ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES

DEPARTMENT OF SURGERY

Surgical outcome of open Liver resection for HCC: A Multi-Center Prospective study, an Experience from Low Income Country.

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Declaration

I, **Yitagesu Aberra Shibiru**, hereby declare that this research paper is a result of the work of mine, except where credit is given in review of this paper by my advisor.

Acknowledgement

I am deeply grateful to my supervisor **Dr. Zeki Abdurrahman** for his critique, support and guidance.

Secondly, my heartfelt appreciation goes to my colleagues, HPB surgery consultants and member of the Department of surgery and Radiology at Addis Ababa University, Addis Ababa, Ethiopia**.**

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Abbreviations

HCC-	Hepatocellular carcinoma
HBsAg-	hepatitis B surface antigen
HCV	-hepatitis C virus
PHLF-	post-Hepatectomy liver failure
PHH-	post Hepatectomy hemorrhage
HIV-	Human Immunedeficiency Virus

Abstract

Introduction

The most common primary malignant liver tumor is hepatocellular carcinoma.it commonly occurs in cirrhotic liver caused by viral infection. There are different management options depending on the tumor burden, performance status of the patient and status of background liver. Liver resection is one of them, with a cure intent intervention, which is the only option we have in Ethiopia. The morbidity and mortality associated with liver resection is decreasing with advent in surgical techniques and improved post-operative care in developed nations.in Ethiopia hepatic resection has been done for decade but its outcome never been studied before. This research will be the first to assess hepatic resection outcome for HCC and serve as a mirror to see the outcome of our surgical practice and compare our stance in the realm of hepatic resection and HCC care**.**

Objective of the study

Evaluate Post-operative morbidity and length of hospital stay of hepatic resection for HCC at different tertiary hospitals in Addis Ababa between June, 2022 and June, 2024 GC.

Methodology of the study

A Two-year prospective multi-center cohort study was conducted from June, 2022 - June 2024 at tertiary referral hospitals in Addis Ababa. Descriptive analysis was done using frequency and cross tabulation parameters. univariate and multivariate logistic regression was done to see association between post-operative complication and independent variables whereas multiple linear regression was used to see association between length of hospital stay and independent variables**.**

Result

There were 101 patients analyzed who undergone Hepatic resection for HCC in the study population. the mean age was 57.42yrs with equal sex distribution. Hypertension (23.8), diabetes mellitus (17.8) and viral infection (39.6%) are the most common comorbidities and risk factor identified. most are right side (58.4%) solitary tumor (79.2%) with a mean tumor size of 6.74cm occurring in Cirrhotic/fibrotic liver in 47.5% of the case. With a rate of higher major (34%) resection and Non-anatomic resection (22.8%) a mean intraoperative blood loss of 849.01 (SD=472.915), transfusion rate of 51.8%, mean intra-operative fluid intake of 2289.74 (SD=809.937) was identified and took a mean operative time of 2.90hr (SD=0.943). there were

48.8% complication rate and most of them were Minor (CD Grade 1 and 2=83.1%) and procedure related complications (79.8%) with hepatic insufficiency/failure being the most common specific complication (22.8%). Major resection (AOR=2.576, P-value-0.002), right Hepatectomy (AOR=2.676, P-value <0.001), blood transfusion (AOR=23.18, P-value <0.001) and amount of blood transfusion (AOR=1.33, P-value <0.001)) were significantly associated with post-operative complications. Whereas, operative time (p-value -0.051), non-anatomic resection (p-value-0.005), and presence of complication (p-value-0.028) were associated with a higher post-operative hospital stay with our mean length of hospital stay of 6.04days (SD=2.872).

Conclusion

Post-operative complications were higher and it is strongly associated with Surgical factors. yet there is comparable Post-operative length of Hospital stay. Improving surgical care will reduce complication.

Key words

Hepatic resection, Hepatocellular carcinoma, surgical outcome, Post-Hepatectomy liver failure, liver.

Introduction

Background of the problem

Hepatocellular carcinoma (HCC) is a malignant epithelial tumor originating from hepatocytes and consisting of liver cell-like but abnormal cells with a basic histologic structural finding of a tumor cell having trabecular arrangement surrounding sinusoidal lamina. At the beginning of the twentieth century, hepatocellular cancer (HCC) was thought to be uncommon, and almost nothing was known of its origin or pathogenesis and treatment option. At the end of the century and in the early 21st century, however, HCC is one of the major malignant diseases worldwide. Its' principal risk factors have been identified, pathogenesis elucidated, different management options and prevention modalities are on table.[1]

Epidemiologically HCC is the 6th most common new cancer case and the 2nd leading cause of cancer related death worldwide. And it is among the top ten new cancer case and the 2nd leading cause of cancer related death in ETHIOPIA.[2] Those countries living in sub-Saharan region are among the highest risk area for HCC with an average annual incidence between 25-100/100,000. There is geographical variation in the incidence of HCC probably related with the different geographical distribution of risk factors.[3]

Worldwide chronic viral (B+-D, C) infections, alcohol, Aflatoxin, insulin resistance stats, metabolic liver diseases and obesity are said to be the common risk factor for the development of HCC. In high incidence areas chronic viral infection is the most common cause with more than 60% of HCC cases being HBsAg positive. Liver cirrhosis is a precancerous condition and each patient with liver cirrhosis, irrespective of its etiology carries an increased HCC risk.[4]

If an HCC patient present with a clinical symptom, then the disease is at an advanced stage. Most of patients with HCC are asymptomatic. Symptoms of HCC are non-specific, like sense of epigastric fullness, pressure, abdominal swelling and significant weight loss. Since 90% HCC patients develop in a background cirrhotic liver, patients will have symptoms related with the underlying chronic liver disease. Few patients may present with complications related with bleeding, local compression of adjacent structures and jaundice due to diffuse parenchymal infiltration. Occasionally patients might present with Para neoplastic syndromes like hypoglycemia, erythrocytosis and hypercalcemia. And around 13% of patients will have extra hepatic metastasis.[5]

Diagnosis of HCC depends upon either the presence of a typical imaging finding, a liver mass with arterial enhancement and washout on subsequent phases with delayed phase rim enhancement, or histopathology finding suggestive of HCC. Serum tumor markers like AFP, CEA, liver transaminases, ALP, GGT, TBILL, DBILL, coagulation profile, viral markers, serum albumin, and sign and symptoms of portal hypertension must be checked. Performance status of the patient the presence of comorbidity and nutritional status of the patient are also essential in the management of this patients.[6]

There are different scoring systems in practice to help guide management and prognosticate the outcome of HCC. But there is disagreement how best to stage and characterize this tumor despite enormous discussions and validation studies. This made standard and uniform staging and management protocols to be absent. There are scoring systems used to assess the underlying liver function in cirrhotic liver. These are Child-Pugh (CTP) and Model for End Stage Liver Disease(MELD-Score). The other group of scoring system is to assess the burden of the tumor. These are the TNM staging, BCLC staging, Okuda staging and others. Currently the most widely used staging system is the BCLC staging system which takes the size and number of the tumor plus the CTP score of the liver and performance status of the patient in to consideration.[7] Historically, the treatment of HCC was complicated by the late presentation of patients at an advanced stage of the tumor. But current advances in imaging and strict surveillance made those patients to present early. Plus, the presence of those scoring system helped in shaping the management of HCC. The major advantage of the BCLC system is that it can be used to identify the patients with early-stage HCC, who may benefit from curative therapies from those patients with advanced-stage disease who would benefit more from palliative treatment but has a drawback in identifying appropriate treatment for those in intermediate stage. Management options for curative intent in early stage tumors as per the BCLC staging system are Ablation, surgical resection and liver transplantation whereas for palliative treatment are loco regional treatment like TACE, TARE, PTEI, and Systemic therapies.[8]

Surgical resection is one of the curative management option for patients with HCC having a specific characteristics mentioned on BCLC staging system like single in number, small in size, good performance status ,ECOG 0, and CTP score of A. the presence of portal hypertension depicted either through HVPG >=10mmgh or clinical surrogate markers like splenomegaly

above 12cm or platelet <100,000/mm3 is a contraindication for resection as resection might lead to liver decompensation in cirrhotic liver.8 The resectability rate in western has reached up to 37% and 20% in japan, but in low income countries like Uganda the resectability rate is only 8%.[9]

Through advances in perioperative care, development of new technologies to assist surgical resection, better understanding of the surgical anatomy of the liver and new invention of imaging modalities, post resection outcome has improved. With a 5-year survival being 58% and 71% with and without portal hypertension, resp. recurrence is also one of the feared complications with a rate of 70% at 5-years. other complications are liver failure, bile leakage, hemorrhage and infection just to mention a few.[10]

There are factors which will influence the outcome of surgical resections. These factors are in general patient related, type of surgical resection and the status of the underlying liver. Plus, the volume of resection procedures done in the institution is said to influence the outcome.[11]

Statement of the problem

Epidemiologically HCC is the 6th most common new cancer case and the 2nd leading cause of cancer related death worldwide. And it is among the top ten new cancer case and the 2nd leading cause of cancer related death in Ethiopia.[2] those countries living in sub-Saharan region are among the highest risk area for HCC with an average annual incidence between 25-100/100,000.3 Owing to the highest prevalence of HBsAg (5.2-12.7%),HCV antibody(0.5-22%) positivity , increasing alcohol consumption(20-40%) and an exposure to aflatoxin containing food products, the burden of HCC in Ethiopia is expected to be higher than what is mentioned in those institution based articles.in addition, there is lack of awareness and low health seeking behavior supplemented by lack of access to antiviral medication and vaccination further increasing the incidence of HCC in those populations with risk factor.

HCC is a vaccine preventable disease. And WHO recommends vaccination of infants and those at risk like health care workers to prevent HBV infection. Those with HBV and HCV infection should get antiviral treatment to decrease their risk of developing cirrhosis and HCC. Proper public education on alcohol consumption, use of aflatoxin containing food products and exercise is said to decrease the incidence of HCC.

