Reviewer #1:

Query 1. The authors used an epidemiologic approach to investigate the occurrence of HCC in BCS in two area. We know that there are significant geographic differences in BCS, and that the causative factors and incidence can vary; therefore, this paper needs to further explain whether there are geographic factors that contribute to the inconsistency of the results in Mumbai cohort and New Delhi cohort.

Reply 1. We thank the reviewers for their comments. There is a distinct difference between the etiological factors that lead to Budd Chiari syndrome in various geographical areas. This distinction is known to exist between the Western world (predominantly myeloproliferative neoplasm) and the Eastern world (predominantly idiopathic and inherited procoagulant states).[1,2] The site of obstruction is also variable, with a combined involvement of the inferior vena cava and hepatic veins being more common in the East as compared to isolated hepatic vein involvement in the West. However, changes within a single geographical region (in this case India) are uncommonly reported. Prior studies have identified that BCS is associated with poverty, malnutrition, bacterial infections, filariasis and hygiene in India. With improvements in the healthcare scenario, these associations have become less common.[3,4] There have been changes in the presentation of BCS (such as a more common presentation of combined IVC and HV block as compared to isolated IVC block alone) as well.[4] Thus, it is unlikely that geographical variations would contribute to the differences in presentation and outcome in the two cohorts. A more plausible reason would be factors like malnutrition, poverty, varying degrees of healthcare disparity, accessibility to healthcare and hygiene practices between individuals, which are subject to regional and cultural differences.[5] Further, the duration of follow-up between the two cohorts is variable and predates the introduction of the BCLC guidelines for HCC management in 1999.[6] Prior to this the management protocols placed greater emphasis on available technical expertise and clinical experience rather than adherence to standardised protocols and personalised medicine.

As the data is retrospective, we were unable to identify potential biases in outcomes based on the decision of the treating physician and adherence to established guidelines. There may also be external influence from social factors (malnutrition, stigma, poverty, accessibility), which may have influenced outcomes differently in the two cohorts.

Query 2. In the abstract section, the authors presented that the median survival among patients who did not undergo interventions for HCC, compared with those who did, was 3.5 years vs 3.1 months (P=0.0001), Why patients who underwent TACE had significantly lower survival time than untreated patients.

Reply 2. We sincerely thank the reviewer for pointing out the inadvertent typographical error from our side. It has been changed in the revised manuscript. The new statement reads as follows: "The median survival among patients who underwent interventions for HCC, compared with those who did not, was 3.5 years vs 3.1 months (P=0.0001)".

Query 3. In the Definitions section, lack of references for the definition of vena cava obstruction in short (<3 cm) and long segments (≥3 cm).

Reply 3. We thank the reviewer for the comment. We have added the citation as suggested by the reviewer.

Query 4. In the Management protocol for HCC section, the author illustrated that "AFP levels were not done routinely for surveillance", I'd like to know why AFP isn't used for routine follow-up.

Reply 4. We thank the reviewer for the comments. AFP was discovered as a marker in 1941 and subsequently used for HCC since 1972, although it has relatively low sensitivity (63%) and specificity (88%) as a standalone biomarker for HCC. The first RCT in HCC for surveillance by USG and AFP was done in 2004, which showed that bi-annual screening with a combined modality reduced HCC-related mortality by 37%. Our cohort dates back to 1985 (19 years before the RCT recommended surveillance); hence, routine implementation of AFP or surveillance was unavailable for all patients. This may also have a potential impact on the survival estimates provided and is a limitation of the retrospective nature of our data. We have accounted for this potential bias in the manuscript and modified our statement to read:

As per expert guidelines, patients with cirrhosis should undergo surveillance with ultrasound and serum alpha-fetoprotein every 6 months.[7] These recommendations are available since 2004. AFP has been available since 1972 [8], As our study spans 3 decades. In the initial part

of the study due to non availability of the recommendations for routine surveillance. To clarify better, we have modified the statement as follows in the manuscript.

“Surveillance with AFP in patients with HCC has been recommended by the expert guidelines. Our cohort dates back to 1985 (19 years prior to the RCT recommending surveillance); hence, the routine implementation of AFP or surveillance was unavailable for all patients. This may also have a potential impact on the survival estimates provided and is a limitation of the retrospective nature of our data.”

