THESIS PROTOCOL

TITLE

Role of Allopurinol in Prevention of Complications related to Decompensated Cirrhosis of Liver

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ABBREVIATIONS

AD : Acute Decompensation

ALD : Alcoholic Liver Disease

ALT : Alanine Aminotransferase

AST : Aspartate Aminotransferase

ATP : Adenosine triphosphate

BT : Bacterial Translocation

CTP : Child-Turcotte-Pugh

DGDA :Director General of Drug Administration

DSMB :Data Safety Monitoring Board

EVL : Endoscopic Band Ligation

HBV : Hepatitis B Virus

HCV : Hepatitis C Virus

HE : Hepatic Encephalopathy

HRQL : Health-Related Quality of Life

HRS AKI : Hepatorenal Syndrome Acute Kidney Injury

IL1β : Interleukin 1 Beta

IL18 : Interleukin 18

INR : International Normalized Ratio

MAFLD : Metabolic Associated Fatty Liver Disease

MASLD : Metabolic Associated Steatotic Liver Disease

MELD : Model for End-Stage Liver Disease

MLN : Mesenteric Lymph Node

NAD : Nicotinamide Adenine Dinucleotide

NADH	: Reduced Nicotinamide Adenine Dinucleotide
NASH	: Non-Alcoholic Steatohepatitis
NF-κB	: Nuclear Factor kappa-light-chain-enhancer of activated B cells
NLRP3	: NOD-, LRR- and Pyrin Domain-Containing Protein
PAMP	: Pathogen-Associated Molecular Pattern
PDGF	: Platelet-Derived Growth Factor
PT	: Prothrombin Time
ROS	: Reactive Oxygen Species
SBP	: Spontaneous Bacterial Peritonitis
SCFA	: Short-Chain Fatty Acids
TGF Beta	: Transforming Growth Factor Beta
TMA	: Trimethylamine
TJ	: Tight Junction
TNF alpha	: Tumor Necrosis Factor Alpha
TRX	: Thioredoxin
TXNIP	: Thioredoxin-Interacting Protein
XDH	: Xanthine Dehydrogenase
XO	: Xanthine Oxidase
WHO	:World Health Organization

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ABSTRACT

Title : Role of Allopurinol in Prevention of Complications related to Decompensated Cirrhosis of Liver

Background: Cirrhosis, a leading cause of global mortality, progresses to life-threatening complications like ascites, hepatic encephalopathy, and hepatorenal syndrome. Oxidative stress and gut-liver axis dysfunction drive disease progression. Allopurinol, a xanthine oxidase inhibitor, has shown potential in reducing complications in cirrhosis, but robust clinical evidence is lacking. This study will evaluate allopurinol's efficacy in preventing complications in decompensated cirrhosis.

Aim: To assess whether allopurinol reduces cirrhosis-related complications (ascites, variceal bleeding, hepatic encephalopathy, SBP, HRS-AKI) and improves MELD/CTP scores in Child-Pugh B/C cirrhosis patients.

Patients: We will study 54 patients with decompensated cirrhosis (Child-Pugh B/C). Patients aged 18-70 years, with any etiology of cirrhosis (viral, alcoholic, NAFLD) will be included.Patients with acute decompensation, allopurinol hypersensitivity, advanced renal impairment (CrCl <30 mL/min), pregnancy, or concurrent use of interacting drugs will be excluded .

Method: This randomized controlled trial will be conducted in Hepatology department of BMU after IRB clearance. 54 patients aged 18 to 70 years with Child-Pugh class B or C cirrhosis, admitted to or attending the Outpatient Department of Hepatology at Bangladesh Medical University will be enrolled. After thorough clinical and laboratory evaluation and informed consent, Participants will be randomized into two treatment groups using block randomization. One group will receive oral allopurinol (titrated from 100 mg to 300 mg daily for six months) along with standard medical therapy. Another group will receive placebo along with standard medical therapy . Patients will be followed at 3,6 months to see the progression of cirrhosis-related complications. Data collection will include clinical parameters, laboratory tests, imaging, and endoscopy.

All data will be analyzed using the statistical package SPSS (version 29.0 IBM Corp: Armonk NY, USA). Demographic and baseline clinical characteristics will be analyzed using the chi-square test for categorical variables. For continuous variables that follow a normal distribution, the Student's t-test will be applied. Time to first complication will be analyzed using the Cox proportional hazards model, and Kaplan-Meier curves will be used to compare event-free survival between groups.

Ethical Considerations: The study protocol will be approved by the institutional review board. Written informed consent (Bengali version) will be obtained, ensuring confidentiality and voluntary participation. Participants may withdraw anytime.

Anticipated Impact: If effective, allopurinol will offer a low-cost, widely accessible therapy to prevent complications and improve survival in decompensated cirrhosis. To the best of my knowledge this is the first study in Bangladesh to evaluate the efficacy of Allopurinol in prevention of cirrhosis associated complications.

1.1 INTRODUCTION

Cirrhosis of liver accounts for approximately 1 million deaths per year. In addition to its clinical burden, it causes significant morbidity, impairment of health-related quality of life (HRQL), and economic burden (Younossi et al. 2023).

It is the final pathway for a wide variety of chronic liver diseases, a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by nodules (Feldman et al. 2015). It is currently the 9^{th} leading cause of death in South East Asia and Europe; 10^{th} leading cause of death in Africa ; and the 5^{th} leading cause of death in the Eastern Mediterranean (Devarbhavi et al. 2023).

According to World Health Organization, cirrhosis of liver is the 10^{th} leading cause of death in Bangladesh for both male and female (World Health Organization , 2021).
Alcohol consumption, chronic hepatitis C infection, and NAFLD are the most common causes of cirrhosis in Western countries, while chronic hepatitis B is the predominant cause in the Asia-Pacific region. Other causes include inherited conditions like hemochromatosis and Wilson's disease, along with primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis. In some cases, the cause of cirrhosis is unknown or cryptogenic (Zhou et al. 2014).