Once they develop HCC there are different management options available based on the tumor burden, performance status of the patient and condition of the background liver. These options are ablation therapies (RFA, PEI, MWA), TACE, TARE, surgical resection, liver transplantation and systemic treatment with a target from palliation to cure. The one widely available option in Ethiopia is surgical resection with RFA and TACE being practiced in few private setups. Palliation being its target, sorafenib is the only drug available in the market.[8]

Being a lonely option with curative intent available in our country, surgical resection is given in different tertiary hospital in the country in both private and government setups. Taking the limited resource available in this centers and high disease burden augmented with unfavorable tumor burden at presentation assessing the outcome of such an intervention is very important.

Literature review

Hepatocellular carcinoma is becoming one of the most common cancers worldwide with a greatest share of burden of disease being in low income countries owing to the high prevalence of risk factor in those areas. Currently there are different options of management for hepatocellular cancer in the horizon. With intent for cure, ablation, liver resection and transplantation are being done for HCC based on validated and internationally accepted criteria's or certain institution based selection criteria's. During the writing of this proposal surgical resection is the only curative intent treatment options available in the country and remains a crucial component in the multimodal treatment approach for HCC.

Numerous studies have been conducted to evaluate the surgical outcome of hepatic resection for HCC worldwide.

Patient characteristics

The median age of those patients, who undergone surgical resection for HCC follows the age trend at presentation of patients with HCC.in one retrospective article with sample size of 97 which was conducted in Ethiopia to examine the pattern of hepatic resection for any cause, the median age at resection was 50.71 and most of them were females(51.5%).[36] another retrospective study conducted to evaluate the characteristics and response to therapy of HCC patients showed a median age of 54yrs with equal gender distribution.[37] a multicenter

retrospective review done in Europe examining post-operative outcome of liver resection for HCC of 1413 patients showed a median age of 59.4yrs and most them were males(78%).[38] a retrospective study conducted with a sample size of 229 patient over 11yrs to assess liver resection outcome for HCC, the median age was 60yrs and 188 patient were males.[39]

Comorbidities

Associated comorbidities in patients with HCC is said to have an impact in their post-operative outcome. A two year retrospective multi-center study of 97 patients who undergone hepatic resection for HCC shows that 47.4% of them had comorbidities. Hypertension (23.9%) was the most common and diabetes (15.2%) cardiac (4.3%), cirrhosis (2.2%) are the other comorbidities identified.[36] a retrospective review of 888 patient ,who undergone hepatic resection for HCC over 15years ,performed to identify predictors of post-operative complications and identified diabetes mellitus (37%), hypertension (51%) , cardiac disease (13.7%) and CKD (12%).[40] retrospective study conducted with a sample size of 229 patient over 11yrs to assess liver resection outcome for HCC showed 49.8% of comorbidities with DM (28%),EG-varices (18.3%) and gallstone (9.6%) being the most common complications.[39]

Risk factor

Most patients with HCC have an underlying risk factor with viral infections, alcohols and MAFLD being the most commonly studied causative factors. Retrospective study done in Ethiopia among patient with HCC who undergone liver resection, 22% of them had risk factor with HBV (10.3%) and HCV (10.3) being the most common.36 multicenter retrospective review done in Europe examining post-operative outcome of liver resection for HCC of 1413 patients showed that among those patients with chronic liver disease 24% are alcoholic, 57% viral (HCV 58% and HBV42%) and 19% are of other causes.[38] retrospective review of 888 patient ,who undergone hepatic resection for HCC over 15years ,performed to identify predictors of post-operative complications identified that HBV(52.4%) and HCV(7.8%) are the most common risk factor.[40] Another retrospective study conducted with a sample size of 229 patient over 11yrs to assess liver resection outcome for HCC and 107 patients(46.7%) said yes for an alcohol abuse.[39]

ASA grade and Performance status

In a Retrospective study done in Ethiopia to examine the pattern of hepatic resection and postoperative outcome, 45% and 48% of patient were ASA grade 1 and 2 respectively.[36] But, in a retrospective review of 888 hepatectomy patients with HCC over 15yrs only 9% were grade 1, 70% grade 2, 19%grade 3.[40]

A retrospective assessment of 210 hepatectomy patients was done to examine the ISHLS definition of PHLF. And 206 0f 210 patients had an ECOG 0 performance status and the remaining 4 patients had ECOG of 1 performance status.[41]

Status of the liver

One of the most determinant factors affecting post-operative outcome post hepatectomy is the status of the background liver.[36] In a retrospective evaluation of 97 patients in Ethiopia only one (2%) patient was found to have cirrhosis. But a multicenter retrospective review of 1467 hepatectomy patients most of them had chronic liver disease (85%).[38] and another retrospective review of 229 hepatectomy patients also showed a 77% of cirrhosis in their study population.[39] as it is expected most of those patient with cirrhosis in the study population had CTP score of A.[36, 38, 39]

Tumor characteristics

Morphologic characteristics of the tumor are taken as one factor determining the post-operative outcome. One factor is size of the tumor and in a review of 1467 hepatectomies for HCC 53% of them had <5cm tumor size and the remaining >5cm. in this study 80% of the tumor is solitary with 50% vascular invasion. Here also those patient with an AFP of >100 were 49.8%.[38] In a retrospective study of 888 hepatectomy patients a median tumor size of 4.5cm and 3.5cm with and without complication is reported. And 86% are solitary with 25% vascular invasion and 30% had AFP >200.[40]

Surgical factors

The type of hepatectomy has a direct correlation with surgical outcome.in a review of 1467 hepatectomies done to assess post-operative outcome 77% were minor resection and 22% major resection, vascular inflow control was done in 60% of the case, and intraoperative blood transfusion was done in 65% of hepatectomies.[38] In another retrospective assessment of 229

hepatectomy patients only 15% had major resection, inflow control was done for major hepatectomies and sectionectomies(25%),.39 in a single institution based retrospective evaluation of 625 patients 12% of them had major liver resection with transfusion rate of 18%, blood loss (ml) median -1133ml(496, 2400ml).[42] in a retrospective study of 888 hepatectomy patients only 30% had major resection and 22% blood transfusion rate with a median blood loss of 500ml(200-1000).[40]

Post-operative mortality

Because of advancements in surgical techniques, post-operative ICU care and improved patient selection there is significant improvement in post-operative mortality.in a retrospective analysis of 97 hepatectomy patients of different indications, in Ethiopia, there were only (1.03%) one in hospital death.[36] but in a retrospective review of 1467 hepatectomy patients for HCC in Europe there were 142 (10.6 +-5.9%,mean mortality) deaths within one month after surgery.[38] on the other side of the world, japan, a retrospective analysis of 229 patients showed a 7% 30-day mortality rate.[39] in the same country retrospective analysis of 625 hepatectomies done over 17yrs(1985-2002) shown 19 (3%) postoperative death over the study period.[42]

Post-operative morbidity

The morbidity associated with hepatectomy has not changed for the past half a century. In a multicenter retrospective analysis of 97 hepatectomies 26.8% patients developed complications.[36] the mean morbidity rate in a retrospective multicenter evaluation of 1467 hepatectomies in Europe was 38.5 +-15% .[38] another studies in japan, a retrospective analysis of 229 patients, also showed a 20.1% complication rate.[39] in the same country retrospective analysis of 625 hepatectomies done over 17yrs (1985-2002) shown 40% post-operative complications.[42]

One of the most commonly cited classification system used to assess post-operative morbidity is the Clavien-Dindo classification system based on an article published by Daniel dindo and his colleagues.[43] in a retrospective analysis of 888 hepatectomies for HCC done in Singapore there were 27% complications of Clavein dindo grade>=2.[40]

PHLF

One of the feared complications of hepatectomy is post-hepatectomy liver failure.as per the ISGLS report the incidence of PHLF ranges between 1.2-33%.[44] in a multicenter retrospective analysis of 97 hepatectomies in Ethiopia, there were 1% of PHLF.[36] In a retrospective multicenter evaluation of 1467 hepatectomies in Europe transient liver failure ranges between 4.9-19%.[38] Another study in japan, a retrospective analysis of 229 patients, showed 6.5% PHLF.[39] In The same country, retrospective analysis of 625 hepatectomies done over 17yrs (1985-2002) shown 3.36% of PHLF.[42]

Post hepatectomy hemorrhage

In the 1970s hepatectomy were associated with high operative mortality (20%), though advances in imaging, surgical techniques and Peri-operative management improved the outcome, with hemorrhage takes the major share (20%). There were variations among published articles in the incidence of PHH (1-8%).[45] but, in a multicenter retrospective analysis of 97 hepatectomies in Ethiopia, there were 62% intraoperative blood transfusions with 17.5% primary hemorrhage making it the most common complication.[36] a retrospective analysis of 625 patients ,with hepatectomy for HCC, in japan showed 13 (2%) patients developed intraoperative hemorrhage with 18% blood transfusion rate.[42] in a multicenter retrospective evaluation of 888 hepatectomies for HCC from 2001-2016, in Singapore, 29 (3%) patients developed hemorrhage requiring either transfusion or operative intervention. and there were 21% transfusion rate.[40]

Post hepatectomy bile leak

Bile leak is one of the major procedure related post-operative complication of hepatic resection with an incidence varying between 3 and 33%.[46] but a retrospective analysis of 97 patients done in Ethiopia only one (1%) patient developed bile leak.[36] in another retrospective analysis of 625 hepatectomies for HCC in japan showed a bile leak rate of 5% (32).[42] but, in a multicenter retrospective evaluation of 888 hepatectomies for HCC from 2001-2016, in Singapore, the reported bile leakage were 0.3% (3).[40]

Post hepatectomy infection

One of the most common non-procedure related complication of hepatectomy is infection of different sites. And it was the second common complication (11.6%) in a retrospective analysis of 97 patients done in Ethiopia.[36] in a multicenter retrospective analysis of 625 hepatectomies for HCC in japan there were a 9% wound infection rate.[42] another study in the same continent with a retrospective evaluation of 888 patients over 15yrs showed a 10% infection rate (pneumonia=3.2%, wound infection=0.1%, others=6.9%).[40]

Justification of the study

Currently there are different options of management for hepatocellular cancer. These options are ablation therapies (RFA, PEI, MWA), TACE, TARE, surgical resection, liver transplantation and systemic treatment.[8]

Surgical resection is the only option currently available in the country. Despite so many years of hepatic resection of HCC practice we didn't see a research done to assess the outcome and associated factors in Ethiopia. At the time of writing this proposal there is a paper done by an HPB Fellow, not yet published, that focuses on hepatic resection outcome for different indications.

