven (22.4%) patients [all patients had stable liver functions, three cases were asymptomatic cases and three cases had RA; five patients with HVT (two short-segment and three long-segment) and six patients with IVCT-HVT (two long-segment HVT and four with short-segment HVT)] were treated with anticoagulation in addition to symptomatic therapy (mean duration of follow-up = 28.4 ± 10.8 mo, range = 1-74 mo). Two patients with RA, who were not willing to undergo radiological intervention, underwent placement of PVS. Of these, one patient had blockage of PV shunt and died of sepsis after five years; the other patient was all right at four years follow-up. Of the remaining nine cases, one patient with RA (unwilling to undergo any intervention) died of progressive liver failure after 3 mo; two patients (one at 6-mo and one at 1-year follow-up) with HVT showed complete resolution of ascites, normalisation of liver function tests and re-canalisation of HV on USG-D (repeat HV was not done); three asymptomatic patients remained asymptomatic until 6-mo follow-up, but were lost to follow-up then; three patients were lost to follow-up after 1 mo.

Overall, in 42 cases who completed at least 6 mo of follow-up, mortality was seen in 4/42 cases (9.5%), and evidence of HCC in 1/42 (2.3%) cases.

DISCUSSION

Our study is distinct from previous Indian reports in many aspects. It showed predominance of HV thrombosis and identification of etiologies in more than three out of four of cases, the majority being hypercoagulable states. To the best of our knowledge, IVC leiomyoma and acute myeloid leukemia are being reported as etiologies for the first time in India. Also, cases showing transition from IVC thrombosis to MOV and development of hepatocellular carcinoma in MOV are well documented. For the first time in India, the experience of using covered TIPS in BCS is presented.

In our series, HV thrombosis represented the majority of cases (59.1%), which were followed in decreasing order by combined IVCT/HV thrombosis (20.4%), IVC thrombosis (16.3%) and MOV (4%). All previous Indian series, except two[29,32], describe the predominance of IVC up to 79.2%;[29,32,11,13,15,30,39,42] or IVC-HV obstruction up to 57.7%;[14,24,25,30,33,39,40,42] IVC involvement was described in 0%-32% of cases in these series[7,9,11-15,24,25,30,33,39,40,42]. Of the two distinct previous series, one (total 53 cases) showed similar frequency of HV (35.8%), IVC (33.9%) and combined IVC-HV involvement (30.1%)[10]; whereas the other series involving only chronic BCS showed predominance of HV (45.9%) followed by combined IVC-HV (29.7%) and IVC involvement (24.3%)[32]. In the western countries, hepatic vein thrombosis remains responsible for majority of BCS cases, IVC obstruction is rarely found. In Asian and African countries, more common is IVC involvement. In Japan, over span of last 30 years, there is change in the spectrum i.e. marked decrease in cases of IVC...
obstruction\[6,49-52\]. Is similar trend is following in India or this is just reflection of selection bias at tertiary care centre? For definite answer, reports from all over the country will be needed in support.

Previously, MOVc was thought to be the predominant cause of IVC involvement (20.4%-58.6%) and of BCS in India\[5,7,11-13,17,20,35,39\] as well as in Asian countries\[9,56,53\]. In two recent Indian studies, MOVc was present in 0% and 17.2%, while IVC involvement was seen in 56.2% and 62% cases, respectively\[24,46\]. In our series, IVC involvement in the majority of cases was due to IVC thrombosis. Previously, MOVc and IVC thrombosis were considered to be idiopathic in origin by most Indian and Asian workers\[5,59,60\], but this view has been challenged recently in a few reports\[26,46\]. In cases of IVC thrombosis in our study, the etiology was identified in 50%. In our series, one of two MOVc cases had a hypercoagulable state and in that case, we were able to demonstrate evolution of IVC thrombosis to MOVc. Transition from IVC thrombosis to MOVc is well described in worldwide literature\[9,90,91\]. The other patient with MOVc in our study developed hepatocellular carcinoma, without any other predisposing factors, such as: hepatitis B, hepatitis C or alcohol. Reports of hepatocellular carcinoma developing in MOVc are rare in Indian literature\[7,12-15\]. However, such an association is commonly described in most other countries\[5,6,13,20,35,39,42,55-58\].

