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STRATEGIC MANAGEMENT APPROACHES FOR ESOPHAGEAL VARICES: A COMPREHENSIVE ANALYSIS

Dr. Aanchal Mogri*, Drishti Chouhan, Neelam Dangi and Krishna Hingad

India.

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***Corresponding Author**
Dr. Aanchal Mogri
India.

ABSTRACT

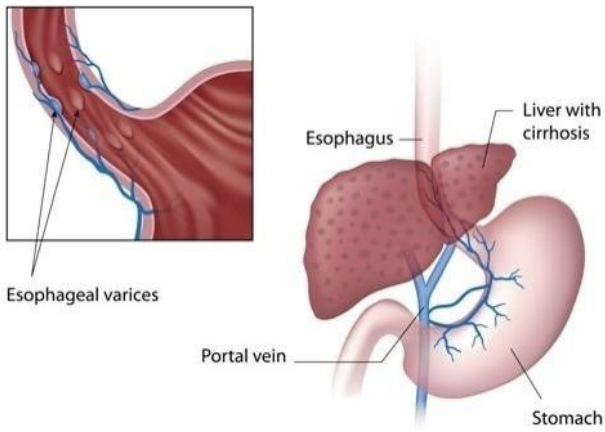
Esophageal varices, enlarged submucosal veins connecting portal and systemic circulations, are a critical consequence of portal hypertension, often associated with cirrhosis. The risk of variceal rupture and bleeding becomes significant when hepatic venous pressure gradient (HVPG) exceeds 12 mmHg, highlighting the importance of early diagnosis and management. Superior endoscopy remains the gold standard for diagnosing esophageal varices, particularly in cirrhotic patients, with varices present in 60% of decompensated and 30% of compensated cases. The risk of bleeding from esophageal varices is closely correlated with variceal size and morphology. Treatment options encompass non-selective β blockers, endoscopic band ligation, and vasoactive agents like octreotide, terlipressin, somatostatin, and vasopressin, which aim to reduce portal pressure. Early administration of vasoactive agents is crucial for confirmed or suspected variceal bleeding and should continue for 2-5 days, with potential early cessation if the patient undergoes a transjugular intrahepatic portosystemic shunt (TIPS) procedure. The literature review delves into the pathophysiology of esophageal varices, emphasizing their role as portal-systemic collaterals and the complications arising from variceal bleeding. Laplace's law is discussed as a determinant of variceal rupture, with increased intravariceal pressure and reduced wall thickness contributing to this phenomenon. Various diagnostic modalities, including endoscopy, transient elastography, and imaging techniques like CT scan and Doppler sonography, are explored for their role in assessing variceal risk and evaluating portal hypertension. Management of esophageal varices involves a three-stage approach: prevention of initial bleeding, acute bleeding management, and prevention of rebleeding. Pharmacologic, endoscopic, and shunt therapies are considered, with a focus on the efficacy of long-acting somatostatin analogs and terlipressin in

controlling variceal bleeding. Antibiotic prophylaxis is recommended to reduce the risk of rebleeding, and non-selective β blockers are explored as an essential component of treatment. Endoscopic treatments, including endoscopic sclerotherapy (EST) and band ligation (EBL), aim to reduce variceal wall strain and promote variceal obliteration. The significance of spontaneous hemodynamic responders to endoscopic treatments is highlighted, suggesting potential synergies with beta-blockers for enhanced efficacy. This comprehensive review provides valuable insights into the complex landscape of esophageal varices in portal hypertension, emphasizing the multifaceted approach required for their diagnosis and management.

INTRODUCTION

Esophageal varices are enlarged submucosal distal esophageal veins associating the portal and fundamental flows. They structure because of portal hypertension, which usually is a consequence of cirrhosis, protection from portal blood stream, and expanded portal venous blood inflow **(Meseeha and Attia, 2023)**. In cirrhotic patients, the security flow starts to create when HVPG transcends 10 mmHg. At the point when HVPG is raised over 12 mmHg, there is a critical risk of variceal crack and bleeding.