This research will assess the outcome of hepatic resection for a patient with hepatocellular carcinoma. There are papers assessing outcome of hepatic resection of hepatocellular carcinoma done in Africa.[12,13,14] but no paper yet from Ethiopia. And this article will be the first to assess the outcome of hepatic resection for HCC. This will serve as a mirror to look where our surgical practice stands as compared to others. And it also shows the gap in our hepatic resection practice.

Most of the research in hepatic resection outcome analysis used retrospective method.[12,13,14] our research will be a prospective study for the coming two consecutive years. This will improve our data quality and produce a reliable result. Being multicenter will further improve its representativeness across the country where hepatic resection is done.

Objective of the study

Primary objective

A. Evaluate Post-operative morbidity and length of hospital stay of hepatic resection for HCC at different tertiary hospitals in Addis Ababa between June, 2022 and June, 2024EC.

Secondary objective

A. Describe pre-operative and intraoperative characteristic of the tumor

B. Describe intraoperative characteristics of hepatic resection

C. Determine factors associated with higher morbidity

D. Determine factors associated with longer hospital stay

Methodology and materials

Study design,

A Two-year prospective multicenter cohort study of 101 patients.

Study setting (area and period)

The study was conducted from June 2022 up to June 2024 at Two public teaching hospitals (Tikur-ambesa specialized Teaching Hospital and Yekatit Referral Teaching Hospital) and Three high volume private hospitals (Lancet Medical and Surgical Center, Addis-Hiwot General Hospital, and Amin General Hospital), where hepatic resection for hepatocellular carcinoma is being practiced. All are found in Addis Ababa, capital city of Ethiopia where HPB Surgeons are doing the hepatic resection and both imaging and pathology service being provided by specialist in the respected field.

Study population

All patients who visited tertiary referral hospital in Addis Ababa (TASH, Yekatit referral hospital, which are government hospitals and Lancet Medical and Surgical Center, Addis-Hiwot General Hospital, Amin General Hospital which are private hospitals) for hepatectomy with a diagnosis of HCC between June 2022 and June 2024 was considered the study population.

Sample size determination and sampling procedures

All the data of patients with hepatic resection for a pre-operative diagnosis of hepatocellular carcinoma under the study period (June 2022 up to June 2024) and in the study area, were collected.

Inclusion and exclusion criteria

Inclusion criteria

A. Those patients who will undergo any type of open hepatic resection for hepatocellular carcinoma**.**

Exclusion criteria

A. Those patients who underwent open hepatic resection for other indications

B. Those who underwent laparoscopic or robotic liver resection

C. Those patients who underwent hepatic resection and turned out to be other causes intra-operatively or post operatively based on pathologic analysis

D. Those with incomplete data

Data Quality Assurance and Data Collection

All data was collected using data collection sheet by PI and HPB fellows who was given a training on the purpose of the study and the procedure to be followed during data collection by the PI of the study. Then, data was checked for completeness and consistency. Subsequently, Data was coded, entered and cleaned using Epi-info version 3.1 statistical software and exported to SPSS (statistical package for social science) version 29 for analysis.

Study variables

Independent variables

Age, sex, comorbidities (hypertension, diabetes mellitus, HIV), risk factors (viral infection, alcohol intake, fatty liver disease), ASA Grade and performance status, pre-operative hemoglobin and platelet, Pre-operative serum liver function tests, Status of background Liver, tumor characteristics (site, size, BCLC Staging, Serum AFP level, number, vascular invasion) and surgical characteristics (type of resection, inflow control, Blood transfusion, Blood loss, fluid intake and operating time)

Dependent variables

Post-operative serum hemoglobin, platelet and Liver function tests, Post- operative Death, post-operative complications and Post- operative length of hospital stay.

Data processing and analysis

Data was coded, entered and cleaned using Epi-info version 3.1 statistical software and then exported to SPSS (statistical package for social science) version 29 for analysis. Descriptive information was obtained through frequency analysis and cross-tabulations whereas association between independent variable and post-operative complication was done using both univariate and multivariate logistic regression while association between independent variable and post-operative length of hospital stay were analyzed using multiple linear regression. Correlation between length of post-operative hospital stay and operative time were done using Pearson

correlation analysis. With a confidence interval of 95%, a cut of P-value of less than 0.05 were taken for statistical significance**.**

Operational definitions

- **Type of Hepatectomy**
    - We will use the Brisbane terminology of liver anatomy and resections

      1-Right Trisectionectomy- resection of segment 4 up to 8

      2-Left Trisectionectomy-resection of segment 2, 3, 4a and b, 5, and 8

      3-Right Hepatectomy- resection of segment 5 up to 8

      4-Left Hepatectomy- Resection of segment 2,3 and 4

      5-Left Lateral Sectionectomy- Resection of segment 2 and 3

      6-Left Medial Sectionectomy- resection of segment 4a and b

      7-Right Anterior sectionectomy- resection of segment 5 and 8

      8-Right Posterior sectionectomy- resection of segment 6 and 7

      9- Segmentectomy - resection of a single segment (e.g.- segment 6 segmentectomy)

      10-Wedge resection- a non-anatomic wedge shaped resection of the liver

- **Major Hepatectomy**
    - Three and above segment resection
- **Minor Hepatectomy**
    - Less than three segment resection plus non Anatomic resection
- **Risk factor assessment**
    - Possible risk factors were assessed using history taking for alcoholic intake, serum viral marker test for Viral infection, intraoperative finding and Histology report for liver steatosis

- **ASA Grading and Performance status assessment**
    - We used ASA Grading report made by Operating team anesthesiologists and
    - We took performance status assessment made by the operating surgeon using ECOG (Eastern Cooperative Oncology Group)
- **Background liver assessment**
    - Assessment of background liver was made either through imaging or/and intraoperative surgeons examination or/and post-operative histologic evaluation**.**
- **Tumor characteristics**
    - Tumor assessment was done pre-operatively on imaging, intra-operatively by operating surgeon and post operatively by Histologic examination.
    - Maximum diameter of a single lesion and the largest (maximum diameter) of those multiple tumors were taken for size characterization.
    - BCLC Staging of the patient was made by the operating surgeon.
- **Procedure related outcome**

We will use ISGLS definition

1-Post hepatectomy liver failure (PHLF) -postoperatively acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying function was characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia (according to the normal cutoff levels defined by the local laboratory) on or after postoperative day Five.

2- Post hepatectomy Bile leak- drain/serum bilirubin ratio>3 at day 3 or the interventional/surgical revision due to biliary peritonitis

3- Post hepatectomy hemorrhage – a drop in hemoglobin level >3 g/dl post-operatively compared with the post-operative baseline level and/or any post-operative transfusion of packed red blood cells (PRBC) for a falling hemoglobin and/or the need for radiological intervention (such as embolization) and/or re-laparotomy to stop bleeding

4- Primary hemorrhage during surgery - was defined as a 3 g/dl decrease in the post transfusion hemoglobin level from the preoperative level that required transfusion without radiological or surgical intervention**.**

5 – Post hepatectomy infection: Any clinical or laboratory evidence of surgical or other site infection within 30 days of operation**.**

6- Postoperative hepatectomy ascites: postoperative daily drainage of clear ascitic fluid exceeding 200 ml/day

7- 30-day Mortality: Patient mortality within 30 days after hepatectomy**.**

8- anemia was defined based on WHO definition Post–operative serum Hemoglobin level cut off value <12g/dl

9- post hepatectomy hematoma collection is defined as imaging evidence suggestive of intraperitoneal hematoma collection but that doesn't qualify the criteria for post-hepatectomy hemorrhage.

Ethical consideration

All data and measurements obtained from this research study was stored confidentially. Only researcher will have access to view any data collected during this research. The research didn't cause any physical or psychological harm or offense and abided by all commonly acknowledged ethical codes. And also the researcher summited a proposal for ethical approval and to access the medical document of the participant**.**

Result

A two-year prospective cohort multicenter study of 101 patients to analyze peri-operative surgical outcome of hepatic resection for HCC were done. Open hepatic resection for HCC were done by consultant and fellow HPB surgeons and imaging was reviewed by consultant and fellow radiologists. All of these patients are seen at one tertiary public teaching Hospital (Tikur-Ambesa specialized hospital), and three High volume Private hospitals (Addis-Hiwot general hospital, Lancet medical and surgical center and Amin general Hospital), where HPB surgery services are being provided, between June, 2022 up to June, 2024.

1. Descriptive Part

1.1. Patient demographics

The median age of those patients, who undergone surgical resection for HCC follows the age trend at presentation of patients with HCC. The mean, median and mode of our study population were 57.42yrs, 60yrs and 70yrs, respectively. Whereas, the minimum and maximum age were 16yrs and 80yrs. The majority (78%) of our study population are above the age of fifth decade and they have almost equal gender distribution (50:51, =101).

