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Early radiological intervention and haematology screening is associated with excellent outcomes in Budd–Chiari syndrome

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INTRODUCTION

Budd Chiari Syndrome (BCS) is a rare disorder with an annual incidence of 0.8 per million¹. Primary BCS is defined as thrombosis of the hepatic veins or the terminal portion of the inferior vena cava (IVC) due to primary venous disease, whereas secondary BCS is related to extrinsic compression from an external source such as intraabdominal malignancy².

The majority of patients with primary BCS have an identifiable risk factor¹, the commonest being a myeloproliferative neoplasm (MPN). Other risk factors include acquired and congenital thrombophilia and oral contraceptives. Primary BCS can occur in the context of a previously recognised MPN or be the presenting feature of a hitherto unrecognised MPN³. In a meta-analysis of 1062 patients with BCS, 41% had an MPN³. However, as only 38% of the patients had a complete diagnostic workup for MPN, including clinical, laboratory, and JAK2V617F mutation testing (which is positive in 95% of patients with polycythemia vera (PV) and approximately 50% of patients with essential thrombocythemia (ET))^{3 4}, this may have underestimated the prevalence of MPN.

Various treatment strategies have been proposed for primary BCS. A therapeutic algorithm of successive interventions has been reported^{5 6 7}, consisting of anticoagulation with warfarin or heparin (unfractionated or low molecular weight [LMWH]), followed by percutaneous hepatic venoplasty/stenting if this is unsuccessful, followed by transjugular intrahepatic portosystemic shunt (TIPS) or a surgically created portosystemic shunt and finally, as rescue therapy, orthotopic liver transplantation (OLT). TIPS creates a low resistance channel between the hepatic and intrahepatic portal veins. Under radiological guidance, a wire is inserted into the hepatic vein via the jugular vein,

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then advanced through the hepatic parenchyma into an intrahepatic branch of the portal vein. An expandable metal stent is inserted over the wire to create the low-resistance conduit. This reduces portal venous hypertension and results in rapid decompression of the liver sinusoids, which improves hepatic perfusion and synthetic function. At one institution, this sequential interventional approach resulted in a one and five year survival of 96% and 89% respectively, with 22% of patients ultimately requiring OLT⁵.

With increasing expertise, the long-term outcome following TIPS has improved. It is now possible to overcome technical barriers to TIPS placement, such as complete obstruction of all hepatic veins, by directly accessing the portal vein, and placing a covered stent directly into the vena cava. Therefore we increasingly have opted for the early use of TIPS as the primary therapeutic strategy in BCS.

Another important advance has been the routine use of specific testing for underlying MPN including testing for the JAK2V617F mutation and more recently for the calreticulin receptor gene mutation (CALR), described in 74-80% of patients with JAK2 negative MPN⁸.

In the light of these advances, we aimed to describe our recent experience in the management of patients with primary BCS including the epidemiology, underlying risk factors and outcomes.

METHODS

This retrospective study was performed, with approval of the Human Research Ethics committee, at Austin Health, Victoria, Australia. All cases of primary BCS, including new and recurrent

presentations, presenting between January 2000 and August 2012 were identified from the hospital's computerised database. Patients with hepatic venous outflow obstruction at any point from the small hepatic veins to the IVC were included. Patients with secondary BCS due to malignancy or local mass compression were excluded.

Information on the presentation, investigations, treatment and outcomes was extracted from the medical records. Data was collected on investigations intended to identify an underlying aetiology such as thrombophilia and MPNs, along with specific laboratory and clinical markers used to calculate BCS prognostic scores. Thrombophilia screening included antiphospholipid antibodies, protein C and S levels, genetic testing for the factor V Leiden mutation and prothrombin gene mutations, and flow cytometry for paroxysmal nocturnal haemoglobinuria screen. MPN screening consisted of a peripheral blood count and film, JAK2V617F mutation testing and CALR testing where feasible in JAK2 negative patients. The results of bone marrow biopsies were documented.

The model of end-stage liver disease (MELD) score⁹ was used to assess severity of liver disease at diagnosis and at time of the first interventional procedure (TIPS, stent or surgical shunt). MELD, which was originally derived to predict 3-month survival following elective TIPS insertion in a cirrhotic population, is a continuous function of bilirubin, international normalised ratio (INR), and creatinine derived by Cox proportional hazards regression analysis. Given its accuracy in predicting short-term mortality in cirrhotic patients, it has become the most commonly used predictive tool in cirrhosis and forms the basis by which organs are allocated for liver transplantation. In this setting a higher MELD score is associated with poorer three month survival: 1.9% mortality scores <11; 6%

mortality scores 11-19; 19.6% mortality scores 20-29; 52.6% mortality 30-39; 71.3% mortality scores 40+¹⁰ and high mortality post TIPS¹¹.