Cirrhosis is classified in two main prognostic stages: compensated and decompensated cirrhosis. Decompensation means cirrhosis with one of the following: ascites, bleeding varices, hepatic encephalopathy or jaundice. Median survival in the compensated stage exceeds 12 years where as it is only 2 years in patients who develop decompensation (D'Amico et al. 2006). Cirrhosis advances from a compensated stage to a decompensated stage at a rate of 5%–7% annually (Kaur et al. 2025).

The gut-liver axis functions as a crucial system that helps protect the body from potentially harmful substances and microorganisms, while also preserving the balance and stability of the immune system (Ponziani et al. 2018). Individuals with cirrhosis experience alterations in their gut microbiota. Factors such as reduced small intestinal motility, impaired bile secretion, and disruptions in the production of immunoglobulin A and antimicrobial molecules all contribute to this alteration (Bhat et al. 2016). Alteration of gut microbiota causes increased absorption of endotoxins. As a consequence, systemic endotoxemia develops (Bauer et al. 2002). The raised level of

plasma endotoxin is closely related to the severity of cirrhosis and is an important factor (Lin et al. 1995).

The production of Reactive oxygen species (ROS) in the gut is a necessary defense mechanism against pathogens and aids in mucosal recovery, but when produced in excess, it can undermine the integrity of the mucosal lining and the epithelial barrier (Kunst et al. 2023). ROS also play a crucial role in the process of fibrogenesis. Not only that, the majority of hepatocellular carcinomas develop in cirrhotic livers, where the key mechanism behind their formation is long-term inflammation coupled with intense oxidative stress (Muriel et al. 2009). Multiple studies have demonstrated an increase in xanthine oxidase (XO) activity in patients with different types of liver injury including cirrhosis (Stirpe et al. 2002; Ramboer et al. 1972; Aldaba-Muruato et al. 2012). Studies on experimental cirrhosis have indicated subcellular alterations in the intestinal mucosa, which are linked to increased oxidative stress from the overactivity of xanthine oxidase (Spahr et al. 2007).

Therefore, we can postulate that using an intervention that inhibits XO can result in reduced ROS overproduction, intestinal permeability, bacterial translocation, and endotoxemia and its consequences.

The management of cirrhosis typically focuses on controlling the underlying disease, managing complications, and improving quality of life. However, specific therapies to prevent the complications of cirrhosis are limited. Allopurinol, a competitive inhibitor of the enzyme xanthine oxidase, has been proven to exert antioxidant properties (Pacher et al. 2006).It has shown promising antioxidant (Spahr et al. 2007) and anti-inflammatory (Aldaba-Muruato et al. 2012) effects in cirrhotic patients. It has also been proven to reduce complications such as ascites, hepatic encephalopathy, Spontaneous bacterial peritonitis (SBP), and Hepatorenal syndrome –Acute Kidny Injury (HRS-AKI) in cirrhosis (Glal et al. 2023).

This study aims to investigate whether Allopurinol can reduce the incidence or severity of complications (hepatic encephalopathy, ascites, and variceal bleeding, SBP, HRS-AKI) in patients with cirrhosis. The findings may provide important insights into a potentially low-cost, widely available therapeutic option for cirrhotic patients if proven to be effective .

To the best of my knowledge this is the first study in Bangladesh to evaluate the efficacy of Allopurinol in prevention of cirrhosis associated complications.

1.2 Literature Review

Glal et al. (2023) conducted a quadruple-blinded, randomized, placebo-controlled trial, where patients with cirrhosis were administered 300 mg of allopurinol daily for a duration of six months as a form of secondary prophylaxis. After 6 months of treatment, the incidence of any first cirrhosis-related complication was significantly lower in the allopurinol group compared to the placebo group—32% versus 72%, respectively. This difference corresponds to a hazard ratio (HR) of 0.44 with a 95% confidence interval (CI) of 0.27–0.62, indicating a 56% relative risk reduction in patients treated with allopurinol over the six-month period ($P < 0.001$). Additionally, the absolute risk reduction (ARR) was 40%, translating to a number needed to treat (NNT) of 2.5.Moreover, allopurinol demonstrated a substantial reduction of 67% in the relative risk of developing overt ascites (HR 0.33; 95% CI, 0.0098–0.94; $P = .039$), a notable decrease in relative risk of spontaneous bacterial peritonitis by about 75% (HR 0.25; 95% CI, 0.05–0.76; $P = .01$), and an 80% reduction in the risk of developing hepatorenal syndrome (HR 0.2; 95% CI, 0.04–0.87; $P = .033$). The allopurinol group showed a statistically significant reduction in the MELD score after 6 months of treatment as compared with placebo ($P < .035$).

Muruato et al. (2012) stated that allopurinol protects against experimental liver damage by preventing oxidative stress and by inhibiting the translocation of NF-κB to the nucleus, as well as by modulating the expression of pro-inflammatory and anti-inflammatory cytokines. Moreover, this drug presents antifibrotic effects, probably because of its ability to reduce TGF-β expression and to increase the activity of MMP-13, a proteolytic enzyme that has a central role in the modulation of the MMP activation cascade.

Spahr et al. (2007) conducted a study to evaluate the effects of allopurinol on oxidative stress in patients with stable cirrhosis. The study included 19 patients with stable cirrhosis, who were treated with 400 mg of allopurinol per day for 10 days. Various

markers were assessed at baseline and after the 10-day course, including oxidative stress (via serum malondialdehyde (MDA) levels), intestinal permeability (measured by the lactulose/mannitol (Lac/Man) ratio), and markers of systemic inflammation such as TNF-soluble receptor-1, interleukin-6 (IL-6), and lipopolysaccharide-binding protein (LBP), which indicates endotoxin exposure.