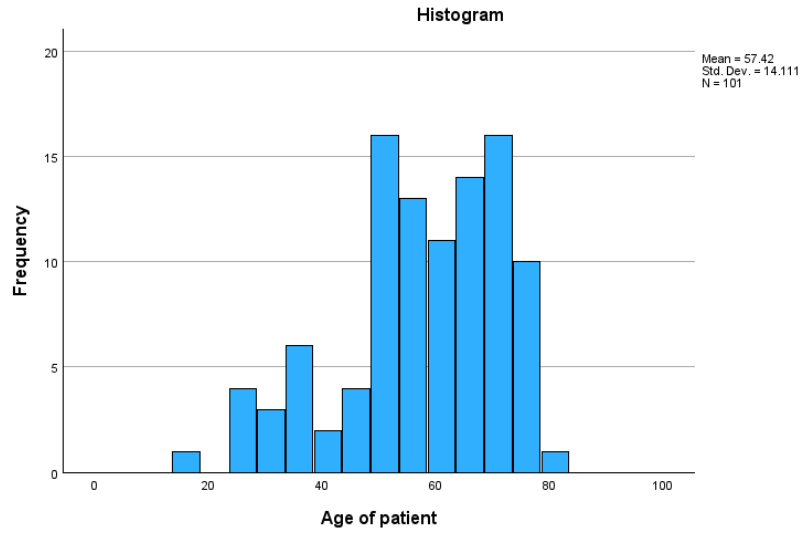


Figure 01: - distribution of age of patients

1.2. Pre-operative blood chemistry profile (n=101)

Taking the difference in laboratory values between age group, sex, different laboratory machines, and its clinical relevance in to consideration, we grouped them based on internationally accepted criteria.

	Normal range(>12g/dl)	Mild (10-12g/dl	Moderate (7-9g/dl	Severe <7g/dl	Mean /SD
Hemoglobin (g/dl)	85.1%	11.9%	3%	nil	13.95g/dl/2.3
	Normal range (10^3) (150-450)	Mild (10^3) (100-150)	Moderate (10^3) (50-100)	Severe (10^3) (<50)	
Platelet (cells/µl	94.1%	5.9%	nil	nil	265,491cell/µl/123,675.11

Table 01: - Pre-operative serum hemoglobin and platelet value frequency of study population, Addis Ababa (n=101)

The majority of the patient has a pre-operative hemoglobin (85.1%) and platelet count (94.1%) within Normal range with their mean value of 13.95g/dl, 265,491cell/µl, respectively. Similarly, almost all patients have an AST, ALT and ALP laboratory values within normal range, 93.1%, 93.1% and 92.1%, with a mean value of 26.23units/l, 22.04units/l and 70.94units/l, respectively. Whereas, using CTP- score INR, ALB and TBILL grouping criteria, nearly all patients have a preoperative INR and TBILL value of <1.7 and <2mg/dl, respectively. of those patients with TBILL <2mg/dl around 94% has <1mg/dl serum value. unlike other laboratory values serum albumin level was normal (>3.5g/dl) only in 83.2% of patients.

	Normal (10-36 units/l)	Elevated (2-3x ULN)	Mean/SD
AST(Units/L)	93.1%	6.9%	26.23units/l/20.93
	Normal (4- 30 units/l)	Elevated (2-3x ULN)	
ALT(Units/L)	93.1%	6.9%	22.04units/l/14.66
	Normal (30-120 units/l)	Elevated (2-3x ULN)	
ALP(Units/L)	92.1%	7.9%	70.94units/l/27.44

Table 02: - Pre-operative serum Liver Function test frequency of study population, Addis Ababa (n=101)

	<1.7		1.7-2.3	>2.3	Mean /SD
INR	98%		2%	nil	1.12/0.24
	>3.5 g/dl		2.8-3.5 g/dl	<2.8 g/dl	
Albumin g/dl	83.2%		16.8%	nil	3.91g/dl/0.57
	<2mg/dl		2-3mg/dl	>3mg/dl	
	<1mg/dl	1-2mg/dl			
Bilirubin (Total) mg/dl	94.1%	5.9%	nil	nil	0.72mg/dl/0.13

Table 03: - Pre-operative serum synthetic liver function test frequency of study population, Addis Ababa (n=101).

1.3. Comorbidities and Risk factors

Approximately 43.6% (44/101) of the study population has comorbidities. The most common comorbidities were hypertension (23.8%, 24/101) followed by diabetes mellitus (17.8%, 18/101) and HIV infection (4%, 4/101).

interestingly, majority of the patients were found to have risk factor (53.5%, 54/101). Viral infection (39.6%, 40/ 101) is the most common risk factor identified of which HBV (26.7%, 27/101) is the most common followed by HCV (13.9%, 14/101). Others are alcohol intake (10.9%, 11/101) and liver steatosis (8.9%, 9/101).

Variables		Frequency	Percentage
No known comorbidities		57	56.4%
Known comorbidities	Total	44	43.6%
	Hypertension	24	23.8%
	Diabetes mellitus	18	17.8%
	HIV	4	4%
	Others(CKD, COPD, Other malignancy)	3	3%

Table 04: - Comorbidity frequency table of the study population, Addis Ababa (n=101).

Variable			Frequency		Percentage	
No risk factor			47		46.5	
With risk factor	Total		54		53.5	
	Viral infection	HBsAg +ve	27	40	26.7	39.6
		HCV +ve	14		13.9	
	Hx of alcohol intake		11		10.9	
	Fatty liver disease		9		8.9	

Table 05: - Risk factor frequency table of the study population, Addis Ababa (n=101).

1.4. ASA grade and Performance status (n=101)

The majority (96.3%,97/101) of the study populations are ASA Grade I (34.7%) and Grade II (61.4%) at the time of surgery. There were ASA Grade III and Grade IIIE patient each accounting for 2% of the study population. Approximately 82.2%(83/101) of the study population were ECOG O followed by ECOG I and ECOG II accounting for 16.8%(17/101) and 1%(1/101) of the study population, respectively.

		Frequency	Percentage
ASA grade	Grade 1	35	34.7
	Grade 2	62	61.4
	Grade 3	2	2
	Grade 3E	2	2
Performance status(ECOG)	ECOG 0	83	82.2
	ECOG 1	17	16.8
	ECOG 2	1	1

Table 06: -ASA Grade and Performance status frequency table of the study population, Addis Ababa (n=101).

1.5. Status of Background Liver (n=101)

Background liver was found to have neither Cirrhosis nor Fibrosis in 52.5%(53/101) of the study population. Among those having either Cirrhotic or Fibrotic (475, 48/101) background liver, Cirrhosis is the most common (31.7%, 32/101) followed by Fibrosis (15.8%, 16/101). All patients with cirrhosis are Child-Pugh-score A, of which ALBI Grade I accounts for 90% (29/32) and ALBI Grade II accounts for 10%(3/32) of the case.

Variable			Frequency		Percentage	
Without cirrhosis or fibrosis			53		52.5	
With cirrhosis or fibrosis	Total (Cirrhosis and Fibrosis)		48		47.5	
	Fibrosis		16		15.8	
	Cirrhosis (CTP-A)	ALBI Grade 1	29	32	28.7	31.7
		ALBI Grade 2	**3**		**3**	

Table 07: - frequency table of Background Liver of the study population, Addis Ababa (n=101).

1.6. Tumor characteristics

Tumor assessment was done pre-operatively on imaging, intra-operatively by operating surgeon and post operatively by Histologic examination.

1.6.1. Number of Lesion (n=101) and Size of the lesion. (n=99, missing=2)

Approximately three-fourth of the patient (79.2%, 80/101) has a single lesion. Multiple lesion (two and above) were seen in 20.8% (21/101) of the case. The mean and median size of the tumor was 6.74cm(SD-2.534)/6cm with an asymmetric distribution ranging between 3cm up to 17cm. More than 65% of the study population has a size greater than 5cm.

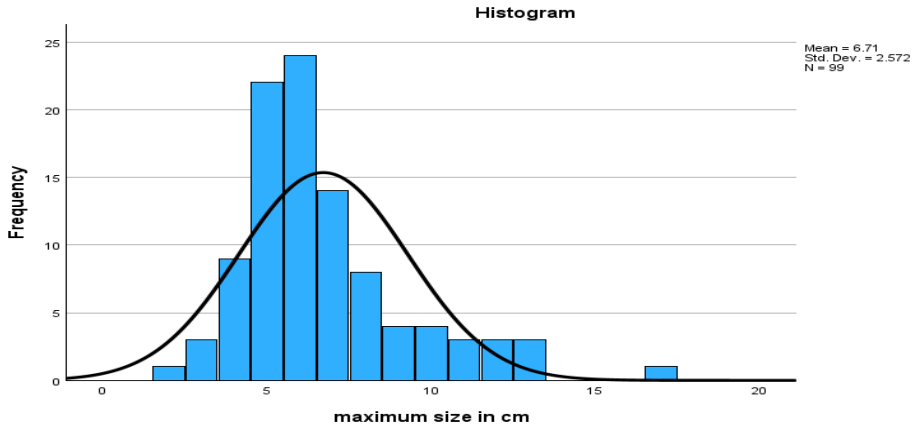


Figure 02: - Distribution curve of tumor size of the study population, Addis Ababa, n=99, missing=2

1.6.2. Location of the tumor(n=101)

Right lobe was the commonest site (58.4%, 59/101) for HCC followed by left lobe (34.7%, 35/101), both right and left lobe involved (5.9%, 6/101) and there were one (1%) patient with caudate lobe HCC. Among eight Segments, Segment VI were the commonest (44.8%, 45/101) site for HCC followed by Segment VII, V, III, II, VIII, IVb, and IVa in descending order**.**

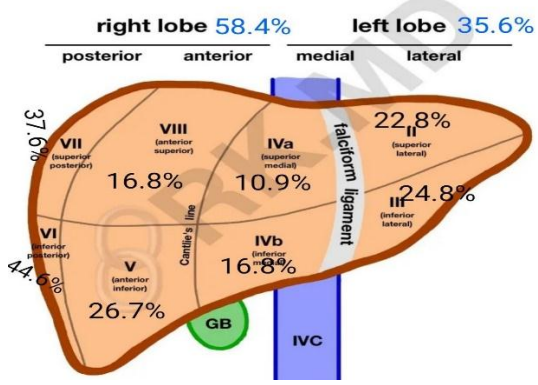


Figure 03: - frequency distribution of tumor location in the liver among the study population, Addis Ababa, n=101**.**

1.6.3. Vascular invasion (n=101)

In the majority (78.2%, 79/101) of the patient gross vascular invasion was not witnessed on imaging, intra-operative assessment and post-operative histologic examination. Of those with vascular invasion (21.8%, 22/101) almost all were intra-hepatic vascular invasion (95%, 21/22).