The Rotterdam score, demonstrated to predict survival in BCS¹², was calculated for all patients using the equation: $1.27 \times \text{encephalopathy} + 1.04 \times \text{ascites} + 0.72 \times \text{prothrombin time} + 0.004 \times \text{bilirubin}$. Ascites and hepatic encephalopathy were scored as present [1] or absent [0] and prothrombin time as higher [1] or lower [0] than an INR of 2.3¹². Patients were categorised into three prognostic groups based on their Rotterdam score: class I (good prognosis) with total score <1.1 ; class II (intermediate prognosis) between 1.1 and 1.5 and class III (poor prognosis) total score >1.5 ¹².

The BCS-TIPS prognostic index score (TIPS-BCS PI score) was calculated in all patients who received TIPS. This risk stratification score was developed to predict OLT free survival in patients receiving TIPS and is defined as: $\text{age (years)} \times 0.08 + \text{bilirubin (mg/dL)} \times 0.16 + \text{INR} \times 0.63$. A score >7 predicts death or need for OLT 1 year after TIPS with a sensitivity of 58% and specificity of 99%¹³.

Overall survival was defined as time from diagnosis until death, or until end of follow up at September 2012. In terms of liver outcome, decompensated liver disease was defined as the presence of one or more of: jaundice, abdominal ascites and hepatic encephalopathy. Coagulopathy was difficult to assess given the use of anticoagulation in these patients.

Statistical Analysis

Quantitative variables are expressed as mean, median and range and qualitative variables as absolute and relative frequencies.

RESULTS

During the 12-year study period, 27 patients with primary BCS were identified. This included five patients with prior history of BCS who presented with recurrent disease, and the remainder newly diagnosed. Two patients, lost to follow up at 2 and 105 months respectively, were censored for survival at this time and included in the analysis. Median follow up of the 25 remaining patients was 59 months (range 2-248 months).

Clinical characteristics

Table 1 describes the demographics of the patient population. Eight patients (29.6%) had concomitant portal vein thrombosis (PVT). Abdominal pain and ascites were the commonest presenting features. The median Rotterdam score was 1.16 (range 0.07–2.11). Of the 18 patients who received TIPS, the median TIPS-BCS PI score was 5.1 (range 3.0–6.8).

Risk factors for BCS

Myeloproliferative Neoplasm

Twenty-four of 27 (88.9%) patients had investigations for MPN, consisting of a bone marrow biopsy (n=10) and/or JAK2V617F mutation molecular testing (n=19). Of the remaining three patients, two

have died (one due to end stage cirrhosis; the second due to intracranial haemorrhage) and one had other identifiable risk factors (Bechet's disease and Prothrombin gene mutation). MPN was detected in 17/24 (71%) of tested patients, diagnosed based on JAK2V617F positivity (n=13), either alone (n=8) or with a confirmatory bone marrow biopsy (n=5); or marrow biopsy alone (n=4). Of nine patients tested for the calreticulin mutation, two tested positive. This included one patient with JAK2 negative MPN and one patient with ET with unknown JAK2 mutation status. PV was the most common MPN subtype (n=8, two of whom had transformed into myelofibrosis) followed by ET (n=6), MPN unclassified (n=2) and one case of chronic myeloid leukaemia which was also JAK2V617F positive.

Figure 1 demonstrates the breakdown of MPN diagnosis in relation to time of BCS diagnosis. Four patients had a delayed diagnosis due to a normal FBE at presentation of BCS. The median haemoglobin at diagnosis for patients with and without MPN was 134 g/L (range 97–192 g/L) versus 131 g/L (range 108–181 g/L) respectively. The median platelet count at diagnosis for patients with and without MPN was $346 \times 10^9/L$ (range 97–192 $\times 10^9/L$) versus $268 \times 10^9/L$ (range 133–638 $\times 10^9/L$) respectively.

Other risk factors

Table 2 shows other risk factors in patients with and without MPN. Overall 24 patients (89%) had at least one identifiable risk factor.