Superior endoscopy is the only way to diagnose esophageal varices and is obligatorily when a liver cirrhosis is diagnosticated, considering that esophageal varices are present in 60% of decompensated cirrhosis and 30% of patients with compensated liver cirrhosis **(D'Amico et al., 1986).** Platelet count decrease, splenomegaly, portal vein dilatation, perisplenic circulation or ultrasound visible collateral, reduced portal flow velocity at Echo-Doppler may be suggestive of portal hypertension **(Săftoiu and Ciurea., 2003).** Regarding esophageal varices, regardless of the staging, the endoscopic description of the esophageal varices correlates the increased risk of bleeding with two criterion: the size and the form of the variceal vein. Treatment options include non- selective β blockers for varices, irrespective of size, or endoscopic band ligation for medium or large varices. Vasoactive agents such as octreotide, terlipressin, somatostatin, and vasopressin cause splanchnic vasoconstriction and thus reduce portal pressure. All patients with confirmed or suspected variceal bleeding should be started on vasoactive agents as early as possible and should be continued for 2-5 d. They can be stopped early if the patient undergoes a TIPS procedure **(Boregowda et al., 2019).**



REVIEW OF LITERATURE

Esophageal varices are Porto-systemic collaterals — i.e., vascular channels that interface the portal venous and the systemic venous circulation. They structure as an outcome of portal hypertension (an ever-evolving complexity of cirrhosis), specially in the sub mucosa of the lower esophagus. Burst and draining from esophageal varices are significant inconveniences of portal hypertension and are related with a high death rate. Variceal draining records for 10-30% of all instances of upper gastrointestinal bleeding. The elements anticipating the gamble of variceal drain incorporate the size of the varix, red variety signs, and the level of weakening of liver capability **(Jalihal et al., 2019).**

Variceal crack is represented by Laplace's regulation. Expanded wall strain is the final product of expanded intravariceal pressure, expanded width of the varices, and diminished wall thickness. The variceal wall thickness can be assessed outwardly by the presence of red wale markings. These markings reflect regions where the wall is particularly slim. Variceal break frequently happens at the level of the gastroesophageal intersection where the varices are exceptionally shallow and in this way have more slender walls **(Hilzenrat et al., 2012).** The disintegration speculation recommended that variceal hemorrhage came about because of an external trauma dissolving the dainty and delicate mass of the varices. Esophagitis and resulting ulceration were the most commonly proposed erosives, albeit a few different elements, like deglution of strong food, were likewise embroiled. Nonetheless, this hypothesis has been deserted due to absence of goal supporting evidence. As of now, most authors acknowledge the explosion hypothesis, that proposes that the primary component prompting rupture of the varices is the expanded hydrostatic strain inside the varix and its following outcomes, expanding variceal size and decreasing the thickness of its wall. Many examinations have shown that variceal bleeding doesn't happen on the off chance that the

PPG isn't more prominent than 12 mmHg. Conversely assuming the PPG is diminished to under 12 mmHg - through pharmacological therapy. TIPS or spontaneously - there is complete security from the gamble of bleeding, the varices decline in size and may even disappear. Likewise patients diminishing the HVPG significantly (for example over 20% from benchmark values) have an extremely generally safe of further variceal bleeding, regardless of whether their last HVPG still more prominent than 12 mmHg. The presentation and approval of techniques for the estimation of variceal pressure has permitted interesting perceptions in patients with portal hypertension. The utilization of pressure -sensitive gauge permits a precise, re- producible estimation of variceal tension at endoscopy. Past examinations from our lab utilizing this strategy show that, despite being essentially co-related, variceal pressure is fundamentally lower than portal pressure, most likely in view of a critical opposition along the guarantees taking care of the varices, which causes a tension drop from the portal vein to the varix. These outcomes propose that collateral circulation (and protection from blood stream in collaterals) is a significant component modulating variceal pressure. Patients who have drained from varices have bigger varices than the people who have not. Moreover, the gamble of draining is straightforwardly related with the size of the varices. Nonetheless, around 20% of patients with variceal discharge have "small" varices (of under 5 mm in assessed diameter). In any case, endoscopy isn't the most ideal strategy for estimating variceal size. Endosonography permits more goal and exact estimations of variceal size. Variceal draining is remembered to happen when the tension applied over the dainty mass of the varices goes beyond a not entirely set in stone by the versatile furthest reaches of the vessel. At the end of the day, the progressive vessel distension produces a rising protection from further distension (wall tension). While arriving at the flexible furthest reaches of the vessel, the variceal wall can't expand its protection from additional dilatation, prompting variceal rupture**(Berzigotti et al., 2001).**