Query 5. The researcher said that “The response at 1 month based on mRECIST criteria”, why follow up only 1 month, please give me the reasons.

Reply 5. We thank the reviewer for the comments. The response to intervention was evaluated at 1 month post intervention; hence, 1 month mRECIST was provided to maintain uniformity in the data. Due to variable follow-up of patient, and lack of available imaging at pre-specified intervals, we have not provided response details after 1 month.

Query 6. The question that worries me the most is that median survival time of BCLC stages A is significant shorter than B stage, is it possible to try to analyse the two regions together (Mumbai and New Delhi cohort or increase sample size for further analysis) ?

Reply 6. We agree that the calculated median survival in BCLC-A is less than the BCLC-B. The reason for this discrepancy is the small number of patients leading to a sparse data bias- only 5 patients in the cohort had BCLC A, and out of these only 2 underwent therapy. Unfortunately the Mumbai cohort does not have any BCLC A patients so we are unable to combine the data for further analysis. Due to rarity of the disease it will be difficult to increase the sample size for analysis at the present time point. We calculated the survival as per the duration of the last follow-up at our centre. Thus considering the limited number of cases, the data may not portend to a meaningful statistical analysis and may be misleading. We have acknowledged this in limitations.

Query 7. None of the pre and post-treatment images of the BCS-HCC patients, please add pictures to illustrate.

Reply 7. We thank the reviewer for the comment. We have added the representative images of a patient pre and post-treatment as suggested by the reviewer.

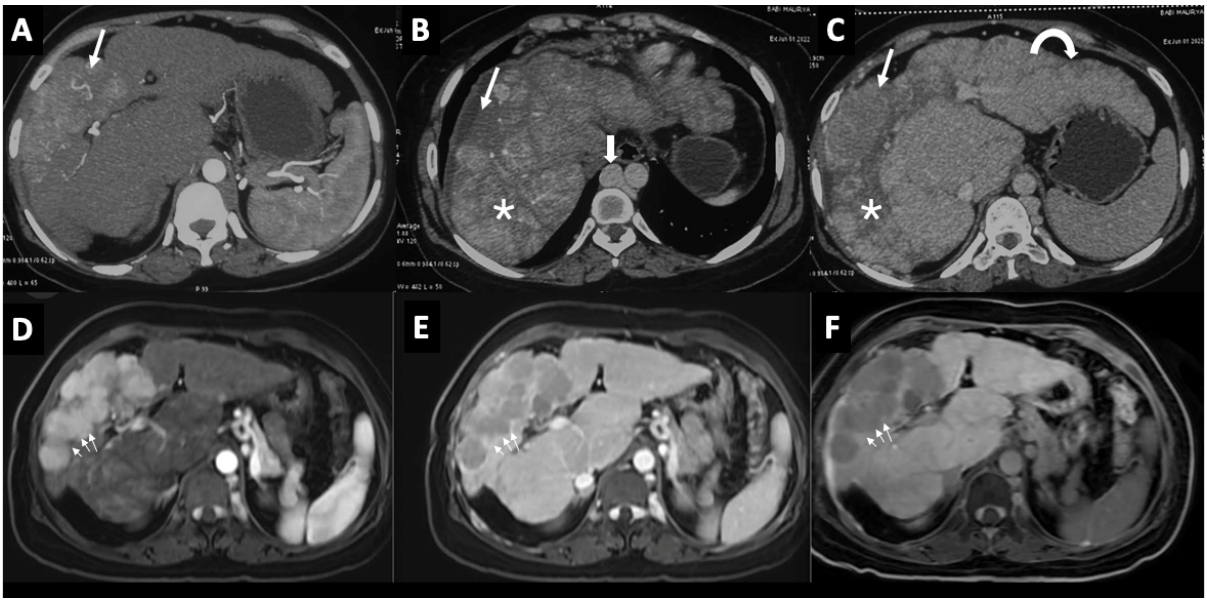

Figure 3. Axial Multiphase CT images (A-C) showing large arterial phase enhancing lesion (arrow) in arterial phase and washout in portovenous phase (B) and delayed phase (C) in segment VIII and IV of liver with back ground liver showing features of congestive changes (Asterix) and cirrhotic changes (curved arrow). Note: Dilated azygous system due to IVC obstruction (block arrow)