The findings from the study demonstrated that allopurinol therapy led to a significant reduction in oxidative stress, as evidenced by a 23% decrease in serum malondialdehyde (MDA) levels ($P < 0.05$). MDA is a byproduct of lipid peroxidation and is commonly used as a marker of oxidative stress. The reduction in MDA levels indicated a decrease in oxidative damage, suggesting that allopurinol may help mitigate oxidative stress in patients with cirrhosis.No significant changes were observed in intestinal permeability (measured by the Lac/Man ratio) or in the markers of endotoxin-associated systemic inflammation (TNF-soluble receptor-1, IL-6, and LBP).

1.3 Rationale of the study

The rationale for this study is rooted in the need to explore an affordable, widely available, and well-tolerated pharmacological intervention that could improve the prognosis of patients with cirrhosis by preventing or mitigating the complications associated with the disease. Allopurinol, given its established safety profile and its emerging role in liver disease management, offers a promising option that seeks further investigation.

Despite advancements in the management of cirrhosis, the prevention of cirrhosis-related complications remains a major clinical challenge. Current therapeutic strategies primarily focus on managing individual complications—such as ascites, variceal bleeding, or hepatic encephalopathy—after they occur, rather than preventing their onset.

Several studies have suggested that allopurinol have potential to attenuate liver damage and reduce the risk of cirrhosis-related complications is an area of growing interest. Allopurinol's antioxidant properties may help mitigate the oxidative stress that exacerbates liver injury in cirrhotic patients, potentially preventing or delaying the onset of severe complications such as ascites, hepatic encephalopathy, and variceal bleeding

Up to now, few well-designed clinical studies have systematically evaluated the role of allopurinol in preventing the development or progression of cirrhosis-associated complications in a defined patient population. The lack of large-scale, controlled trials or robust longitudinal data leaves an important gap in understanding the clinical efficacy and safety of allopurinol in this context.

This study aims to assess the efficacy of allopurinol in preventing cirrhosis-related complications. By evaluating the potential benefits of allopurinol in this patient population, the study seeks to provide evidence that may influence clinical practice, offering a novel approach to managing cirrhosis-related complications and improving patient outcomes.

1.4 Research Question

Does allopurinol reduce the complications associated with Decompensated cirrhosis of liver ?

1.5 Objective of the study

General objective:

To evaluate the role of allopurinol in preventing decompensated cirrhosis-associated complications.

Specific Objectives:

- To compare the time to event and overall complication rate between the Allopurinol group and the standard medical therapy group.
- To evaluate the effect of allopurinol in the prevention of hepatic encephalopathy in patients with cirrhosis.
- To evaluate the effect of allopurinol in regression of ascites in patients with cirrhosis.
- To evaluate the potential of allopurinol in preventing variceal bleeding among patients with cirrhosis.
- To evaluate the effect of allopurinol in prevention of spontaneous bacterial peritonitis (SBP) in cirrhotic patients.
- To evaluate the role of Allopurinol in prevention of hepatorenal syndrome-acute kidney injury (HRS-AKI) in cirrhosis.
    - To evaluate the impact of Allopurinol on MELD(Model for End-stage Liver Disease) and CTP(Child-Turcotte-Pugh)score

1.6 Endpoint

Primary Endpoint

The occurrence of any cirrhosis-related complications (Time to event and number of patients) -

- Ascites (new onset or worsening)
- Variceal bleeding
- Hepatorenal Syndrome–Acute Kidney Injury
- Spontaneous bacterial peritonitis: raised ascitic fluid absolute Neutrophil count (≥250 cells/mm3)
- Hepatic encephalopathy according to West Haven criteria within the 6-month follow-up period.

Secondary Endpoints

- Change in Alanine Aminotransferase (ALT) reported in U/L.
- Change in Aspartate Aminotransferase (AST) reported in U/L.
- Change in Serum Bilirubin reported in mg/dl.
- Change in Serum Albumin reported in g/dL.
- Change in Prothrombin Time-International Normalized Ratio (PT-INR) reported as INR.
- Change in Child-Turcotte-Pugh (CTP) Score (Score 5–15; Higher score = worse liver function) from baseline to study completion
- Change in Model for End-Stage Liver Disease (MELD) (Score: 6-40 ; Higher score = worse liver function) Score from baseline to study completion
- All cause mortality during 6 months follow up period

2. Materials & Methods

2.1 Type of study: Randomized Controlled Trial

2.2 Sampling technique: Simple Random Sampling of those who fulfill the criteria.

2.3 Study population: Patients with decompensated cirrhosis of liver (CTP B,C)

2.4 Place of study: Department of Hepatology, Bangladesh Medical University, Dhaka.

2.5 Period of study: From IRB clearance to December 2026

2.6 Sample size determination: Khadija A.M. Glal et al. reported a significant reduction in cirrhosis-related complications with allopurinol treatment. Specifically, the incidence of any first complication was 32% in the allopurinol group compared to 72% in the placebo group, resulting in an absolute risk reduction (ARR) of 40% and a hazard ratio (HR) of 0.44 (95% CI: 0.27–0.62; P < .001).