By CT scan: The CT pictures were checked on to identify the presence of highrisk esophageal varices with a 4-point certainty scale for the improvement of variceal draining as per their greatest width (scores 1-4): most certainly okay or no varices; likely generally safe;) presumably high-hazard; and most certainly high-risk. The maximal short-hub width of the biggest upgrading varix was estimated by the utilization of an electronic caliper on one-design PACS pictures. A certainty score of 4 was relegated in the event that the width was most certainly >3 mm, a score of 3 assuming the breadth was somewhere in the range of 2 and 3 mm, a score of 2 on the off chance that the measurement was somewhere in the range

of 1 and 2 mm and a score of 1 in the event that the width was <1 mm 11, 12. A limit of ⩾ 2 mm was utilized for segregation between high-risk (score 3 or 4) and low- risk varices (score 2). Cases with no Esophageal varices or exceptionally generally safe i.e., <1 mm (score 1) were isolated in a singular gathering. Esophageal varices were reviewed by endoscopy into 4 grades as indicated by their size, and the presence of mucosal red signs (i.e., red wale, hemocystic, or cherry red spots). Grade 3 was picked as an endpoint to characterize high-risk varices, in view of the likelihood to foster esophageal bleeding. Cases with somewhere around one of the accompanying rules were characterized as high gamble: any grade III or IV, mucosal red signs, and suggestion of endoscopic or clinical prophylactic treatment (**Moftah et al., 2014).**

Grade I: varices that vanish with insufflation of air, Grade II: varices that don't vanish with insufflation of air with sound in the middle between; they are non-blended and take up short of what 33% of the esophageal lumen, Grade III: huge intersecting varices possessing more than 33% of the esophageal lumen that don't vanish with insufflation of air **(Cushman et al., 2018).**

Paleness: Hemoglobin might be ordinary in dynamic draining and may require six to 24 hours to equilibrate. Different reasons for weakness are normal in cirrhotics. Thrombocytopenia is the most delicate and explicit lab parameter that relates with port hypertension and large esophageal varices, Elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin; prolonged PT, low albumin recommend cirrhosis, BUN is much of the time raised in GI bleed, Sodium level might drop in patients treated with terlipressin, Coagulation profile, Renal capability, Arterial blood gas, Hepatitis serology. Esophagogastroduodenoscopy can recognize effectively bleeding varices as well as enormous varices and blemish of ongoing bleeding, can be utilized to treat bleeding with esophageal band ligation (liked to sclerotherapy); forestall rebleeding; distinguish gastric varices, entrance hypertensive gastropathy; analyze elective draining locales, can recognize and treat non bleeding varices (protuding submucosal veins in the distal third of the esophagus).Transient elastography (TE) for recognizing CLD patients in danger of growing clinically critical portal hypertension (CSPH)Hepatic vein pressure gradient (HVPG) more prominent than 10 mmHg is the best quality level to analyze CSPH (typical: 1 mmHg to 5 mmHg)HVPG reaction of equivalent or more noteworthy than 10% or to not exactly or equivalent to 12 mmHg to intravenous propranolol may distinguish responders to