Axial Multiphase MRI (post angioplasty) images (D-E) showing resolution of congestive changes and normal caliber azygous system. Large arterial phase enhancing lesion (small arrows) in arterial phase (A) with washout in portovenous phase (E) and non retention of contrast in hepatobiliary phase (F)

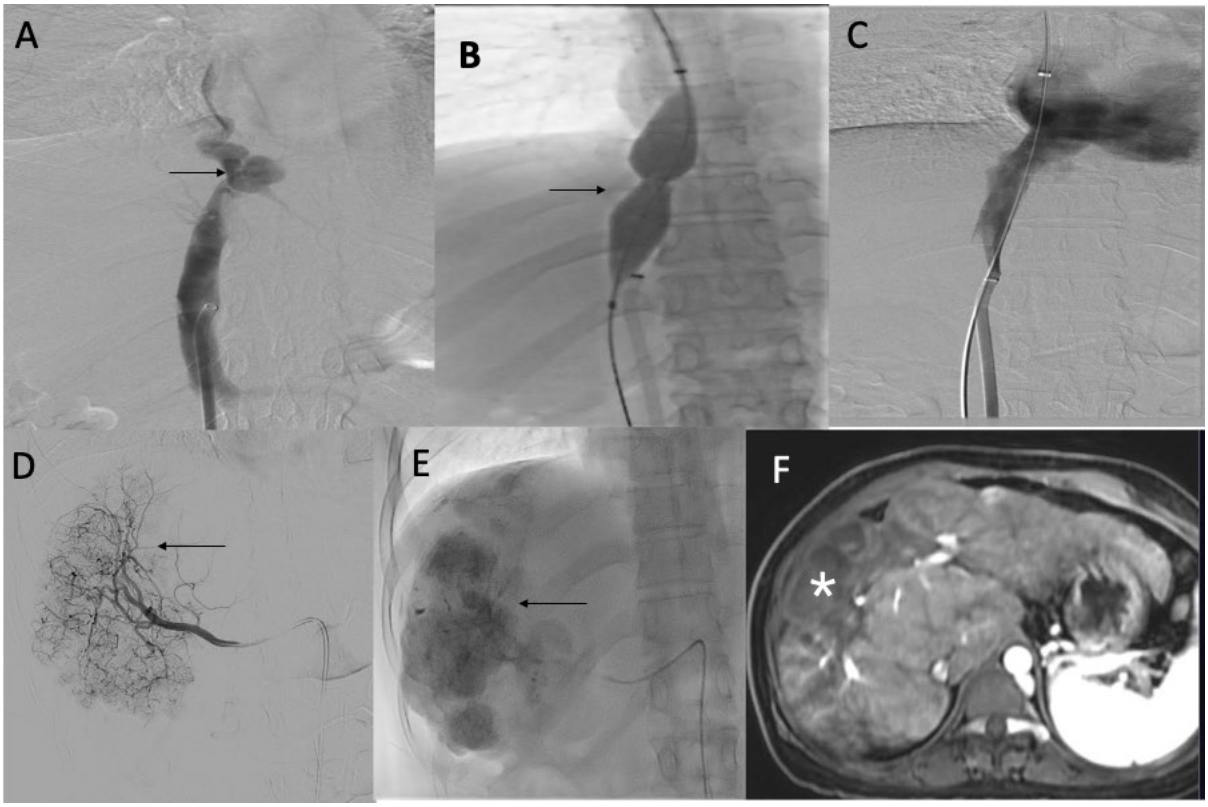

Figure 4. Digital Substraction spot images (A-E) showing short segment narrowing of IVC (A, arrow) which was dilated using 20mmX40mm balloon catheter (B, arrow), post angioplasty angiogram (C) good flow across the IVC without any residual narrowing. Selective right hepatic angiogram showing tumor blush (D, arrow) which was treated using lipiodol TACE (E, arrow), follow up MRI after TACE no residual enhancing lesion in the treated lesion (F, Asterix)

Query 8. The Discussion is too long, Please make the necessary reductions.