An additional thrombophilic state was present in six of the patients with MPN: the oral contraceptive pill (OCP: n=4), factor V Leiden heterozygosity (n=1), anticardiolipin antibody positivity and recent in-

vitro fertilisation (IVF) treatment (n=1). Overall six of the sixteen women were taking the OCP, four of whom had a concomitant MPN.

Eighteen patients were tested for protein C and/or protein S deficiency, however as these tests were all performed subsequent to BCS diagnosis, the results are difficult to interpret in the setting of acute clot and anticoagulation.

Distribution of thrombosis

The majority of cases (n=16, 59%) had involvement of the large hepatic veins (LHV) or a combination of LHV and IVC involvement (n= 11, 44%).

Medical treatment and interventions

Haematological management

All patients were anticoagulated with warfarin or LMWH (enoxaparin), complicated by nine episodes of major bleeding in six patients, mainly variceal (n = 4) or intracranial haemorrhage (n =3, fatal in 2). In three cases this was in the setting of supratherapeutic INR (>3) on warfarin or anti-Xa levels (>1.0 taken at least four hours post dose) on enoxaparin.

Of the 6 patients with a known diagnosis of MPN prior to BCS, 3 were on active treatment with hydroxyurea, aspirin or venesection. None were on anticoagulation prior to BCS diagnosis; all were subsequently commenced on long-term warfarin with two patients treated with warfarin and aspirin

concurrently. Of the 11 patients with newly diagnosed MPN, additional treatment consisted of hydroxyurea alone (n=3), venesection alone (n=2), hydroxyurea and venesection (n=2), hydroxyurea and splenectomy (n=1) and interferon (n=1). Three patients with MPN were not given cytoreductive treatment: two due to normal peripheral blood counts, and one diagnosed just prior to death. One patient did not have MPN treatment documented.

Hepatological management

Twenty-five (92.6%) patients had primary radiological interventions, in addition to anticoagulation, consisting of TIPS in 18 (67%) patients and/or angioplasty/stenting in 11 (40%). There was one serious complication of splenic rupture during TIPS insertion.

Patients with TIPS were screened with six-monthly Doppler ultrasounds followed by a TIPS venogram if there were abnormalities. Attempts at radiological recannulisation were rapidly undertaken on any suspected stenosis. Fourteen patients developed TIPS stenoses requiring a median of 1.5 (range 1 - 14) revisions. No patient developed TIPS failure requiring alternative therapy.

Outcome and survival

Overall survival was 96% at one year and 81% at five years. Six patients died: 2 from intracranial haemorrhage, 2 from liver related causes (one of whom had had a TIPS) at five and 20 years post diagnosis, and 2 from non-liver related causes.

Of the remaining 9 patients who did not have TIPS, 6 had compensated liver disease and 3 had decompensated liver disease at the conclusion of the study period.

No patients underwent OLT.

Of the 7 patients with high MELD scores (≥ 18) at diagnosis, one died of hepatopulmonary syndrome at 248 months post diagnosis, 2 died from intracranial bleeding, 3 remain alive with compensated liver disease and one has been lost to follow up. Of the 14 patients with a low MELD scores ≤ 17 , 10 remain alive with compensated liver disease, 2 are alive with decompensated liver disease, one died of non-liver related causes and one lost to follow up.

DISCUSSION

The two main findings of this study were the high incidence of MPN in patients with primary BCS and that excellent medium-term outcomes can be achieved with early aggressive radiological intervention aimed at rapid decompression of the congested liver.

MPN was documented in more than two-thirds of tested patients, an incidence higher than reported in a meta-analysis (41%)³. This may reflect undertesting in the latter, as 70% of patients in our cohort were tested for JAK2V617F versus 40% in the meta-analysis³. The true MPN incidence may be even higher as JAK-2 testing only became widely available in the latter years of our study period.

Regarding other molecular mutations found in MPN, we do not routinely perform JAK2exon12 or MPL mutation testing as part of the diagnostic workup for BCS, as these mutations are rarely found in splanchnic vein thrombosis³. The recently described CALR mutation has been found patients with JAK2 negative MPN⁸, and is worthy of future investigation, noting that two of our patients were

found to have this mutation. This is higher than recent retrospective reports of the CALR mutation being rarely found in patients with splanchnic vein thrombosis^{14, 15}, however our study was enriched for patients with BCS.