nonselective beta-blocker (NSBB) and is connected to a critical lessening in hazard of variceal bleeding Video capsule endoscopy screening might be an option in contrast to conventional endoscopy Doppler sonography (second line): shows patency, measurement, and stream in the portal and splenic veins, and guarantees; delicate for gastric varices; records patency after ligation or transjugular intrahepatic portosystemic shunt (TIPS)CT or X-ray angiography (second-line, not daily practice): shows huge vascular diverts in abdomen, mediastinum; exhibits patency of intrahepatic entry and splenic vein Venous-stage celiac arteriography: exhibits portal vein and collaterals; analyzed hepatic vein occlusion Portal pressure estimation involving a retrograde catheter in the hepatic vein. Ultrasound of the abdomen might uncover biliary obstacle **(Meseeha et al., 2023).**

The board of varices can be ordered into three stages: 1) counteraction of initial bleeding, 2) the executives of acute bleeding, and 3) anticipation of rebleeding. Modalities for treatment incorporate pharmacologic, endoscopic, and shunt treatment. For the avoidance of first variceal drain, cirrhotic patients ought to go through endoscopy to distinguish patients with huge varices. Need for evaluating for varices ought to be given to patients with low platelet count, splenomegaly, and advanced cirrhosis (**Zaman, 2003).**

The standard portion of somatostatin is a bolus infusion of 250 ug followed by continuous infusion of 250 ug/h. A higher portion of 500 ug/h with a few bolus infusions was exceptionally fruitful in controlling bleeding and brought about expanded endurance.' A disadvantage of somatostatin is its short half life in vivo: 1.1-3.0 min in ordinary subjects and 1.2-4.8 min in patients with chronic liver disease. hence requiring a ceaseless imbuement to get sufficient plasma levels. This issue was tackled with the improvement of long-acting somatostatin analogs including octreotide, lanreotide, vapreotide and seglitide. The standard portion of octreotide is 50 g bolus infusion followed by 25-50 ug/h. Viability of octreotide in intense variceal bleeding has not been sufficiently surveyed in double-blind trials. Vasopressin is the most strong splanchnic vasoconstrictor. It lessens blood stream to every single splanchnic organ, prompting an optional reduction in portal venous inflow and portal pressure. In any case, these equivalent powerful vasoconstrictive properties limit the clinical handiness of vasopressin. Its utilization is related with numerous after effects, including cardiac and peripheral ischemia, dysrhythmia and hypertension, with a general withdrawal pace of up to 25%. Albeit the relationship with nitrates works on the viability and decreases intricacies of vasopressin, aftereffects are still altogether higher than those of terlipressin or

somatostatin and its analogues. Hence, it stays the last decision among pharmacological treatment (**Reynaert et al., 2003).** Octreotide diminishes the inflow of blood to portal framework by tightening the splanchnic arterioles and essentially lessens intravariceal pressure. Octreotide in a portion of 50 microgram intravenous bolus followed by a continuous infusion of 50 microgram each hour for 48 hours and emergency sclerotherapy have been viewed as similarly successful in the control of variceal bleeding. This study proposes that octreotide can be regulated when infusion sclerotherapy isn't available and is most likely likewise helpful for repetitive bleeding after sclerotherapy. Terlipressin is a synthetic analogue of vasopressin with longer movement and less incidental effects. It diminishes portal pressure and its belongings are as yet critical 4 hours after administration. The general viability of terlipressin in controlling variceal draining is 75%-80% at 48 hand 67% at 5d. Terlipressin has been displayed to altogether further develop control of bleeding and endurance when contrasted with placebo and is the main medication that has displayed to further develop endurance. Nonetheless, terlipressin can incite ischemic complication and serious dysrhythmia. In this manner, it ought to be utilized with intense caution or even kept away from in those patients with a background marked by ischemic heart or cerebral disease. Disease is areas of strength for a marker in intense variceal dying, both for rebleeding and mortality. Anti-microbial prophylaxis has been displayed to diminish the gamble of rebleeding and mortality in intense variceal bleeding. Antibiotic prophylaxis ought to be established from confirmation and the presence of contamination ought to be examined. Norfloxacin, 400 mg/12 h, is the best option antibiotic prophylaxis because of its more straightforward organization and lower cost. This ought to be a nonselective one, acting both on 1 cardiovascular receptors and 2 vascular receptors. There appears to be no distinction in the adequacy of propranolol and nadolol, the just nonselective - adrenergic blockers tried in clinical preliminaries.