In this study study, aiming to detect a similar effect size with 80% power and a 5% significance level, we use the following formula for comparing two proportions:

$$n = \frac{\left\{u\sqrt{2\pi(1-\pi)} + v\sqrt{\pi_1(1-\pi_1) + \pi_2(1-\pi_2)}\right\}^2}{(\pi_1 - \pi_2)^2}$$

Where:

π_1 = event rate in the control group (0.72) (Glal et al. (2023)

π_2 = event rate in the treatment group (0.32) (Glal et al. (2023)

$\pi = \frac{\pi_1+\pi_2}{2}$

u = $Z_{1-\alpha/2}$ = Z-score for a 5% significance level (1.96)

v= $Z_{1-\beta}$ = Z-score for 80% power (0.84)

After putting this values,

$$\pi = \frac{0.72+0.32}{2} = 0.52$$

$$n = \left(\frac{1.96\sqrt{2 \times 0.52(1-0.52)} + 0.84\sqrt{0.72(1-0.72) + 0.32(1-0.32)}}{0.72 - 0.32}\right)^2$$

$$= 23.2449$$

From calculation , n_{required} ≈23.25 per group

Considering a whole number of sample size , round up to, $n_{\text{adjusted=24}}$ per group

Considering 10% of participants drop out , the final sample size will be ,

$$n_{final} = \frac{n_{adjusted}}{1 - dropout\ rate}$$

$$= \frac{24}{1-0.10}$$

$$= \frac{24}{0.90}$$

$$\approx 26.67$$

After considering the nearest round number $n_{final=27}$

So the final sample size will be 27 in each group that is total $27 \times 2 = 54$

2.7 Selection of patients

Inclusion Criteria

- Adult patients (age : 18-70 years) diagnosed with Decompensated cirrhosis of liver with any etiology of cirrhosis .
- CTP score B or C .

Exclusion Criteria

- Patients with known hypersensitivity or allergy to allopurinol.
- Patients with active HE or SBP or HRS-AKI or a history of any of these events within the last 4 weeks.
- Patients with advanced renal impairment (e.g., creatinine clearance <30 mL/min).
- Pregnant or breastfeeding women.
- Patients with severe comorbidities (e.g., uncontrolled cardiovascular disease, cancer, or severe infections).
- Patients currently using medications that interact with allopurinol (e.g., azathioprine, mercaptopurine, Cyclophosphamide, Thiazide diuretics ,Warfarin, Theophyllin).

2.8 Variables

(A)Demographic variables:

- Age: Participants aged 18–70years.
- Sex: Male and female patients.

(B) Clinical Variables:

- Presence or history of jaundice
- Presence or history of ascites
- Presence or history of HE
- Presence or history of variceal bleeding

(C) Biochemical variables:

- Alanine aminotransferase (ALT).
- Aspartate aminotransferase (AST).
- Total bilirubin.
- Serum albumin.
- Prothrombin time/international normalized ratio (INR).
- Erythrocyte sedimentation rate (ESR).
- Hemoglobin.
- White blood cell count.
- Platelet count.
- Serum Creatinine
- Serum Electrolytes

(D) Radiological Variables:

Ultrasound Assessments: Evaluation for the presence of ascites.

(**E) Outcome variables:**

Incidence of any decompensation event, including:

- Variceal bleeding.
- Hepatic encephalopathy
- Jaundice
- Ascites
- Spontaneous bacterial peritonitis.
- HRS-AKI
- Changes in laboratory parameters (e.g., liver enzymes,Serum Billirubin , Serum Albumin , PT with INR, CRP, ESR).
- Changes in CTP, MELD score.
- Mortality in 6 months follow up period

2.9 Operational Definitions

liver cirrhosis: Liver cirrhosis is a chronic liver disease characterized by progressive fibrosis, architectural distortion of the liver parenchyma, and the formation of regenerative nodules.

Diagnosis of liver cirrhosis will be based on following criteria:

1. Clinically stigmata of cirrhosis (vascular spider, palmer erythema, gynaecomastia, leukonychia, ciubbing, testicular atrophy) and laboratory features (APRI , FIB4 , prlonged prothrombin time, reduced serum albumin)
2. Abdominal ultrasound: features of cirrhosis like irregular and coarse liver, enlarged spleen, dilated portal vein, ascites
3. Endoscopy of upper GIT: Any grade varix or portal hypertensive gastropathy
4. Fibroscan liver stiffness
5. Liver histology supporting cirrhosis of liver.

Compensated cirrhosis of liver : refers to a stage of liver cirrhosis in which the liver is still able to maintain its basic functions despite the presence of structural damage and fibrosis , patients do not exhibit overt symptoms of liver failure.

Criteria for defining compensated cirrhosis in this study include: Clinical absence of decompensated complications such as ascites, hepatic encephalopathy, gastrointestinal bleeding from varices, or jaundice.

Decompensated cirrhosis of liver : refers to a more advanced stage of liver cirrhosis where the liver can no longer maintain its normal function, resulting in the onset of overt symptoms of complications.

Criteria for defining decompensated cirrhosis in this study include Presence of clinical complications such as:

- Ascites
- Hepatic encephalopathy
- Variceal bleeding
- Jaundice

Acute decompensation (AD) : Acute development (within ≤4 weeks) of one or more major complications (Jaundice, HE, variceal bleeding, and/or infection) in a patient with cirrhosis, with or without prior decompensation, often associated with a precipitating event (Sarin et al. 2025).

Spontaneous Bacterial Peritonitis (SBP): Ascitic fluid polymorphonuclear cells >250/ml with or without positive fluid bacterial cultures.

Gut dysbiosis: The imbalance of gut microbiota associated with an unhealthy outcome.

Child-Turcotte-Pugh Score : Child-Turcotte-Pugh (CTP) score has usually been used to assess the prognosis of patients with cirrhosis, since it is related to the severity of the liver disease. It has been elaborated by using five 5 parameters: hepatic encephalopathy, ascites, prothrombin time, serum albumin in g/L and bilirubin in mg/dl..