1.6.4. BCLC Staging (n=101) and Serum AFP Level (n=94, missing=7)

The majority of the patient are BCLC stage A (91,9%, 92/101) followed by BCLC B (7.9%,8/101) and BCLC stage O (1%). The mean serum AFP level were 582.85 (SD=2823.8) with a median of 54.00. there is a wide range (26920) of report in serum AFP level ranging between one and 26921.the distribution curve is unimodal (1000) and significantly skewed to the right. and AFP >100 is 40% whereas >200 is 35%.

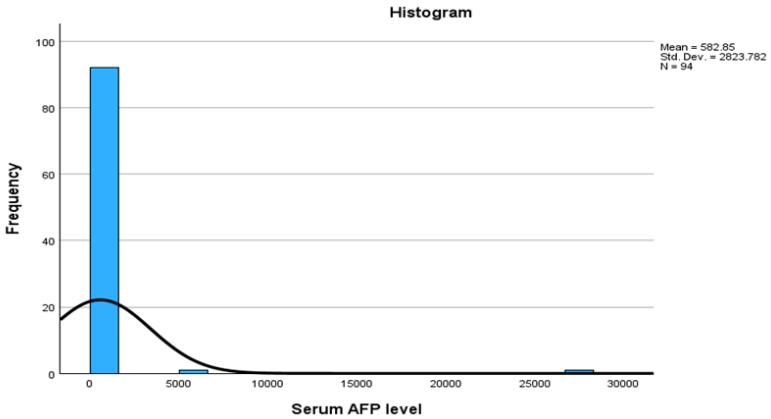


Figure 04: - Distribution of serum AFP level of the study population, Addis Ababa, n=94, missing=7

Variable			Frequency		Percentage	
number	single		**80**		**79.2**	
	multiple		**21**		**20.8**	
location	Right lobe	Seg V	**27**	**59**	**26.7**	**58.4**
		Seg VI	**45**		**44.8**	
		Seg VII	**38**		**37.6**	
		Seg VIII	**18**		**17.8**	
	Left lobe	Seg II	**23**	**35**	**22.8**	**34.7**
		Seg III	**25**		**24.8**	
		Seg IVa	**11**		**10.9**	
		Seg IVb	**17**		**16.8**	
	Caudate lobe	Seg I	**1**		**1.0**	
	Both (right and left lobe)		**6**		**5.9**	
Vascular invasion	No vascular invasion		**79**		**78.2**	
	Intrahepatic vascular invasion		**21**		**20.8**	
	Extrahepatic vascular invasion		**1(IVC)**		**1.0**	
	Both intra and extrahepatic vascular invasion		**nill**		**nill**	
BLCLC stage	BCLC Stage 0		**1**		**1.0**	
	BCLC Stage A		**92**		**91.1**	
	BCLC Stage B		**8**		**7.9**	
	Mean/median		Standard deviation		Range /min-max	
Size (cm)	6.74/6.00		**2.534**		**14 (3-17)**	
AFP (	582.85/54.00		**2823.782**		**26920**	

Table 08: - frequency distribution of tumor characteristics of the study population, Addis Ababa.

1.7. Surgical resection characteristics (n=101)

1.7.1. Type of Hepatectomy

Majority of the patient had minor resection (66.3%, 67/101) of which right Posterior Sectionectomy were the most common (22.8%, 23/101) followed by Non anatomic resection, left lateral hepatectomy, bi-segmentectomy, and segmentectomy in descending order. close to 34% were Major resection with right hepatectomy (18.8%, 19/101) being the most common tailed by left hepatectomy (12.9%, 13/101) and central hepatectomy (3%, 3/101). The rate of Non-anatomic resection was 22.8%(23/101). There was one caudate lobe resection done for pre-operative diagnosis of HCC

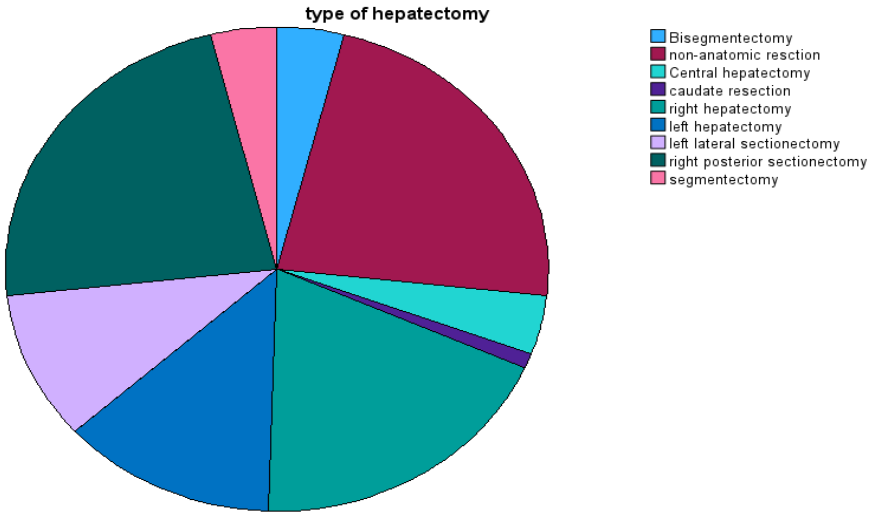


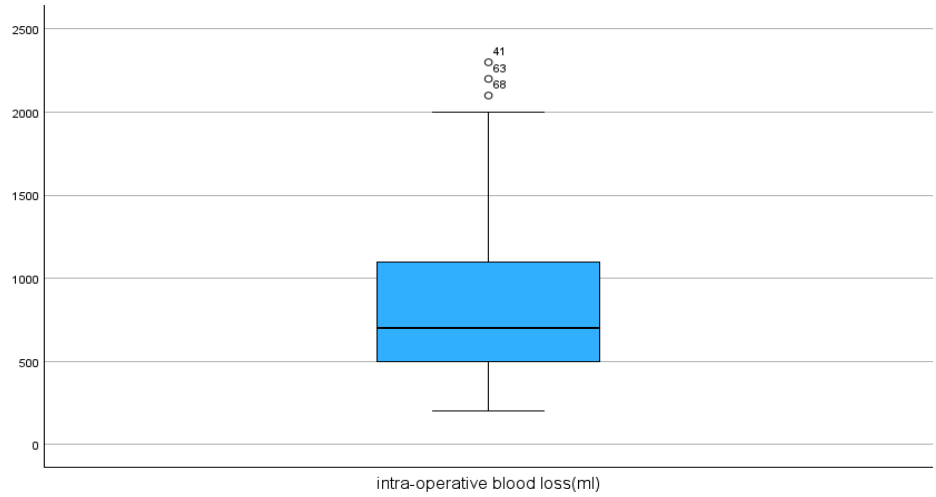
Figure 05: - Frequency of hepatic resection type of the study population, Addis Ababa, n=101

1.7.2. Inflow control

Intermittent Non selective inflow control (51.5%, 52/101) was the most commonly used inflow control method, with a mean ischemia time of 33.44min, trailed by selective intrahepatic inflow control (27.7%, 28/101) and selective extra-hepatic inflow control method (20.8%, 21/101). all parenchymal transection was made through Clamp-crush (kelyclaysis) technique.

1.7.3. Blood transfusion, Blood loss, fluid intake and operating time

The mean/median intraoperative blood loss was 849.01/700ml (SD=472.915) with wide range (2100ml, min-max=200ml up to 2300ml) of blood loss. With a mean/median blood transfusion of 2.09/2 units the transfusion (whole blood and component) rate was 51.5 % (52/101). The mean/median Intra-operative fluid intake was 2289.74ml/2000ml (SD=809.937) and the mean/median operating hour was 2.9hrs/3hrs (SD=0.943) with a wide range of 5hrs (min-max= 1hr up to 6hrs).



Variable			Frequency		Percentage	
Type of Resection	Major resection	Right hepatectomy	**19**	**34**	**18.8**	**33.7**
		Left hepatectomy	**13**		**12.9**	
		Central hepatectomy	**3**		**3.0**	
	Non – anatomic resection		**23**		**22.8**	
	Minor resection	Right posterior sectionectomy	**23**	**44**	**22.8**	**43.5**
		Right anterior sectionectomy	**1**		**1.0**	
		Left lateral sectionectomy	**10**		**9.9**	
		Caudate resection	**1**		**1.0**	

		Bi-segmentectomy	**4**		**4.0**	
		Segmentectomy	**4**		**4.0**	
Inflow control	Non selective		**52**		**51.5**	
	Selective	Extrahepatic	**21**	**49**	**20.8**	**48.5**
		Intrahepatic	**28**		**27.7**	
Parenchymal transection	Kelyclayasis		**101**		**100.00**	
Blood transfusion			**52**		**51.5**	

Variable	Mean/SD	**Median**	**Range**
Operative time (hrs.)	2.90/0.943	**3.00**	**5**
Intra-operative fluid intake (ml.)	2289.74/809.937	**2000.00**	**3000**
Amount of blood transfusion (units.)	2.09/1.024	**2**	**5**
Intraoperative blood loss (ml.)	849.01/472.915	**700**	**2100**
Ischemia time among non- selective inflow control group (min.)	33.44/11.857	**30**	**50**

Figure 06: - right side skewed asymmetric distribution of intraoperative blood loss among the study population, Addis Ababa, n=101

Table 09: - Frequency distribution of Surgical characteristics of the study population, Addis Ababa.