In the full insight, bigotry to one might be overwhelmed by moving to the next. Nadolol might be more helpful since it is administered one time per day, and because of its lowlipid dissolvability might have lower potential for focal aftereffects (**Chaudhary et al., 1997).** Endoscopic treatments for varices plan to lessen variceal wall strain by obliteration of the varix. The two head techniques accessible for esophageal varices are endoscopic sclerotherapy (EST) and band ligation (EBL). Endoscopic treatment is a neighborhood treatment that has no effect on the pathophysiological components that lead to portal hypertension and variceal rupture. In any case, an unconstrained decline in HVPG happens in

around 30% of patients treated with one or the other EST or EBL to forestall variceal rebleeding. It has been shown that patients with such an unconstrained hemodynamic reaction require less meetings of endoscopic treatment until variceal obliteration, and have a higher pace of variceal destruction than patients treated with endoscopic techniques who have no unconstrained response. Besides, spontaneous responders have an essentially lower likelihood of rebleeding and better endurance. These information propose that adding beta-blockers to endoscopic treatment might upgrade the adequacy of treatment by expanding the pace of hemodynamic responders **(Cordon et al., 2012).**

AIM AND OBJECTIVE

Aim: The primary aim of this analysis is to investigate Esophageal Varices, focusing on unraveling the optimal management strategies for achieving enhanced treatment outcomes.

Objective: The study aims to unravel optimal management strategies for Esophageal Varices.

MATERIAL AND METHODS

Study design and site: Patients of esophageal varices reporting at tertiary care hospital, Rajsamand.

Study population: Adult patients with Esophageal Varices who were being treated in a tertiary hospital were included in the investigation's study population.

Study material: Data was collected from old case records of medical record department.

Data was collected from patients reporting to general medicine between November 2022 to April 2023.

Study Duration

6 Months Prospective and 2 Years Retrospective.

Inclusion Criteria

Male or female subject aged between 18 -70yrs.

Subject with diagnosis of Esophageal Varices (based on clinical, laboratory, endoscopic and ultra sonographic features.)

Subject who has been hospitalized for Esophageal Varices

Exclusion Criteria

Below 18 years

Pregnant women and lactating women.

Patients on other medication (AYUSH)

Patients having no diagnostic evidence of cirrhosis.

STUDY PROCEDURES

Study was retrospective and prospective, of patients of Esophageal Varices reporting at Ananta Institute of Medical Sciences and Research Centre. Data will be collected from case records of patients maintained in medical record department and also from general medicine department.

Data collection sheets were prepared which included the details of patient's, such as name, age, sex, including relevant history, examination details, diagnostic test (USG abdomen, endoscopy, CT SCAN, MRI) and laboratory investigation including level of serum SGOT, SGPT, serum total bilirubin, serum albumin, AG ratio, platelet count and PT- INR was collected and recorded.

Mentioned data was compiled and analyzed to record incidence and prevalence of liver cirrhosis during the duration mentioned. Analysis was also done to check the comorbidity occurring in such patients. It was further analysed to find out the treatment options.

INVESTIGATIONS FOR ESOPHAGEAL VARICES

1) Esophagogastroduodenoscopy

A procedure done to examine the lining of the esophagus, stomach, upper part of the small intestine, i.e, duodenum.

2) Endoscopy

Endoscopic exam. A procedure called upper gastrointestinal endoscopy is the preferred method of screening for esophageal varices.

RESULTS

Table 5.1: Laboratory Investigations With Their Reference Range.