Parameter	1 point	2 points	3 points
Total bilirubin µmol/L mg/dL PBC/PSC	 <34 <2 < 68 (4)	 34–50 2–3 68–170 (4- 10)	 >50 >3 >170 (10)
Serum albumin (g/L)	>35	28–35	<28
INR Prothrombin time	<1.7 < 4	1.71–2.30 4–6	>2.30 > 6
Ascites	None	Mild (or controlled by diuretics)	Moderate to severe (or Refractory to diuretics)
Hepatic encephalopathy	None	Grade I–II (or absent with medication)	Grade III–IV (or recurrent)

Interpretation-

CTP score is obtained by adding the score for each parameter.
CTP A=5-6points

B=7-9points
C =10-15 points
(McCormick & Jalan, 2018)

MELD(Model for End-stage Liver Disease) :

MELD = 9.57× log_e(serum creatinine) + 3.78× log_e (total bilirubin) + 11.2× log_e (INR) + 6.43.

Serum creatinine, bilirubin, and INR are assigned a minimum value of 1.0 for the purpose of calculation (Kamath and Kim 2007).

Standard Medical treatment :

1. Treatment of etiology
2. Non specific Beta blocker (NsBB) for portal Hypertension
3. Diuretics for ascites
4. Lactulose for Hepatic encephalopathy
5. Dietary management
6. Treatment of co morbidities
7. Life style modification
8. Nutritional support

Dose adjustment of Allopurinol:

If CrCl is more than 60 ml/min – Dose will be started at 100mg and then titrated 2 weekly by 100 mg to 300mg

If Crcl is 30-60 ml/min - Dose will be started at 50mg and then titrated 2 weekly by 100mg upto 300mg

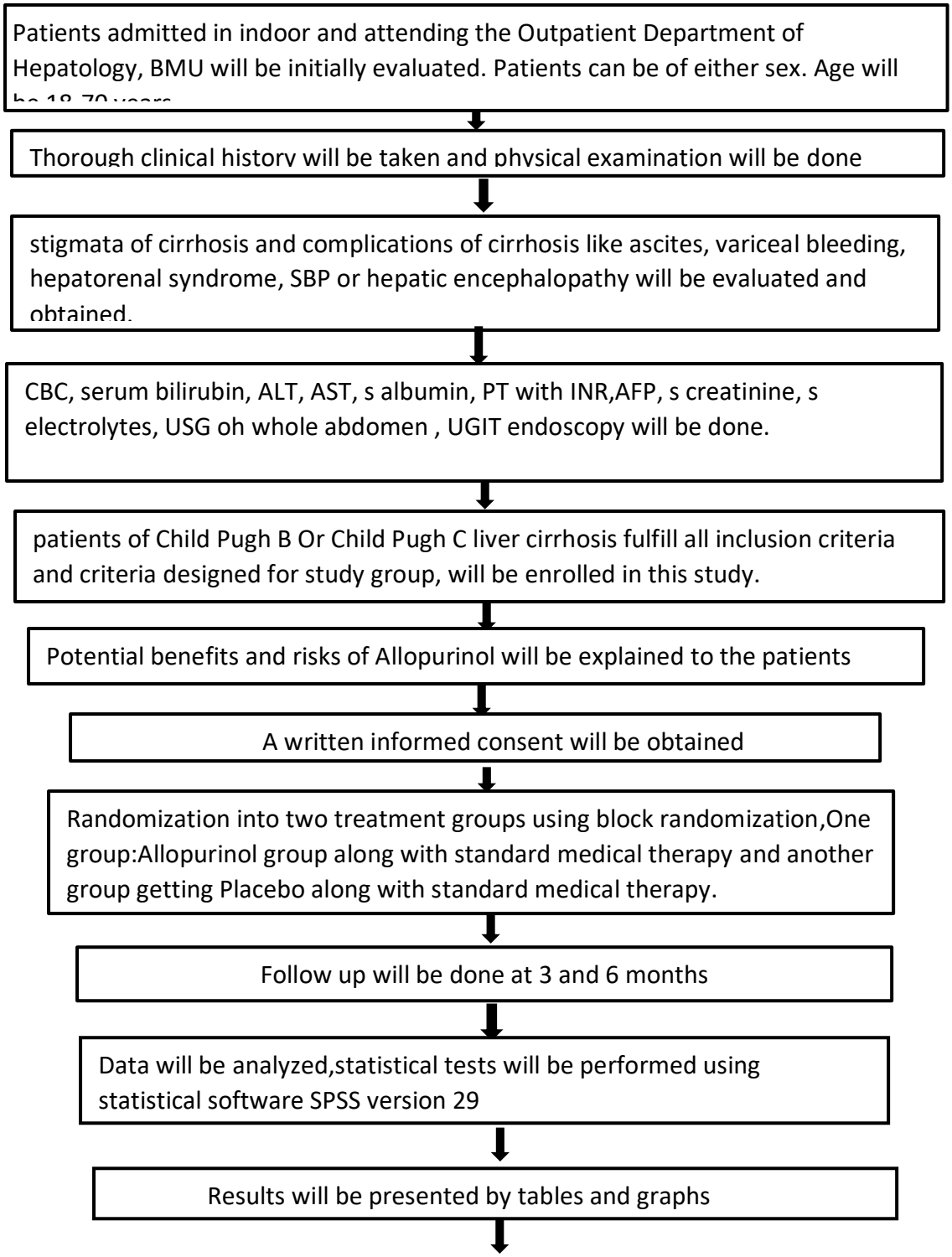
(Richette et al. 2016; FitzGerald et al. 2020)