1.8.Post-operative laboratory values (n=101)

The percentage of study population with normal range serum INR, TBILL and Albumin has dropped from their pre-operative ratio down to post-operative normal serum value ratio of 85.1%, 77.2% and 81.1%, respectively**.** All were taken at POD 5.

	< 1.7		1.7-2.3	>2.3	Mean/SD
INR	**85.1%**		**10.9%**	**4%**	**1.42/1.56**
	<2mg/dl		2-3mg/dl	>3mg/dl	
	<1mg/dl	1-2mg/dl			

Bilirubin (T)	**77.2%**	**17.8%**	**3%**	**2%**		**1.98mg/dl/2.78**
	Normal range(>12g/dl		Mild (10-12g/dl)	Moderate(7-9g/dl)	Severe (<7g/dl)	
Hemoglobin	**81.1%**		**11%**	**7.9%**	**nill**	**12.11g/dl/3.4**

Table 10: - frequency distribution of serum INR, TBILL and Albumin, Addis Ababa, n=101

1.9.Post-operative complications (Morbidity) (n=101)

Among our patient population, admitted and operated for HCC, 48.5%(49/101) developed post-operative complication. of those patients with complication the majority were CLavian-Dindo Grade II (57.1%, 28/49) followed by Grade I (26.5%, 13/49), Grade IV and V each accounting for 8.2%(4/49). Most complications were procedure related complication (79.5%, 39/49) while pulmonary complication (46.9%, 23/49), anemia (38.8%, 19/49), gastrointestinal complication (30.65, 15/49), surgical site infection (22.4%, 11/49), genitourinary complication (16.35, 8/49), and cardiovascular complication (4%, 2/49) follows in descending order. In case of specific diagnosis, the most common complications were Hepatic insufficiency/failure (46.9%, 23/49) trailed by anemia (38.8%,19/49), pleural effusion (28.6%, 14/49), ascites (28.6%, 14/49), Primary hemorrhage during surgery (18.4%, 9/49) and pneumonia (18.4%, 9/49).

	Frequency	percentage
Grade 1	13	26.5
Grade 2	28	57.1
Grade 3	nil	nil
Grade 4	4	8,2
Grade 5	4	8.2

Table 11: - Frequency of Clavien - Dindo classification of post-operative complications, Addis Ababa, n=49

1.9.1. Procedure related complication

Procedure related complication is the most common post-operative complication (79.5%,39/49). Of which hepatic insufficiency/failure, primary hemorrhage during surgery, post hepatectomy hematoma being the most common complication while Portal vein thrombosis and post hepatectomy hemorrhage being the least common complication**.**

1.9.2. Pulmonary related complication

Pulmonary complication is the second most common complication (46.9%, 23/49). Out those with pulmonary complication pleura effusion is the most common followed by pneumonia**.**

1.9.3. Gastrointestinal and genito-uirinary complication

Ascites is the most common GI related complication (28.6%, 14/49) and renal failure (12.2%, 6/49) among genito-urinary related complication others are ileus (2%, 1/49) and UTI (4%, 2/49) in their respective side**.**

1.9.4. Miscellaneous complication

Anemia is among the most common post-operative complication (38.85, 19/49) seen in our study. others are wound infection, wound dehiscence, sepsis, DVT and arrhythmia, in descending order**.**

Variable			Frequency	Percentage
No complication			**52**	**51.5**
Complications	Total complication		**49**	**48.5**
	Procedure related	Hepatic insufficiency/failure	**23**	**22.8**
		Primary hemorrhage during surgery	**9**	**8.9**
		Post hepatectomy hemorrhage	**1**	**1.0**
		Post hepatectomy hematoma collection	**3**	**3.0**
		Portal vein thrombosis	**2**	**2.0**
		Peri-hepatic abscess	**1**	**1.0**
	Pulmonary	Pleural effusion	**14**	**13.9**

		pneumonia	**9**	**8.9**
	Gastrointestinal	Ascites	**14**	**13.9**
		ileus	**1**	**1.0**
	Genitourinary	Renal failure	**6**	**5.9**
		Urinary tract infection	**2**	**2.0**
	Miscellaneous	Anemia	**19**	**18.8**
		Wound infection	**5**	**5.0**
		Wound dehiscence	**3**	**3.0**
		sepsis	**3**	**3.0**
	Cardiovascular	DVT	**1**	**1.0**
		Arrhythmia 2ry to AF	**1**	**1,0**

Table 12: - Frequency of post-operative complications among the study population, Addis Ababa n=101

1.10. Post –operative length of Hospital stays and mortality (n=101)

The mean/median post-operative hospital stay in days was 6.04/5 with a minimum and maximum hospital stay of 3days and 20days.

	Mean/median	Standard deviation	Range (min- max)
Post –operative Length of Hospital stay (days)	6.04/5.00	2.871	17(3-20)

Table 13: - Frequency of post-operative length of hospital stay

1.11. Post- operative mortality

Of the total patients operated for HCC, there were 4 deaths (4%). Three of them have comorbidities, viral infection and liver cirrhosis. Right hepatectomy was done for two and non-anatomic resection and bi-segmentectomy for the remaining two patients. all were transfused with blood peri-operatively with an average intra-operative blood loss of1,275ml. the average

operating hour was 3.5hrs with a mean intraoperative fluid intake of 3000ml. all of them have hepatic insufficiency/failure and pneumonia while two of them having renal failure, ascites and wound infection. The possible cause of death was related with Hospital acquired pneumonia in all case (multi-organ failure secondary to sepsis of chest focus on three and respiratory failure secondary to sepsis of chest focus in one case). there was no intra-operative death and all were post-operative intra-hospital deaths. The mean hospital stay was 14.25dyas with a minimum and maximum stay of 5 and 20days.

		Frequency	Percentage
Death	Total	4	4%
	Intra-operative	nil	nil
	Post-operative (in hospital)	4	4%

Table 14: - frequency of post-operative mortality

2. Analytical part

2.1.Factors associated with postoperative complication

First a Bi-variable Bi-nominal logistic regression was done for each of our independent variables and post-operative complication. With Confidence interval of 95%, a P-value less than 0.05 was taken as a cut of value for statistical significance. So, those having a statistically significant association were tumor characteristics (site of the lesion (right lobe), size of the lesion), and Surgical factors (type of hepatectomy (major resection and right hepatectomy), operative time, intra-operative blood loss, intra-operative fluid intake, blood transfusion, and amount of blood transfusion), and post-operative hospital stays.

Variable		Bi-variable binominal logistic regression	
		COD (95% CI)	P-value
Age		1.023 (0.994- 1.053)	0.118
Sex (male /female)		1.977 (0.896 – 4.365)	0.092
P-status	ECOG 0	.889	0.889
	ECOG 1	1.098 (0.386-3.123)	0.861
	ECOG 2	-	-
ASA Class	ASA 1	1	1
	ASA 2	0.944 (0.055-16.327)	0.969
	ASA 3	0.906 (0.054-15.158)	0.945
	ASA 3A	2.00 (0.051- 78.250)	0.711
Comorbidities	Comorbidities	1.935 (0.873-4.291)	0.104
	Hypertension	1.152 (0.459- 2.886)	0.763
	Diabetes mellitus	0.208(0.063 – 0.687)	0.010
	HIV	2.939 (0.295 – 29.251)	0.358
Pre –operative liver synthetic function	Pre-operative INR	0.435 (0.026 – 7.184)	0.561
	Pre-operatie-Albumin	2.219 (0.751 – 6.558)	0.149
	Pre-operative-Tbill	5.795 (0.652 – 51.504)	0.115
Risk factor	HBsAg	0.680(0.280 - 1.650)	0.394
	HCV	0.933 (0.302– 2.886)	0.905
	Cirrhosis	1.900(0.811 – 4.450)	0.139

Tumour factors	**Site**		Right	**3.492 (1.511 – 8.069)**	**0.003**
			Left	0.078 (0.046 - 2.982)	0.002
	size			**1.332 (1.098 – 1.616)**	**0.004**
	Vascular invasion			0.398(0.145-1.092)	0.074
	Serum AFP			1.001 (1.000– 1.002)	0.062
	BCLC Stage			1.278(0.473 – 3.452)	0.629
Surgical factors	**Type of Resection**	**Major**		**2.444 (1.052-5.680)**	**0.038**
		Minor		0.692	0.142
		Right hepatectomy		**13.281(2.873 – 61.389)**	**<0.001**
		Left hepatectomy		0.274 (0.071 – 1.063	0.061
		Non anatomic resection		0.611 (0.237 – 1.576)	0.308
		Right posterior sectionectomy		0.769 (0.302 – 1.962)	0.583
		Left lateral sectionectomy		2.385 (0.580 – 9.804)	0.228
	Operative time			**2.501 (1.485 – 4.211)**	**<0.001**
	Intra-op fluid intake			**1.001 (1.000- 1.002)**	**0.001**
	Intra-operative blood loss			**1.002 (1.000 – 1.003)**	**<0.001**
	Blood transfusion			**11.700 (04.587 – 29.841)**	**<0.001**
	Amount of blood transfusion			**4.892 (2.712 – 8.824)**	**<0.001**
Post-operative hospital stay				**1.628 (1.226- 2.161)**	**<0.001**

Table 15: - Factors associated with postoperative complications after hepatic resection for HCC using univariate Bi-nominal logistic regression, n=101

However, a multivariate binomial logistic regression of those variables showed only surgical factors (Major resection(2.5x), right Hepatectomy (2.7x), blood transfusion (23x) and amount of blood transfusion (1.3x)) were significantly associated with post-operative complications**.**

Multivariate logistic regression		
Variable	AOR(95%CI)	P-Value
Type of hepatectomy(major)	**2.576 (1.5440 -48.891**	**0.002**
Intra-operative fluid intake	2.428 (0.632 – 9.332)	0.197
Site of the tumour (right lobe)	0.442 (0.048 -4.061)	0.471
Size of the tumour	0.893 (0.590-1.351)	0.592
type of hepatectomy(right hepatectomy)	**2.676(1.440-4.971)**	**<0.001**
Operative time	0.518 (0.132-2.043)	0.348
Blood transfusion	**23.18 (11.61-46.71)**	**<0.001**
Amount of blood transfusion	**1.33(1.95-9.18)**	**<0.001**
Post-operative Hospital stay	0.788 (0.389-1.596)	0.509

Table 16: - Factors associated with postoperative complications after hepatic resection for HCC using multivariate logistic regression, n=101.