LABORATORY INVESTIGATIONS	NORMAL RANGE
Hb(g/dl)	11.5- 14.5 g/dl
TLC(10*3 cells/mm*3)	4.0- 11.0 (10*3 cells/mm*3)
PLA(per mlc)	150-400 10*3 cells/ul
BT(mg/dl)	0.2-1.3 mg/dl
BD/BI	0-0.3 / 0.0-1.1 mg/dl
SGPT(U/L)	13-41 U/L
SGOT(U/L)	5-35 U/L
Na(mmol/L)	136-145 mmol/L
K(mmol/L	3.5-5.1mmol/L
ALB(g/dl)	3.2-5.0 g/dl
GLO(g/dl)	2.3-3.6 g/dl
A/G	1.2-1.5
PT (secs)	12-4 secs
INR (secs)	0.85- 1.15 sec
S.Cr (mg/dl)	0.7-1.4 mg/dl

Table 5.2: Biochemical Parameters of Patients With Liver Cirrhosis.

S. NO.	PARAMETERS	MEAN ± SD
1	HAEMOGLOBIN	9.73 ± 2.75
2	TOTAL LEUKOCYTE COUNT	9.94 ± 14.08
3	PLATELET COUNT	255.58 ± 824.40
4	BILURIBIN TOTAL	2.7 ± 4.34
5	SGPT	40.3 ± 46.08
6	SGOT	64.38 ± 64.71
7	SODIUM	134.29 ± 9.00
8	POTASSIUM	4.53 ± 4.11
9	ALBUMIN	2.69 ± 0.92
10	GLOBULIN	3.45 ± 1.13
11	PT	18.77 ± 5.76
12	INR	1.58 ± 1.43
13	SERUM CREATININE	1.59 ± 2.51

Table 5.3 Incidence of Cirrhosis By Age Group.

AGE GROUP	21-30	31-40	41-50	51-60	61-70	71-80
NO. OF CASES	**9**	**19**	**29**	**21**	**16**	**6**
Mean Age	49±13.896					

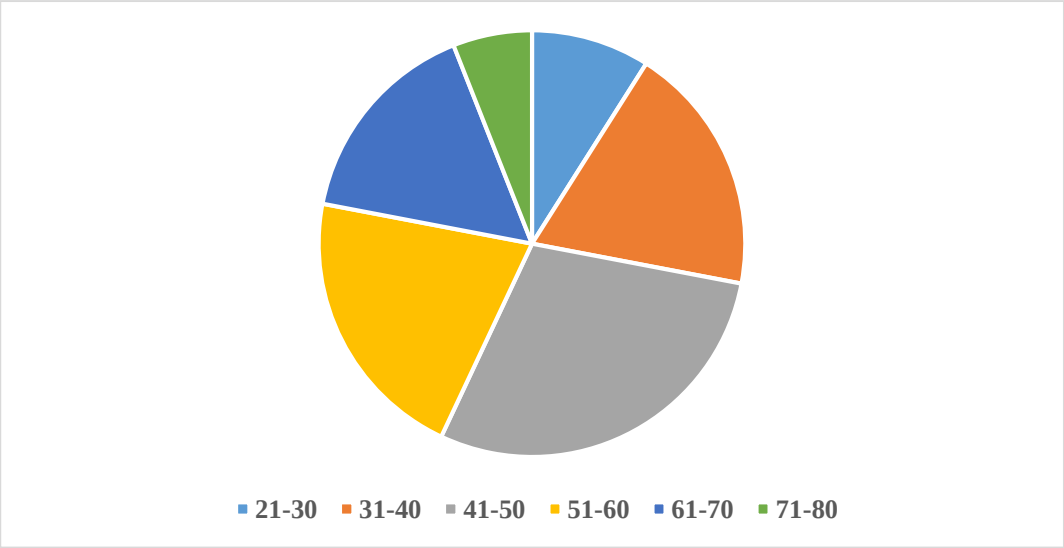


Fig. 5.1: Incidence of Cirrhosis By Age Group.