Almost a quarter of patients with an underlying MPN had normal FBE parameters despite the JAK2V617F mutation being detected. Previous studies have similarly reported patients with 'latent' MPN, diagnosed on a bone marrow biopsy or JAK2V617F mutation positivity, in the context of a normal blood count¹⁶. In a meta-analysis, 11 of 28 (41%) patients with latent MPN subsequently developed overt laboratory features of MPN, ranging from 0.7 to 7 years following the detection of JAK2V617F³. In our cohort, patients were diagnosed with MPN ranging from one to 150 months following BCS diagnosis. Possible mechanisms for peripheral blood counts to remain normal despite an associated MPN include anaemia due to chronic liver disease, portal hypertension leading to hypersplenism, or an MPN 'pre-phase' in which the marrow changes of myeloid hyperplasia may occur before elevation of peripheral blood counts.

Oestrogen therapy was also a common risk factor, identified in 38% of female patients, the majority of whom also had an MPN. This is similar to previous reports that oestrogen therapy is only associated with BCS in the presence of an additional risk factor¹.

All patients in our study were anticoagulated with enoxaparin or warfarin as per international guidelines². Two patients also received concurrent antiplatelet therapy. Long-term anticoagulation, however, is associated with increased bleeding risk. Six patients had major bleeding, including two fatal episodes of intracranial haemorrhage. We plan to prospectively evaluate the safety of switching

from warfarin/enoxaparin to antiplatelet therapy in MPN patients with controlled counts and ongoing TIPS patency at three years, as the underlying pathogenesis of BCS in MPN likely relates to platelet hyperreactivity.

Our current policy in patients with MPN and BCS is to aim for a haematocrit ≤ 0.45 and a platelet count in the low-middle section of the normal range, using venesection and/or cytotoxic therapy. This is arguably aggressive therapy in patients with latent MPN and normal counts as it is unclear in MPN-related BCS whether cytoreductive treatment offers additional long-term survival benefit or prevents recurrent thromboses. We have based this policy, however, on reported observations that splenomegaly is associated with platelet pooling in the splenic circulation, such that resulting peripheral platelet counts may not be representative of the total available circulating platelet mass¹⁷.

The median Rotterdam score of our cohort was 1.16 (range 0.07 – 2.11), which is comparable with published BCS cohort studies⁴. Twelve patients were classified as Class I, 10 as Class II and 5 as Class III, with predicted 5-year survival of 89% (CI: 79-99%), 74% (CI: 65-83%) and 42% (CI: 28-56%) respectively¹. With a median follow-up of five years, the overall survival within our cohort was greater than predicted by the Rotterdam score: 96% at one year and 81% at five years.

This is the only published cohort of BCS patients where no OLT was required. This contrasts with the published outcomes of traditional step-wise approaches⁵, in which between 13%⁷ and 42%¹ of patients required transplantation. Seijo et al reported the longer-term outcomes of this step-wise strategy in a retrospective cohort of 157 BCS patients⁷. Over a 50-month median follow-up period,

69 (44%) did not receive any invasive treatment, 20 (29%) of whom died⁷. Of the remaining 88 (56%) who underwent invasive treatments, 50 patients underwent TIPS as the primary intervention, and 12 required TIPS subsequent to a failed angioplasty or thrombolysis⁷. Twenty patients required OLT⁷. The overall mortality for this study was 23%, with the median time to death of only 10 months.⁷ No information was given regarding the haematological investigations undertaken with respect to the diagnosis of an underlying MPN.

We postulate that the excellent outcomes at our institution are due to early decompression of the liver, allowing prompt restoration of liver synthetic function and minimisation of progressive portal hypertension, together with an intensive TIPS surveillance program, designed to identify early signs of TIPS stenosis or thrombosis and hence prevent TIPS failure. In parallel with this there is intensive haematological screening and aggressive early control of platelet counts and haematocrit and, perhaps, judicious use of long-term anti-coagulation and anti-platelet therapy.

Although no patients in our cohort required OLT, transplantation may still be needed in chronic BCS, for example when the patient has survived the acute insult without TIPS but subsequently develops chronic liver failure.

Furthermore, in a small number of patients, anti-coagulation may lead to rapid remodelling without TIPS, and ascites can be well controlled with diuretic therapy. In our case series, of the 9 patients who did not undergo TIPS, 6 had stable compensated liver disease.