2.2. Factors associated with Higher post-operative Hospital stay (multiple linear regression)

Patients with complication (7.0), blood transfused (6.4), and major resection (6.2) tend to have a higher mean length of hospital stay. however, selected independent variables, based on previous reports and our sample size, versus post-operative length of hospital stay were analyzed for

association using multiple linear regression. Hence, operative time, non-anatomic resection, and presence of complication were associated with a higher post-operative hospital stay. But, using Pearson correlation coefficient, there is weak positive correlation between operative time and length of hospital stay**.**

Variables		Post-operative length of hospital stay			
		Frequency	Mean/median	Min/max	P -value
Liver cirrhosis	Yes	32	6.4/5	3/17	0.571
	No	69	5.7 /8	3/20	
Site of tumor	R. Lobe	59	6.3 /5	3/20	0.667
	L. Lobe	36	5.4/5	3/16	
Major vs minor resection	Major	35	6.2 /6	4/20	0.791
	Minor	66	5.8/6	3/17	
Non - anatomic resection	Yes	23	6.43/6	3/17	**0.005**
	No	78	5.7/5	3/20	
Operative time	In Hrs (mean)		2.88hrs	1/6hrs	**0.051**
Blood transfusion(ml)	yes	52	6.8 /6	4/20	0.395
	no	49	5.0/5	3/10	
Complications	Yes	49	7.0 /6	3/20	**0.028**
	No	52	4.9 /5	3/8	

	Pearson correlation coefficient	P-value
Operative time in hrs. vs post-operative hospital stay in days	**0.267**	**0.007**

Table 17: - Factors associated with Higher post-operative Hospital stay (multiple linear regression)

Discussion

Hepatocellular carcinoma is becoming one of the most common cancers worldwide with a greatest share of disease burden in low income countries owing to the high prevalence of risk factor in those areas. Currently there are different options of management for hepatocellular cancer in the horizon. With an intent for cure ablation, liver resection and transplantation are being done for HCC based on validated and internationally accepted criteria's or certain institution based selection criteria's. During the writing of this paper surgical resection is the only curative intent treatment options available in the country and remains a crucial component in the multimodal treatment approach for HCC.

So, this study tried to evaluate pre-operative clinic-radiologic pattern of HCC, intra-operative surgical characteristics and post-operative complication, length of hospital stay and mortality of patients who undergone hepatic resection for HCC.

2.1. Demographics

The median age of those patients, who undergone surgical resection for HCC follows the age trend at presentation of patients with HCC. With a close to equal gender distribution, the mean (57.42) and median (60yrs) age of our study population is a bit higher than the study done in our country to assess the pattern of hepatic resection for different causes (50.71yrs).[36] this could be due to difference between the two study population. but it is almost similar with other African, Asian and European studies conducted to assess resection outcome for HCC (54-60yrs) with some variation in the report of gender distribution.[39,40] Another research conducted to compare characteristics and outcome of HCC between Egypt and other African countries (including Ethiopia) showed a mean age of 58yrs and 46yrs respectively.[47]

2.2. Comorbidities and Risk factors

Presence of comorbidities is said to have an impact on post-operative outcome of surgical resection for HCC. Our study indicated that 43.6% of patients have comorbidities. With hypertension and diabetes mellitus being the most common, our finding is in line with a report by Yohanna et al., from Ethiopia.[36] but there is a higher report of comorbidities in the other part of the world ranging between 49-55%.[39,40]

Most patients with HCC have an underlying risk factor with viral infections, alcohols and MAFLD being the most commonly studied causative factors. Interestingly, our study shown that 53.5% of patients have risk factor and viral infection (39.6%), (HBV-65%, HCV-32.5% and co-infection-2.5%), is the most common followed by alcohol intake (10.9%) and fatty liver disease (8.9%). In contrast to our finding there is a lower risk factor report but near to close viral infection rate by Yohanna et al from Ethiopia.[36] another report from the same country who tried to assess therapy and outcome of HCC in sub Saharan countries showed a higher report of viral infection rate.[37] this could be due to difference in sample size, study population and study area. but old European and Asian reports who tried to assess resection outcome for HCC shown near close rate of viral infection and alcohol intake.[39,40]

2.3. ASA Grade and Performance Status

There is a contrasting report on the ratio of ASA Grade among patients who undergone hepatic resection. Our study identified that the majority (96.3%,97/101) of our study populations are ASA Grade I (34.7%) and Grade II (61.4%) at the time of surgery. This is near similar with a report from Ethiopia[36] but there is a lower percentage report of ASA Grade 1 and 2 with higher report of ASA grade 3(19%). Which could be due to the presence of higher comorbidities, large sample size and longer study period in this study.[40] with regard to performance status we used ECOG criteria and 82.2% are ECOG 0 followed by ECOG 1 and 2. Others also shown similar report of ECOG 0 predominance.[41]

2.4. Background Liver Status

One of the most determinant factors affecting post-operative outcome post hepatectomy is the status of background liver.[36] so, our study tried to assess the status of background liver in the study population and only 47.5 % of them have cirrhotic (31.7%) and Fibrosis (15.8%). this report is in line with Yohanna et al[36] report who tried to assess post hepatectomy outcome, but lower than Amir et al who tried to assess all treatment outcome for HCC, both from the same country.[37] such significant variation is due to difference in the study population between those articles. but a higher report of cirrhosis is seen in the other part of the world.[38,39,40] in a study conducted to compare characteristics and outcome of HCC between Egypt and other African countries there is a higher rate (60-100%) of cirrhosis than our report.[47] as it is true in most articles, all most all of our study population with cirrhosis has a CTP Score of A.[36,38,39] such a

higher percentage of non- cirrhotic HCC could be due to higher HBV infection, or selection bias for resection or it could be due to some other genetic or acquired factor that needs to be studied.

2.5. Tumor characteristics

Different Morphologic characteristics of the tumor are used for staging and prognostication of HCC.

2.5.1. Number of lesion

Our study depicted that almost 80% of the study population had solitary mass which is lower than a report by Yohanna et al where there were benign causes for resection in the study population.[36] but our report is similar with other report of similar study population (80-86%).[38,40]

2.5.2. Size of the lesion

The mean and median size of HCC in our report is 6.74 and 6cm with asymmetric distribution and 65% of them has a size >5cm. This is higher than a report from Egypt and Singapore but lower than other African reports.[40,47] this is likely due economic difference that is reflected on follow up of patient with underlying risk, healthy seeking behavior and early detection of tumour.[40,47]

2.5.4. Vascular invasion

There are varies report regarding tumor invasion of the vascular structures especially intrahepatic vascular invasion on imaging and microvascular invasion on histopathology. we tried to look the presence of intra and extrahepatic vascular invasion on imaging and intra-operatively. Our analysis showed no gross vascular invasion on imaging and intraoperative assessment in the majority of the patient (78%) and of those with invasion almost all were intrahepatic (21%). But there is a report of vascular invasion ranging between 17-78%.the higher rate of vascular invasion in these studies is because of inclusion of histopathologic report of microvascular invasion.[38, 40]

2.5.5. Serum AFP level

Serum level of AFP is important for diagnosis, staging and prognostic purpose. Hence a number of cut of values for varies purpose has been proposed. So, in our study the number of patients

with AFP level >100ng/ml is 40% whereas those above 200ng/ml is around 35%. which is close to similar with a report from Europe and singapor[38, 40] but the mean AFP level of our study finding is greater than other Ethiopian reports.[36]

2.6. Surgical factors

2.6.1. Type of resection

2.6.1.1. Major vs minor resection

The type of resection is said to be related with postoperative outcome. The rate of major resection varies between different reports, regions and centers but it falls within a range of 12-30%.[38,39,40,42] but, our finding (34%) is higher than those reports which could be due to delayed presentation of patient in our case, higher percentage of non-cirrhotic liver favoring more radical surgery or skill gap in parenchymal preserving surgeries. Just like our reports, right hepatectomy is the most common major hepatectomies followed by left hepatectomy.[29,36,39,42]

2.6.1.2. Anatomic vs non anatomic resection

Even though there are conflicting evidence on the benefit of anatomic resection over non anatomic resection most authors shown better overall survival.[48,49] so a higher rate of non-anatomic resection was reported in the old papers.[39] but these days with advancement in preoperative imaging, surgical techniques and improved understanding of liver anatomy more anatomic resection is being done. our evaluation indicated around 22.8% non-anatomic resection which is lower than old studies.[29,39,48,49] but higher than a report by Yohanna et al from Ethiopia.[36]

2.6.2. Methods of inflow control

It is depicted that the choice of inflow control depends on the type of resection, status of background liver the location of the tumor and the skill of the surgeon. And the establishment of inflow control is critical for safe hepatic resection. but most articles didn't report the techniques used to achieve inflow control.in our study intermittent Pringle maneuver is the most common (51.5%) inflow control method. Followed by selective intrahepatic and selective extrahepatic vascular inflow occlusion. The same report was shown in other papers also.[36, 50]

2.6.3. Blood transfusion, Blood loss, fluid intake and operating time

We do have a higher rate of blood transfusion (51.5%) compared with other reports ranging from 18-22%.[40, 42] but it is lower than a similar study conducted in Ethiopia (61%).36 such a higher rate of blood transfusion could be due to higher blood loss, higher rate of major resection and non-anatomic resection, higher intra-operative fluid intake, plus all parenchymal transection were done with

Kelly-claysis, or it could be due to poor infrastructure or lack of transfusion protocol in the study area. the mean blood loss and intraoperative fluid intake in our study was 849ml and 2289ml. these reports are higher than current reports who tried to assess hepatic resection outcome for HCC.[40, 42] this could be associated with the techniques of parenchymal liver transection and lack of Central catheter for CVP monitoring plus one is positively correlated with the other. The mean surgical operating time in our study is almost similar with other studies done in Ethiopia and previous experience of western countrie.[36, 40, 42] but current report showed a more operating time but less blood loss and transfusion rate.[40, 42]This is due to difference in methods of parenchymal transection, improved anesthesia management.