Table 5.4: Distribution of Cases According To Severity of Anaemia.

NORMAL HB RANGE (12-16 g/dl)	**22**
MILD(10.1-11.9 g/dl)	**23**
MODERATE(8-10 g/dl)	**36**
SEVERE(6.5-7.9g/dl)	**19**

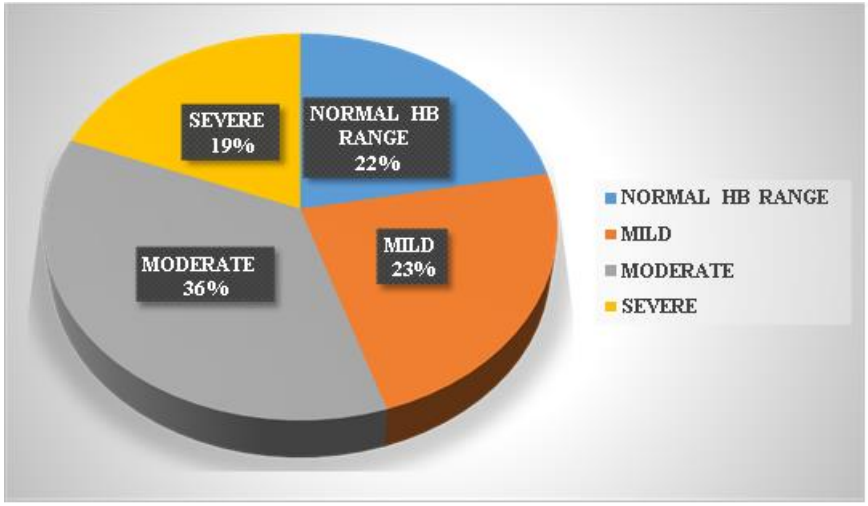


Fig. 5.2: Severity of anaemia.

TREATMENT MODALITIES

In our study of 100 patients with liver cirrhosis, we assessed the treatment modalities used for managing the condition. The distribution of treatment options among the patients is as follows:

1. **Beta blockers**: 38 patients (38%) received beta blockers as part of their treatment. Beta blockers are primarily utilized to reduce portal hypertension, a condition in which there is

increased pressure in the portal vein system. By decreasing portal pressure, beta blockers help prevent or manage complications such as variceal bleeding.

2. **LOLA (L-ornithine L-aspartate)**: 21 patients (21%) received LOLA as part of their treatment. LOLA is a medication that helps reduce ammonia levels in the blood and is commonly used in the management of hepatic encephalopathy.
3. **Ursodeoxycholic acid**: 33 patients (33%) were treated with ursodeoxycholic acid. Ursodeoxycholic acid is a medication that aids in the management of certain liver conditions, such as primary biliary cholangitis, by improving bile flow and reducing liver inflammation.
4. **Terlipressin**: 9 patients (9%) were treated with terlipressin. Terlipressin is a vasoconstrictor that is often used in the management of acute variceal bleeding, as it helps reduce portal pressure and control bleeding.

Table 5.5: Treatment Modalities.

DRUGS	NO. OF CASES
BETA BLOCKERS	38
LOLA	21
Ursodeoxycholic acid	33
Terlipressin	9