In our study, with the application of all commercially available hypercoagulability tests, an underlying etiology could be defined in 85.7% of cases, the majority having a hypercoagulable state. This was in contrast to the initial study period (before 2001), during which few tests were performed, where etiology was evident only in 28.5% cases. None of our patients were pregnant, taking oral contraceptive pills, in a post-partum state, had abdominal obstruction\[4,77-80\]. In most studies, TIPS was used as a temporary measure in cases of liver dysfunction; anatomical difficulties causing success rates as low as 30%; higher post-operative complications and mortality rates (more than 20%); high re-stenosis rates (around 30%) requiring surgical revisions in a minority (around 10%); and poor survival rates as low as 57% at five years have been described\[1,6,70,73-76\]. Surgical treatment has also failed to show a favorable effect in two multivariate analyses\[46,78\], but was successful in one other study\[79\]. In most Indian reports, while surgery for IVC involvement has shown fair results\[14,50\], surgical treatments for HV occlusion have shown poor results\[12,88\]. These were the driving force in deciding not to offer surgical treatment to our patients.

Radiological interventions for both IVC and HV achieved technical success rates of more than 90% and long-term patency rates of more than 80%; also radiological re-interventions are usually successful\[1,69,77-80\]. In our series, radiological intervention protocols according to morphology of the obstruction yielded good results. Previous Indian series have shown the efficacy of balloon angioplasty of IVC with or without stent placement\[11-13,37,39,44,45\], with a re-stenosis rate ranging from 16.6% to 28.5%\[11,59\]. Balloon angioplasty of HV thrombosis has shown variable results throughout the world, restricting its use to short-segment HV thrombosis only\[47,75\]. In India, experience with HV balloon angioplasty is rare\[12,57\]. Patients with combined IVC-HV blockages, which are considered difficult to treat, were treated with balloon angioplasty followed by surgical portosystemic shunting in previous Indian studies, but post-operative complications and mortality were prominent\[12\]. In a recent study from China, a two-stage approach was recommended, the first stage being IVC stenting followed by another session of HV stenting\[77\]. In our work, we successfully performed balloon angioplasty with stent placement in IVC followed by either TIPS or HV balloon angioplasty with stent placement in a single session.

In the last decade, the use of TIPS in BCS is increasingly described in the world literature\[81-94\]. In cases with severe liver dysfunction requiring liver transplantation, TIPS used as an interim bridge to transplantation, can improve the situation dramatically\[81\]. In most studies, TIPS was used as rescue therapy in patients with failed or re-occluded radiological or surgical interventions or was used as a bridge to liver transplantation. Difficulty with TIPS may be associated splanchic venous thrombosis, which can be successfully tackled by radiological interventions in the same session\[89\]. Technical success for TIPS ranges from 75% to 100% in various works\[81,84,88,90,93\]. The problem
of TIPS dysfunction (present in 40% to 75% if followed up for more than two years\textsuperscript{[9,10,62,64,90,91,98]} necessitates re-intervention in up to 70% of cases\textsuperscript{[1,8,7,49,91]}, giving a revision rate of 1.4 revisions per patient\textsuperscript{[91]}. TIPS related complications occur in less than 20% of patients\textsuperscript{[91]}. TIPS provided a survival rate of 85% at four years in one series and 74% at five years in another series\textsuperscript{[82,91]}. Covered TIPS in BCS has shown lower TIPS dysfunction rate (33% vs 87% in uncovered group) and higher primary patency rate at 1-year (67% vs 19% in uncovered group) in one recent series comprising nine patients in a covered TIPS group\textsuperscript{[94]}. Another series using covered TIPS in eight patients showed there was no need for revisions during almost one year of follow-up\textsuperscript{[91]}. In our study, TIPS was used as a primary treatment in the subset of the patients with long-segment HV thrombosis with or without IVCT. During the study period (mean follow-up of more than two years), the technical success rate was 100%; procedural complication rate was 6.6% (post-TIPS peritoneal haemorrhage); total mortality rate was 13.3%, re-occlusion rate was 23%; primary patency rate for uncovered TIPS was 50% and for covered TIPS was 88.9%; and new-onset hepatic encephalopathy rate was 20%. All the re-occlusions were tackled radiologically. Our study, although with a small number of patients, showed promising results with TIPS as the primary therapy in BCS patients. Covered TIPS was better than uncovered TIPS in terms of long-term patency.

COMMENTS

Background

Budd-Chiari syndromes (BCS) has been commonly described in India. It was always considered that the spectrum of BCS in India is different from that of the west.

Research Frontiers

In this study we discussed the changing spectrum of BCS in India which is almost comparable to the west.

Innovation and Breakthroughs

Radiological interventions including TIPS with a covered stent has been useful in managing these patients with good long term efficacy.

Application

This study will help to improve the management of patients with BCS in India.

Terminology

BCS is an uncommon condition induced by thrombotic or nonthrombotic obstruction to hepatic venous outflow. It was first described by Budd in 1845 and Chiari later added the first pathologic description in 1899.

Peer review

It’s an excellent overview of BCS in India, showing a change in the aetiology towards hypercoagulopathic diseases. They authors could as well demonstrate the effectiveness of TIPS, especially when using covered stents.

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