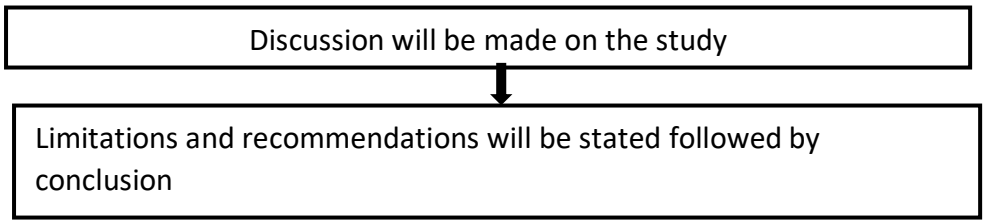
2.10 Study procedure

Patients admitting in indoor and attending the Outpatient Department of Hepatology, BMU will be initially evaluated. Patients can be of either sex. Age will be in between 18 to 70 years. A thorough clinical history will be taken and physical examination will be performed. At baseline, for each patient, demographic and clinical data including age, sex, stigmata of cirrhosis and complications of cirrhosis like ascites, variceal bleeding, hepatorenal syndrome, SBP or hepatic encephalopathy will be evaluated and obtained. Then other investigations like complete blood count(CBC), liver function tests (serum bilirubin, ALT, AST, serum albumin, serum Billirubin , prothrombin time), alpha fetoprotein (AFP), serum creatinine, serum electrolytes, abdominal ultrasonography, Endoscopy of upper gastrointestinal tract will be done.

If the patients of Child Pugh B or Child Pugh C liver cirrhosis fulfill all inclusion criteria and no exclusion criteria designed for study group, they will be enrolled in this study. A written informed consent will be obtained from all selected participants. The potential benefits and risks of use of Allopurinol will be explained to the participants. Participants will be randomized into two treatment groups using block randomization ; either an allopurinol treatment group or a Placebo group. Both of the groups will receive the standard therapy of decompensated cirrhosis. The Placebo will be matched to the active drug .Dose will be started at 100mg followed by titration to 300 mg. If creatinine clearance is less than 60 ml/min , dose will be started at a lower dose. Both groups will be followed up at 3,6 months after starting treatment. Communication will be maintained between all groups of patients. All patients will be advised to contact immediately if any need arises. A Data Safety Monitoring Board will be formed . Members of DSMB will be informed about any side effects mentioned by patients . Any serious adverse effect will be informed to National Drug Administration Authority (Director General of Drug Administration – DGDA).

2.11 Flow Chart





2.12 Data collection technique:

Data will be collected using a preformed data collection sheet which will contain the questionnaires along with baseline, demographic and clinical data. Data will be collected from the patient after exploration of different complaints. All information regarding clinical features will be recorded in a data collection sheet.

Biochemical and Laboratory Analysis:

The biochemistry laboratory will be used for Serum total bilirubin, Alanine transaminase (ALT), Aspartate transaminase (AST), serum creatinine, Serum electrolytes, Serum albumin, Alpha fetoprotein (AFP).
Laboratory Medicine Lab will be used for CBC, prothrombin time with INR and Ascitic fluid cytology.
Abdominal USG will be performed in department of Radiology and imaging, BMU.
Upper GI endoscopy will be done in Department of Hepatology, BMU.

2.13 Statistical analysis:

This study will adopt an intention-to-treat analysis. All data will be analyzed using the statistical package SPSS (version 29.0 IBM Corp: Armonk NY, USA). Demographic and baseline clinical characteristics will be analyzed using the chi-square test for categorical variables, with data expressed as frequencies and percentages. For continuous variables that follow a normal distribution, the Student's *t*-test will be applied, and results will be presented as means with standard deviations.

The time to the first occurrence of any cirrhosis-related complication will be assessed using the Cox proportional hazards model, with a two-sided significance level of 0.05, assuming the proportional hazards assumption is satisfied. Kaplan-Meier survival analysis will be employed for each treatment arm to estimate the proportion of patients who will experience cirrhosis-related events during the study period.

2.14 Ethical consideration:

- The ethical review committee of BMU will approve a research protocol before starting this study.
- Informed written consent will be taken from each patient explaining the benefits and side effects of the drugs and other available alternative treatment options.
- The purpose and procedures will be briefly explained to all participants.
- The participants will have freedom to withdraw themselves from the study any time during the study period.
- Final data base and report will not contain the name of participants.
- There is no major chance of physical risk.
- All sorts of confidentiality will be ensured.
- No money will be given to the participants of the study.

  If any complication arises during this procedure, appropriate management will be started immediately.

Informed Consent:

For this study, a well-informed, voluntarily signed written consent will be taken in an understandable local language from the study subjects after convincing them that their privacy & confidentiality will be safeguarded.

Confidentiality:

To maintain confidentiality, each of the study subjects will be given a special ID number which will be followed during each and every steps of the study procedure. All the research data will be coded and stored in a locked cabinet. Only research personnel will be allowed to access the data.

Use of hospital records:

Hospital records, especially the investigation reports will be needed to fill up the data collection sheet. The data collection sheet will be filled up after taking a brief interview of 20 to 30 minutes with the participants.

Privacy:

Privacy will be maintained during physical examination, interview and also at the time of procedure.

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Appendix-II

Informed Consent Form For Subjects

Title of the Study: The Role of Allopurinol in the Prevention of Complications associated with Decompensated Cirrhosis

Principal Investigator:
Dr Sabrina Mahbub
Department of Hepatology,
Bangladesh Medical University (BMU), Dhaka.

Introduction:
You are being invited to participate in a research study being conducted at the Department of Hepatology, BMU. Please read this form carefully. You may ask the researcher any questions to understand the purpose, procedures, risks, and benefits before giving consent. Your participation is voluntary.

Purpose of the Study:
This study aims to determine whether Allopurinol, a medication commonly used to reduce uric acid levels, can help prevent complications associated with decompensated cirrhosis of the liver.

Study Procedures:
If you agree to participate:

- You will be evaluated through history, clinical examination, blood tests, ultrasound, endoscopy, and other relevant investigations.
- You will be randomly assigned to one of two groups:
    - One group Will receive Allopurinol (300 mg daily) for six months along with standard medical care.
    - Another group will receive Placebo along with standard medical care .
- Your health will be monitored after 3 and 6 months.