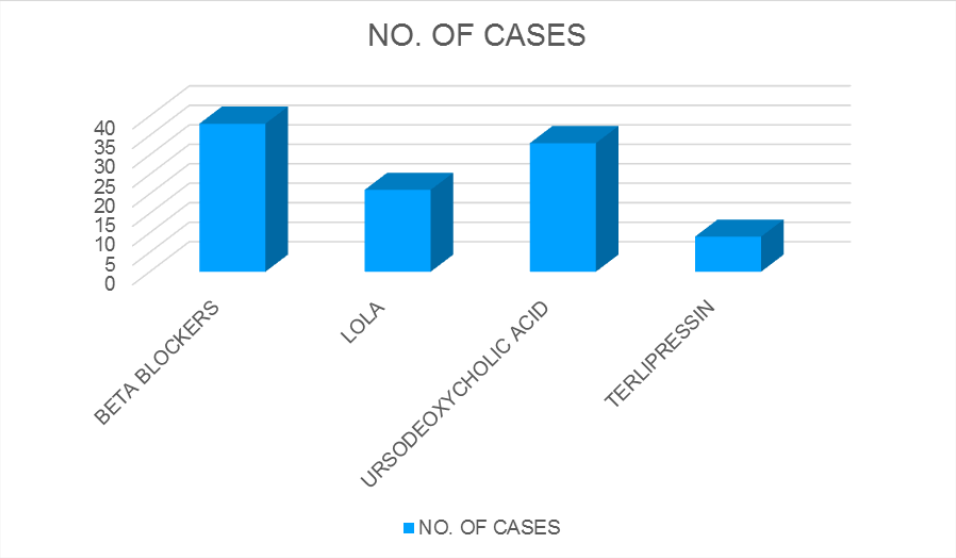


Fig. 5.3: Treatment Modalities.

CONCLUSION

In conclusion, liver cirrhosis is a progressive condition characterized by the development of fibrosis and nodular transformation of the liver tissue, resulting from persistent injury. It can be caused by various factors such as viral infections, toxins, genetic disorders, or autoimmune

processes. The major complications associated with cirrhosis include varices, ascites, hepatic encephalopathy, portal hypertension. Esophageal varices, dilated submucosal veins in the distal esophagus, are a common complication of cirrhosis and pose a risk of bleeding.

REFERENCES

1. Berzigotti A, Escorsell A, Bosch J. Pathophysiology of variceal bleeding in cirrhotics. Annalsgastro.gr, 2001 [cited 2023 Jul 10].
2. Boregowda U, Umapathy C, Halim N, Desai M, Nanjappa A, Arekapudi S, et al. Update on the management of gastrointestinal varices. World J Gastrointest Pharmacol Ther [Internet]. 2019 [cited 2023 Jul 10].
3. Chaudhry R, Singh B, Subhas P. Octreotide in gastroenterology. Med J Armed Forces India [Internet], 1997 [cited 2023 Jul 10]; 53(4): 293–4.
4. Cordon, J. P. Endoscopic management of esophageal varices. World Journal of Gastrointestinal Endoscopy, 2012; 4(7): 312. https://doi.org/10.4253/wjge.v4.i7.312
5. D'Amico G, Morabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. Digestive Diseases and Sciences, 31(5): 468–475.
6. Hilzenrat N, Sherker AH. Esophageal varices: pathophysiology, approach, and clinical dilemmas. Int J Hepatol [Internet]. 2012 [cited 2023 Jul 10], 2012: 795063.
7. Jalihal U, Shivalingaiah P, Bale A. Management of acute variceal bleed by esophageal variceal ligation in an unconventional position—an urban-center insight. J Dig Endosc [Internet], 2019; 10(04): 213–8.
8. Meseeha, M., & Attia, M. Esophageal Varices. StatPearls Publishing, 2023.
9. Moftah SG, Kamal S, Hanna ATK. CT esophagography: Non invasive screening and grading of esophageal varices in cirrhosis. Egypt J Radiol Nucl Med [Internet], 2014; 45(2): 263–70.
10. Reynaert H, Geerts A. Pharmacological rationale for the use of somatostatin and analogues in portal hypertension: REVIEW: USE OF SOMATOSTATIN IN PORTAL HYPERTENSION. Aliment Pharmacol Ther [Internet], 2003; 18(4): 375–86.
11. Săftoiu, A., & Ciurea, T. Hemoragiile digestive superioare non-variceale, 2003; 645–673.
12. Zaman A. Current management of esophageal varices. Curr Treat Options Gastroenterol [Internet], 2003; 6(6): 499–507.