2.7. Post- operative complications

One of the prime outcome of this study was to evaluate 30-day post-operative complications. Current Advancement in surgical techniques, proper patient selection, and improved peri-operative anesthesia management has contributed a lot for improved post-operative complications.[51] but, our finding indicated a higher rate of post-operative complication (48.5%) compared with recent report of current surgical experience .[38, 40, 42] nevertheless, old papers and review of previous experience had close to similar finding with our reports.[42, 52] on account of this, it is clear that we have shortcomings in proper patient selection and optimization, lack of parenchymal transection devices, Poor peri-operative anesthesia management, especially CVP monitoring, fluid management, non-evidence based blood transfusion.

Yet, the severity of complications in our evaluation is comparable with other reports. Based on Clavien-Dindo Grading of severity [43], our study showed that only 16.4% of complications were Clavien-Dindo Grade=> 2.[36, 40, 52] However, there is study period, study population and sample size difference between these studies.

In our study most of the complications were procedure related complications (79.5%) which is followed by pulmonary complication (46.9%, 23/49), anemia (38.8%, 19/49), gastrointestinal complication (30.65, 15/49), and surgical site infections (22.4%, 11/49). Even though it has similarities with previous report from Ethiopia where procedure related complications are the most common[36], infectious and pulmonary complications are the one common complication reported in many old and recent papers.[42,52] this could be explained by the difference used to define liver specific complications where we used the recent ISGLS definition unlike those papers that used non standardized different definitions.

For example, using ISGLS definition the rate of PHLF is reported to range between 1-33%.[38, 44, 53] interestingly, the rate of PHLF in our study is within this range (22.8%). If we use the "50-50" criteria,[54] our study PHLF prevalence will be close to 9% which is still high but close to old reports.[42, 52, 53] the other possible reason is the difference in the study population where our study population is only HCC, high rate of major resection and blood transfusion.

2.7.1. Factors associated with post-operative complications

One of the prime objective of this study is to analyze factors associated with higher post-operative complications.

After testing variables for suitability using assumption test of both univariate and multivariate logistic regression, surgical factors like Major resection(2.5x), right Hepatectomy (2.7x), blood transfusion (23x) and amount of blood transfusion (1.3x)) were significantly associated with post-operative complications in a multivariate logistic regression. there are conflicting report by different authors regarding the factors that has strong association with post-operative complication. There was one research done in Ethiopia by Yohanna et al [36] to assess the pattern of hepatectomy and post-hepatectomy complication for different etiologic diagnosis. In their report they found out that in multiple logistic regression only patients with liver metastasis has strong association with post-hepatectomy complication. But their study population and study design is different and could have an effect on the variable and final regression test. A report by Kingham et al [52] after analyzing 4125 patients undergoing liver resection for a malignant diagnosis from 1993 to 2012 at Memorial Sloan Kettering, showed blood transfusion, major hepatectomy were associated with post-operative morbidity on a multivariate analysis. Another report from japan by Taketomi et al [42] after evaluating 625 patients with hepatic resection for

HCC over a period of 17yrs showed that operative time and blood transfusion in addition to other factors has strong association with post-operative complications. and they noted that there was progressive decrease in blood loss, transfusion rate and post hepatectomy complications. Similar results were reported in a meta-analysis by Liu et al., 2260 patients who underwent hepatectomy for HCC across 7 studies were analyzed and found to have an increased occurrence of complications following autologous blood transfusion. So, our finding goes in line with other reports having a large sample size and comparable study population. Hence, practicing parenchymal preserving surgeries (right anterior resection for right hepatectomy (for seg 5 and 8), left medial sectionectomy for left hepatectomy (for seg4), decreasing blood loss and transfusion rate might reduce the high post-operative complications shown in this study. Since these factors are modifiable and has been shown to reduce in other studies and experience, Surgeon should look for possible mechanisms to reduce these factors.in those studies and experience it is shown that use of techniques of inflow control associated with minimal blood loss and less parenchymal injury, utilizing CUSA and various energy devices for parenchymal transection, employing transfusion protocol and central line for intra-operative CVP monitoring will reduce those factors and associated complications**.**

2.8. Post-operative length of hospital stay

The mean (6.04days) and median (5days) hospital stay in our report is lower than previous report by Yohanna et el from Ethiopia[36] and other reports.[40, 42, 50] however, we only took days spent after surgeries in the hospital unlike other studies who took peri-operative stay**.** In a meta-analysis of 74 randomized clinical trials by Sauro et al[56], the average post procedure hospital stay for major and minor hepatic resection were 5-6days and 2-3dyas respectively. but in our finding there was minimal difference between the two groups (6.2 vs 5.9) of patients in length of hospital stay.

2.8.1. Factors associated with higher Post-operative length of hospital stay

After testing for compatibility through assumption test for multivariate linear regression we found out that operative time, non-anatomic resection, and presence of complication were associated with a higher post-operative hospital stay. Operative time and presence of complication was also reported to have association with a higher length of hospital stay by different authors.[52, 57]

Conclusion

The most common identified risk factor for HCC is Viral infection however most of them had HCC with normal background liver. there is also a higher rate of Major resection, non-anatomic resection, intra-operative blood loss, Blood transfusion and intraoperative fluid intake. Post-operative complications were higher and it is strongly associated with Surgical factors like Major resection and blood transfusion. Operative time, non-anatomic resection and complication were strongly associated with Post-operative length of Hospital stay

Recommendation

1- Reducing /Eliminating HBV and HCV infection through WHO key services delivery targets
2- Promoting parenchyma preserving anatomic hepatic resections
3- Endowing oneself and the setup with techniques that reduces blood loss and duration of surgery
4- Inducting evidence based transfusion protocol
5- Promoting goal directed intra-operative fluid resuscitation

Limitation of the study

1. Missing/incomplete data
2. Lack of complete histopathologic profile

Strength of the study

- The first study in Ethiopia trying to see Surgical outcome of hepatectomy for HCC (the only curative intent management option in the country)
- Being a two-year multi-center prospective analysis with relatively adequate sample size

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Annex

Data collection sheet

Hepatic Resection Outcome of HCC among patients who visited tertiary referral hospitals in Addis Ababa.

This research project is conducted as part of fulfillment of HPB fellowship Program. The aim of this research is to assess Hepatic Resection Outcome of HCC among patients who visited tertiary referral hospitals in Addis Ababa. All data and measurements obtained from this research study will be stored confidentially. Only researcher will have access to view any data collected during this research. The research intends to cause no physical or psychological harm or offense and to abide by all commonly acknowledged ethical codes. The researcher is granted an access to the medical document of the participant by responsible bodies.

Section 1

Demographics

1-Age----------, 2-Sex----------

Section 2

Clinical and Laboratory parameter to assess patients' general condition prior to surgery.

1-Hg----------, 2-PLT----------3-Performance status, ECOG0, ECOG1, ECOG2, ECOG3

4-ASA class, ASA 1, ASA 2, ASA 3, > ASA 3

5-Comorbidities, Hypertension, Diabetes mellitus, HIV, CKD, COPD, Others

Section 3

Status of the Liver

To assess the background liver through Laboratory and Scoring systems

1- AST, ALT, ALP, INR, ALBUMIN, TBILL, DBILL, HBsAg, HCV-antibody, History of Alcohol intake

2- Steatosis, Fibrosis, Chemotherapy related liver injury, Cirrhosis, CTP Score, ALBI score

Section 4

Tumor characteristics

To assess morphologic characteristics of the tumor based on preoperative imaging and intraoperative finding

1- Number, Site, Size, Enhancement pattern, vascular invasion (on imaging and intraoperative)

2- BCLC Staging, HKLC Staging, AFP

Section 5

Hepatic Resection type

To assess the type of resection done

1- Right trisectionectomy, Left trisectionectomy, Right hepatectomy, Left hepatectomy, Left later sectionectomy, Left medial sectionectomy, Right anterior sectionectomy, Right posterior sectionectomy, Segmentectomy 1-8, Wedge resection

Section 6

Intra- Operative Course

To assess the intra-operative course of Hepatectomy done for the patient

1- Total Operative time, Amount of fluid intake, Units of blood transfusion, Amount of blood loss

2- Type of parenchymal transection, Type of inflow control, Total ischemia time

Section 7

Surgical outcome

To assess post-operative outcome in terms of morbidity, pathologic result and death

A- Complication

1- Hepatectomy specific complications

a. Bile leakage/fistula/biloma, Liver failure, Hemorrhage, Ascites ,PVT, Liver abscess, other

2- Pulmonary complication

a. Pneumonia, Pleural effusion, Pulmonary embolism, Pulmonary edema

3- Surgical site infection

a. Superficial wound infection, Deep infection, Organ specific infection

4- DVT, Wound dehiscence, anemia, Other

B- Clavien dindo classification of complication

1- Grade 1, 2, 3, 4, 5

C- Length of hospital status

D- Death: - Intra-operative, In hospital, Within 01-month post-surgery