Reply 8. We thank the reviewer for the comments. We have removed redundant and repetitive sections of the discussion to improve the readability of the document.

Reviewer 2

Query 1. In my view, the most valuable insight derived from this study pertains to the incidence of HCC in patients with BCS. Given the rarity of this disease, assembling a substantial cohort for examination is a formidable task. Consequently, the treatment and outcomes of HCC may be less pivotal, as they are influenced by a multitude of factors and may offer limited insights to the broader medical community. This leads to my perplexity regarding the division of Indian BCS patients into two separate cohorts. Does geographic location play a role in generating substantial differences between the two groups? If not, it might be more beneficial for the authors to merge these cohorts, thereby providing us with the most extensive cohort ever to better address this question.

Reply 1. We thank the reviewers for their comments. There is a distinct difference between the etiological factors that lead to Budd Chiari syndrome in various geographical areas. This distinction is known to exist between the Western world (predominantly myeloproliferative neoplasm) and the Eastern world (predominantly idiopathic and inherited procoagulant states).[1,2] The site of obstruction is also variable, with a combined involvement of the inferior vena cava and hepatic veins being more common in the East as compared to isolated hepatic vein involvement in the West. However, changes within a single geographical region (in this case India) is uncommonly reported. Prior studies have identified that BCS is associated with poverty, malnutrition, bacterial infections, filariasis and hygiene in India. With improvements in the healthcare scenario, these associations have become less common.[3,4] There have been changes in the presentation of BCS (such as a more common presentation of combined IVC and HV block as compared to isolated IVC block alone) as well.[4] Thus, it is unlikely that geographical variations would contribute to the differences in presentation and outcome in the two cohorts. A more plausible reason would be factors like malnutrition, poverty, varying degrees of healthcare disparity, accessibility to healthcare and hygiene practices between individuals, which are subject to regional and cultural differences.[5] Further, the duration of follow-up between the two cohorts is variable and predates the introduction of the BCLC guidelines for HCC management in 1999.[6] Prior to this the management protocols placed greater emphasis on available technical expertise and clinical experience rather than adherence to standardised protocols and personalised medicine.

As the data is retrospective, we were unable to identify potential biases in outcomes based on the decision of the treating physician and adherence to established guidelines. There may also be external influence from social factors as mentioned previously (malnutrition, stigma, poverty, accessibility) which may have influenced outcomes differently in the two cohorts.

This is why we have presented the two groups separately to prevent any misinterpretation of data by the reader.

Query 2. I find myself somewhat puzzled by two aspects of the HCC treatment in this study. Firstly, it raises questions as to why none of the patients, even those classified under BCLC Stage A, received curative treatments, such as surgery or ablation for HCC. Additionally, the study leaves me wondering why most of the patients only underwent a single session of TACE, particularly when it is generally understood to require repeated applications. However, it's worth noting that the treatment of HCC is intricate and multifaceted, influenced by a myriad of factors.

Reply 2. We thank the reviewer for the comment. The New Delhi cohort had 35 BCS-HCC patients, Of the 35 BCS-HCC, 22 (62.8%) patients underwent treatment for HCC (transarterial chemoembolization in 18 (81.8%), oral tyrosine kinase inhibitor in 3 (13.6%) and transarterial radioembolization in 1 (4.5%) patient). Of the 19 patients who received locoregional therapy, 7 (36.8%) received more then 1 sessions of therapy including percutaneous alcohol ablation (PAI) and TACE. In contrast to the New Delhi cohort, Mumbai cohort had 9 BCS-HCC patients, 2 patients underwent liver transplantation and none had received any locoregional therapy. Only 5 patients in the whole cohort had BCLC A, and out of these only 2 underwent therapy. Of the two patients that received treatment one had received a repeat session of TACE while the second patient had a progressive disease and was offered TKI's.

Repeat therapy was offered to all patients as and when required. However, few patients denied consent for treatment. In tables 3, 4 we have provided the details regarding number of repeat sessions in the cohort.

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