- The tests will include liver and kidney function tests, blood counts, and other relevant investigations.

Possible Risks and Discomforts :

- You may experience side effects from Allopurinol, such as skin rashes, nausea, or allergic reactions (though rare).
- Liver enzyme elevation which is reversible.
- Blood draws may cause slight discomfort or bruising.

Possible Benefits:

- You may benefit from prevention of liver complications such as abdominal distension , renal impairment , infection etc.
- The study may help future patients with similar liver conditions.

Confidentiality:

Your personal details will remain strictly confidential. All information will be stored in office of this department. No information will be used for other purpose without this study.

Voluntary Participation and Right to Withdraw:

Participation is entirely voluntary. You are free to withdraw at any point without giving any reason. Your medical care will not be affected in any way if you choose not to participate or withdraw later.

Costs:

For participation in this research, you will not have to pay any additional expense nor will you be given any money.

Right to withdraw:

Your participation in this study is completely dependent upon your free will and it will not affect your current treatment process. You also reserve the right to withdraw your name anytime during this research procedure.

Voluntary expression of consent

I express satisfaction upon discussion over this research with the researching doctor (who will examine me physically). I understand that participation in this research is a voluntary act and at any time I may withdraw from this research without any obligation. Above stated conditions have been gone through by me and it is completely voluntarily that I here in express my consent to participate in this research.

For any query or information about the rights or benefits of your involvement in this study, you are free to contact with:

Dr. Sabrina Mahbub

(MD, Phase-B Resident)

Department of Hepatology,

Bangladesh Medical University

Shahbagh, Dhaka.

Phone No: 01842311954

If you agree to our proposal of enrolling in our study, please indicate this by putting your signature or your left thumb impression at the specified space below.

Thank you for your cooperation.

……...

Signature Or left thumb impression

Date……

Appendix-III

Data Collection sheet

Department of Hepatology

Bangladesh Medical University (BMU), Shahbag, Dhaka-1000

Title of the study: Role of Allopurinol in the Prevention of Complications associated with Decompensated Cirrhosis.

Principle investigator: Dr. Sabrina Mahbub

1. SL No:

2. Date:

Particulars Of the patient:

3. Name:

4. Age (Years):

5	**Sex**	☐ Male ☐ Female
6	**Education**	☐Illiterate ☐Below SSC ☐SSC ☐Bachelor and above
7	**Occupation**	☐Housewife ☐ Service ☐ Farmer ☐ Businessman ☐ Others

8. Contact no:

9. Address:

First visit (Day 0):

Diagnosis of the Patient :

Complaints with duration:

No.	Symptom/Examination	Response (Tick ✓)	If "Yes", Duration
10	**Asymptomatic**	☐ Yes ☐ No	-
11	**Yellow eyes/urine**	☐ Yes ☐ No	____ months/days
12	**Weakness**	☐ Yes ☐ No	____ months/days
13	**Fever**	☐ Yes ☐ No	____ months/days
14	**Blood vomiting**	☐ Yes ☐ No	____ days
15	**Black tarry stools**	☐ Yes ☐ No	____ days
16	**Abdominal pain**	☐ Yes ☐ No	____ months/days
17	**Abdominal mass**	☐ Yes ☐ No	____ months/days
18	**Abdominal distension**	☐ Yes ☐ No	____ months/days
19	**Altered consciousness**	☐ Yes ☐ No	____days
20	**Reduced Urine output**	☐ Yes ☐ No	____days
21	**Weight loss**	☐ Yes ☐ No	____days

Past Medical History

No.	History	Response
22	**History of jaundice**	☐ Yes ☐ No
23	**History of Ascites**	☐ Yes ☐ No
24	**History of Hepatic encephalopathy**	☐ Yes ☐ No
25	**History of HRS-AKI**	☐ Yes ☐ No
26	**History of HBV infection**	☐ Yes ☐ No
27	**History of HCV infection**	☐ Yes ☐ No

Drug History

28.Azathioprine/mercaptopurine/Thiazide/Warfarin/Cyclophosphamide/Theophyllin - ☐ Yes ☐ No

Physical Examination:

29	Anemia	☐ Present ☐ Absent	
30	Jaundice	☐ Present ☐ Absent	
31	Oedema	☐ Present ☐ Absent	
32	**Stigmata of CLD**		
	- Leuconychia	☐ Present ☐ Absent	
	- Palmar erythema	☐ Present ☐ Absent	
	- Spider angioma	☐ Present ☐ Absent	
	- Gynecomastia	☐ Present ☐ Absent	
	- Testicular atrophy	☐ Present ☐ Absent	
33	Altered consciousness	☐ Present ☐ Absent	
34	Flapping tremor	☐ Present ☐ Absent	
35	Blood Pressure	Systolic: _____ mmHg	Diastolic: _____ mmHg
36	Pulse	_____ bpm	
37	Temperature	_____ °F	
38	Respiratory rate	_____ breaths/min	
39	Hepatomegaly	☐ Present ☐ Absent	
40	Splenomegaly	☐ Present ☐ Absent	
41	Ascites	☐ Present ☐ Absent	

41a	- Grade (if present)	☐ Grade 1	☐ Grade 2	☐Grade 3
42	Cachexia/Muscle wasting	☐ Present	☐ Absent	
43	Abdominal mass	☐ Present	☐ Absent	

Laboratory findings:

No	Parameter	Value/Result	Units
44	Hb%	_____	gm/dl
45	ESR	_____	mm/1st hour
46	Total Count (TC)	_____	$\times 10^9$/L
47	Platelet count	_____	$\times 10^9$/L
48	HBsAg	☐ Positive ☐ Negative	
49	Anti-HCV	☐ Positive ☐ Negative	
50	Serum bilirubin	_____	mg/dl
51	AST	_____	U/L
52	ALT	_____	U/L
53	Prothrombin Time	_____	sec
54	INR	_____	
55	Serum albumin	_____	g/dl
56	Serum creatinine	_____	mg/dl
57	**Serum Electrolytes**		
	- Sodium	_____	mmol/L
	- Potassium	_____	mmol/L
58	AFP	_____	ng/mL

Imaging Endoscopy Findings

No.	Investigation	Findings	Response
59	**USG Abdomen**		
	- Hepatomegaly		☐ Yes ☐ No
	- Shrunken liver		☐ Yes ☐ No
	- Coarse liver		☐ Yes ☐ No
	- Nodule in liver		☐ Yes ☐ No
	- Ascites		☐ Yes ☐ No
	- Splenomegaly		☐ Yes ☐ No
60	**UGIT Endoscopy**		
	- Varices		☐ Yes ☐ No
	- Portal Hypertensive Gastropathy (PHG)		☐ Yes ☐ No

61 Ascitic fluid study (if done) – Neutrophil count :

Scoring Systems

No	Score	Value
62	CTP Score	_____
63	MELD Score	_____

Drug started on : Date:

Follow up (After 3 months) :

Symptoms :

No.	Symptom	Response
1	**Yellow coloration of eyes & urine**	☐ Yes ☐ No
2	**Abdominal distension**	☐ Yes ☐ No
3	**Altered consciousness**	☐ Yes ☐ No
4	**Weakness**	☐ Yes ☐ No
5	**Nausea/vomiting**	☐ Yes ☐ No
6	**Rash**	☐ Yes ☐ No
7	**Loose motion**	☐ Yes ☐ No
8	**Others**	Specify: _____

EXAMINATION FINDINGS

General Examination

No.	Parameter	Response/Value
9	**Anaemia**	☐ Yes ☐ No
10	**Jaundice**	☐ Yes ☐ No

No.	Parameter	Response/Value
11	**BP**	_____ mmHg
12	**Pulse**	_____ beats/min
13	**Flapping tremor**	☐ Yes ☐ No
14	**Altered consciousness**	☐ Yes ☐ No

Abdominal Examination:

No.	Parameter	Response/Details
15	**Tenderness**	☐ Yes ☐ No
	If yes, location:	_____
16	**Liver (palpable)**	☐ Yes ☐ No
17	**Spleen (palpable)**	☐ Yes ☐ No
18	**Ascites**	☐ Yes ☐ No
18(a)	**Grade (if present)**	☐ Grade 1 ☐ Grade 2 ☐Grade 3

INVESTIGATIONS:

Laboratory Tests:

No.	Parameter	Value	Unit
19	**Hb%**	_____	gm/dl
20	**Total Count (TC)**	_____	$\times 10^9$/L
21	**ESR**	_____	mm/1st hour
22	**Platelet count**	_____	$\times 10^9$/L
23	**Serum bilirubin**	_____	mg/dl
24	**AST**	_____	U/L
25	**ALT**	_____	U/L
26	**Prothrombin Time**	_____	sec
27	**INR**	_____	-
28	**Serum albumin**	_____	g/dl
29	**Serum creatinine**	_____	mg/dl

30. Ascitic fluid study :

Scoring Systems :

No.	Score	Value
31	**CTP Score**	_____
32	**MELD Score**	_____

Follow up (After 6 months) :

Symptoms :

No.	Symptom	Response
1	Yellow coloration of eyes & urine	☐ Yes ☐ No
2	Abdominal distension	☐ Yes ☐ No
3	Altered consciousness	☐ Yes ☐ No
4	Weakness	☐ Yes ☐ No
5	Nausea/vomiting	☐ Yes ☐ No
6	Rash	☐ Yes ☐ No
7	Loose motion	☐ Yes ☐ No
8	Others	Specify: _____

EXAMINATION FINDINGS
General Examination

No.	Parameter	Response/Value
9	Anaemia	☐ Yes ☐ No
10	Jaundice	☐ Yes ☐ No
11	BP	_____ mmHg

No.	Parameter	Response/Value
12	Pulse	_____ beats/min
13	Flapping tremor	☐ Yes ☐ No
14	Altered consciousness	☐ Yes ☐ No

Abdominal Examination:

No.	Parameter	Response/Details
15	Tenderness	☐ Yes ☐ No
	If yes, location:	_____
16	Liver (palpable)	☐ Yes ☐ No
17	Spleen (palpable)	☐ Yes ☐ No
18	Ascites	☐ Yes ☐ No
18(a) Grade (if present)	☐ Grade 1 ☐ Grade 2	☐Grade 3

INVESTIGATIONS:
Laboratory Tests:

No.	Parameter	Value	Unit
19	Hb%	_____	gm/dl
20	Total Count (TC)	_____	×10⁹/L
21	ESR	_____	mm/1st hour
22	Platelet count	_____	×10⁹/L

No.	Parameter	Value	Unit
23	Serum bilirubin	_____	mg/dl
24	AST	_____	U/L
25	ALT	_____	U/L
26	Prothrombin Time	_____	sec
27	INR	_____	-
28	Serum albumin	_____	g/dl
29	Serum creatinine	_____	mg/dl

30. Ascitic fluid study :

Scoring Systems :

No.	Score	Value
31	CTP Score	_____
32	MELD Score	_____

Signature

RESEARCH WORK SCHEDULE

Topic Selection	:	April, 2024 to September, 2024
Approach to problem	:	September 2024 to December, 2024
Writing Protocol	:	December 2024 to February 2025
Protocol presentation	:	April 2025
Approval of protocol	:	July 2025
Data collection	:	From the date of IRB clearance to November 2026
Data analysis	:	December 2026
Report writing and binding	:	January 2027
Submission	:	March 2027