In conclusion, this study confirms a high incidence of MPN, predominantly JAK2 positive, in primary BCS. All BCS patients should therefore have JAK2 testing and, if negative, CALR mutation testing, and consideration of a marrow biopsy if these are negative in the context of unexplained polycythaemia and/or thrombocytosis. Patients with a detectable mutation but no obvious features of MPN should be closely monitored with regularly blood counts as a proportion of these patients will subsequently develop overt features of MPN. Further we would advocate early radiological hepatic decompression, as an alternative to the step-wise approach, as we have demonstrated a high five-year overall survival associated with TIPS treatment, an intensive TIPS stenosis surveillance program and appropriate management of MPN.

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Figure 1: Breakdown of MPN diagnosis in BCS patients.

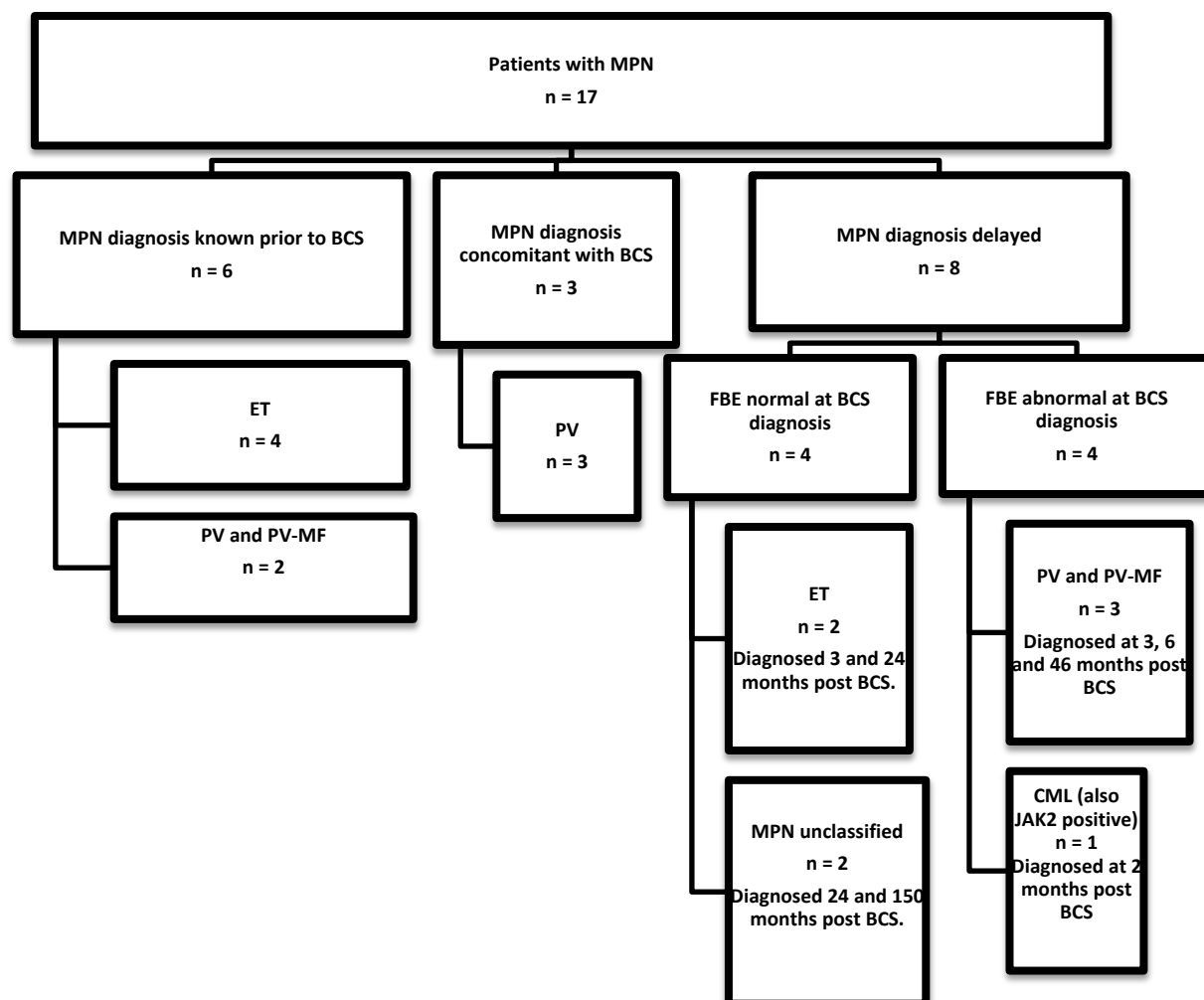


Table 1: Demographics of the 27 patients with primary BCS

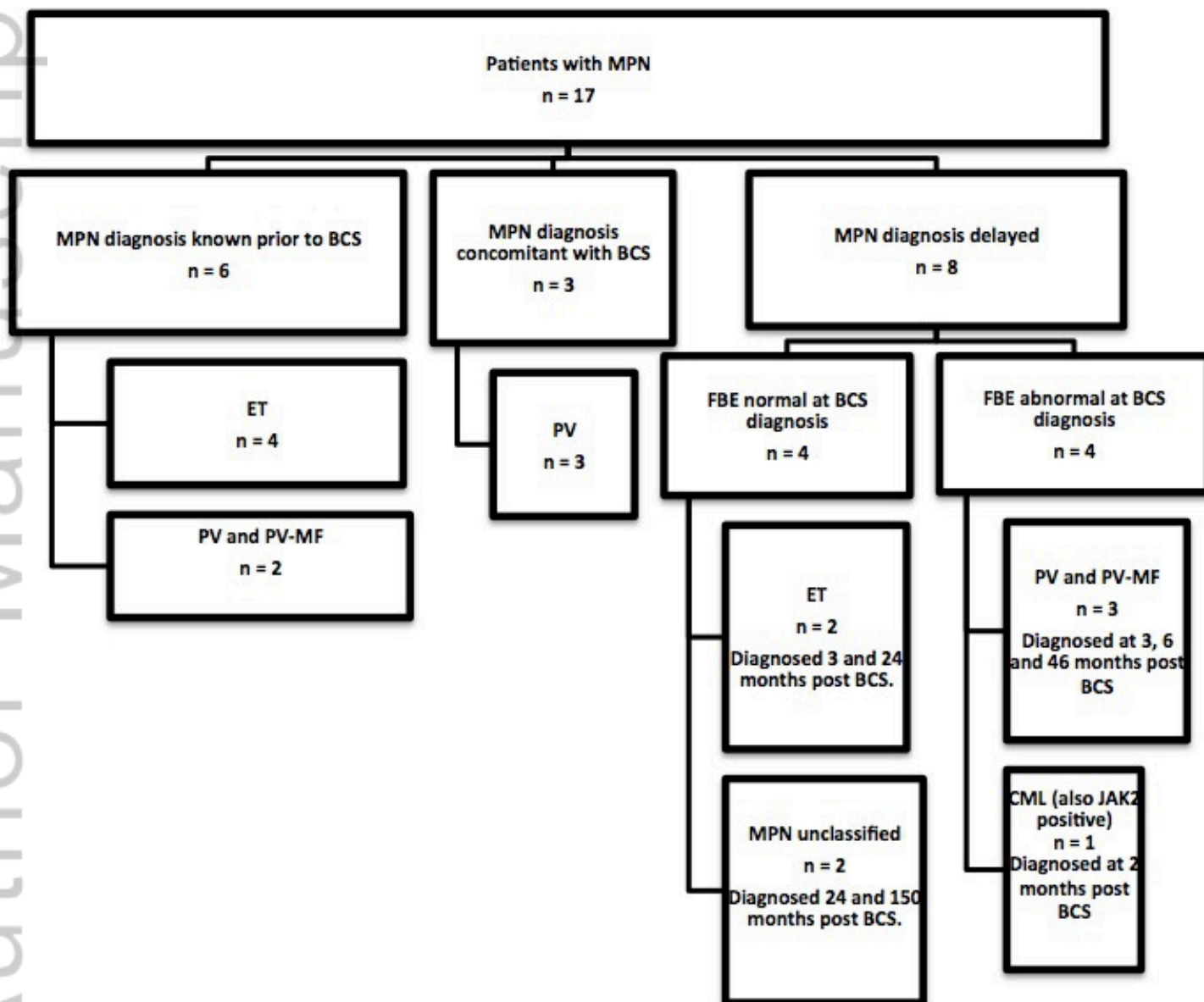
Age at diagnosis in years (median, range)	42 (21 – 76)
Gender (% male)	41%
MELD score at diagnosis (median, range)	14 (7 – 28)
MELD score ≤ 17	14
MELD score ≥ 18	7
MELD score not calculated due to incomplete data	6
TIPS BCS PI at first TIPS (median, range)	5.1 (3.0 – 6.8)
Rotterdam Score (median, range)	1.16 (0.07-2.11)
Rotterdam class (I/II/III)	12(44.4%)/10(37.0%)/5(18.5%)

Table 2: Other laboratory and clinical risk factors for BCS

Risk factors	N / patients tested in patients with MPN (n=17)	N / patients tested in patients without known MPN (n=10)
Factor V Leiden mutation heterozygosity	2/10	3/9
Prothrombin gene mutation	0/9	0/9
Antiphospholipid antibodies (anticardiolipin and beta-2-glycoprotein 1 antibodies and/or lupus anticoagulant).	1/9	0/8
Protein C deficiency †	3/10	4/8
Protein S deficiency †	0/10	1/8
Anti thrombin deficiency	0/6	0/8
Hyperhomocysteinemia	0/4	1/6
PNH	0/4	0/3
Oestrogen therapy (oral contraceptive pill, in vitro fertilisation or systemic hormone replacement therapy)	4/10 females	2/6 females
Crohn's disease	0	2

Bechet's disease	0	1
Alcoholic liver disease	1	0
Sarcoidosis	0	1

† Patients tested whilst on anticoagulation.



IMJ BCS paper figure 1.jpg

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Protein S deficiency †	0/10	1/8
Anti thrombin deficiency	0/6	0/8
Hyperhomocysteinemia	0/4	1/6
PNH	0/4	0/3
Oestrogen therapy (oral contraceptive pill, in vitro fertilisation or systemic hormone replacement therapy)	4/10 females	2/6 females
Crohn's disease	0	2
Bechet's disease	0	1
Alcoholic liver disease	1	0

Sarcoidosis	0	1
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**Early radiological intervention and haematology screening is
associated with excellent outcomes in Budd Chiari syndrome.**

AUTHORS AND INSITUTIONS

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AUTHORSHIP CONTRIBUTIONS

AM and JF designed the project and collected the data; AM analysed the data; AM, JF and AG wrote the paper; AM, AT, JF, MR, PA and AG edited the paper.

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LIST OF ABBREVIATIONS

BCS Budd Chiari syndrome

MPN Myeloproliferative neoplasm

LMWH	Low molecular weight heparin
TIPS	Transjugular intrahepatic portosystemic shunt
IVC	Inferior vena cava
PV	Polycythaemia vera
ET	Essential thrombocythaemia
OLT	Orthotopic liver transplantation
CALR	Calreticulin receptor gene mutation
MELD	Model of end stage liver disease
INR	International normalised ratio
PVT	Portal vein thrombosis
OCP	Oral contraceptive pill
PNH	Paroxysmal nocturnal haemoglobinuria
LHV	Large hepatic veins

ABSTRACT

Background: Budd Chiari Syndrome (BCS) is a rare and life-threatening disorder, resulting from thrombosis of the hepatic veins. Various treatments including pharmacological, radiological and surgical interventions have been used.

Aim: We aimed to retrospectively describe our institution's experience with management of patients with BCS.

Results: Between 2000 and 2012, 27 patients with primary BCS presented with a median Rotterdam score of 1.16 (range 0.07 – 2.11). Twenty-four patients (89%) had at least one risk factor, with the commonest being Myeloproliferative Neoplasm (MPN), detected in 17/24 (71%) of the tested patients, including 4 patients with normal blood counts at diagnosis. All patients were anticoagulated with warfarin or Low Molecular Weight Heparin (LMWH). 25

(92.6%) patients also had primary radiological interventions, consisting of TIPS (transjugular intrahepatic portosystemic shunt) in 18 (67%) patients and/or angioplasty/stenting in 11 (40%). Fourteen patients developed TIPS stenoses requiring a median of 1.5 (range 1 - 14) revisions. No patient developed TIPS failure requiring alternative therapy. Two patients were lost to follow up. At a median follow up of 59 months (range 2 to 248 months), the overall survival was 96% at one year and 81% at five years, much greater than predicted by the Rotterdam score. No patients required liver transplantation.

Conclusion: There is a high incidence of MPN in patients with primary BCS, including patients with normal peripheral blood counts at the time of diagnosis. Our approach of anticoagulation, aggressive and early radiological intervention aimed at rapid decompression of the congested liver resulted in excellent medium-term outcomes.

KEYWORDS: Budd Chiari Syndrome; TIPS; anticoagulation; liver failure; myeloproliferative neoplasm.

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