DISSERTATION MANUSCRIPT

MASTER OF GENERAL SURGERY

Non Alcoholic Fatty Liver Disease Related Hepatocellular Carcinoma: A 7 years Retrospective Observation Study

BY:

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- My appreciation to department of pathology, Hospital SultanahBahiyah, Kedah for assiting me during data collection.

ABSTRAK

Latarbelakang: Barahhati yang disebabkan of NAFLDadalahluarbiasaantarapunca lain sepertiminumankeras, Hepatitis B dan Hepatitis C. Akan tetapi, kemunculaninsidenbarahhatidisebabkan NAFLD semakinmeningkatdalamjangka masa beberapatahunini, dankebanyakanpesakitdenganbarahhatiakibat NAFLD juga mengalamimasalahkesihatansepertikegemukan, danpenyakitkencingmanis, darahtinggidankelebihanlemakdalambadan.

Tujuankajianiniadalahuntukmengenalpastidemografi, punca-punca yang melibatkanbarahhatiakibat NAFLD dankadarkematianbarahhatiakibat NAFLD.

Langkahkajian: Kajianinidilakukandenganmerujukkepada data di Hospital SultanahBahiyah, Kedah, Malaysia untuktempoh 7 tahun (2009-2016).Barahhatiakibat NAFLD dan Hepatitis B/C telahdibedahkeluarmelaluikadarhemihepatectomy, segmentectomy, bisegmentectomy, multiple segmentectomy, left and right hepatectomy, extended right dan left hepatectomy, dalamkeadaankecemasanatauelectif, dilikungidalamkajianini. Kadar bedahlaintidaktermasukdalamkajianseperti excision atau incision biopsy, FNAC of liver nodule. Kajianiniakandijalankansecaraterperincimelaluikajiandemografi, risalahpenyakitlain, Komplikasipembedahandankadarkematianbarahhatiakibat NAFLD melalui survival analysis dan cox regression.

Keputusan: Kebanyakanpesakitadalahlelaki(71.3%), berumurantara60-69 (27.9%), denganberatbadanantara 65.1kg-75kg (33.1%), dan BMI bawah 25 (82.4%). Kumpulan barahhatiakibat NAFLD dankumpulanbarahhatiakibat Hepatitis B/C(Viral)menpunyaidemografi yang serupa.Kumpulan NAFLD menpuyailebihbanyakrisalahpenyakit lainberbandingdengankumpulanViral[Kencingmanis 34

vs 17 viral group (p=0.010); Darah Tinggi 50 vs 29 viral group (p=0.004); kelebihanlemak 19 vs 3 vital group (p=0.00); IHD 9 vs 3 viral group (p=0.095); CKD 6 vs 3 viral group (p=0.298)]. Kumpulan NAFLD juga lebihsenangmerebakkelimpadansalurandarahsetempat, serta organ terdekat(42 vs 33, p=0.269; 36 vs 21, p=0.638). Jumlah masa untukpembedahandalamkumpulan NAFLD lebihpanjangberbandingdengankumpulanViral(158.2 minutes vs 143.9 minutes, p=0.176)manakalajumlahpendarahansemasapembedahanlebihbanyakberbandingdengankumpulan NAFLD(599.8ml vs 489.7ml, p=0.648). Pembedahankumpulan NAFLD melibatipotonganhati yang lebihbesarberbandingdengankumpulanViral(p=0.294). Kadar komplikasipembedahan yang berlaku di antarakumpulan NAFLD dankumpulan Viral adalahsama rata kecualikadarinfeksiparu-paru di hospital yang tinggidalamkumpulanNAFLD(23 vs 9 viral group, p=0.011), dankadarkematian yang rendahdalamkumpulan NAFLD (29/72, 40% vs 29/64, 45%, p=0.338).

Kesimpulan:Pesakitbarahhatiakibat NAFLD yang telahmembuatpembedahan yang dikaji, mempunyailebihbanyakmasalahkesihatansepertikencingmanis, darahtinggidankelebihanlemak. Mereka juga menghadapibanyakkomplikasipembedahan, akantetapimerupakangolongankadarkematian yang rendah.

ABSTRACT

Background: NAFLD related HCC is one of the uncommon causes of HCC compare to Hepatitis B, Hepatitis C and alcoholic. Evidence of NAFLD related HCC is in rising trend in view of increase incidence of obesity and metabolic disease among population. Our aim was to study the NAFLD related HCC in one of the high volume hepatobiliary centre in Malaysia to determined its incidence, various factors associated with NAFLD related HCC and survival outcome.

Methods: It's a retrospective cross sectional study among the patient underwent liver resection in Hospital SultanahBahiyah for HCC in the period of 7 years (2009-2016). Liver resection include anatomical and non-anatomical hemihepatectomy, segmentectomy, bisegmentectomy, multiple segmentectomy, left and right hepatectomy, extended right and left hepatectomy, either in emergency or elective setting. Other surgery or procedure that is not involve in liver resection like excision or incision biopsy, FNAC of liver nodule, are excluded. This study includes demographic, comorbid, intraoperative and postoperative findings and complications, as well as survival analysis using Kaplan Meiyer and cox regression.

Results: Most patients are male (71.3%), fall between age group of 60-69 (27.9%), with weighted mostly between 65.1kg-75kg (33.1%), and BMI below 25 (82.4%). Both groups demonstrated similar characteristic features in age, weight and BMI. Comorbids are overall higher compare to viral group [DM 34 vs 17 viral group (p=0.010); Hypertension 50 vs 29 viral group (p=0.004); Dyslipidemia 19 vs 3 vital group (p=0.00); IHD 9 vs 3 vital group

(p=0.095); CKD 6 vs 3 viral group (p=0.298)]. Lymphovascular involvement and local invasion were observed more in NAFLD group (42 vs 33, p=0.269; 36 vs 21, p=0.638). Operation time was longer in NAFLD group (158.2 minutes vs 143.9 minutes, p=0.176), but blood loss was more in viral group (599.8ml vs 489.7ml, p=0.648). More surgical resection of liver done for NAFLD group in compare to viral group (p=0.294). Post op complications were not significant different among two groups except HAP more in NAFLD group (23 vs 9 viral group, p=0.011), and slightly lower mortality numbers were observed in NAFLD group (29/72, 40% vs 29/64, 45%, p=0.338).

Conclusion: Resected HAFLD HCC associated with more comorbid, and carries more post-operative complications, and lower mortality compare to resected viral HCC.

1.INTRODUCTION

1.1 Introduction

Hepatocellular carcinoma has become a major health issue all over the world. The incidence and cancer related death has risen steadily over the years, render it becoming the Fifth common cancer in the world, and Third leading cause of cancer related death, behind lung cancer and gastric cancer.

Although viral infection is the major aetiology factor for the development of HCC with underlying background of chronic liver disease and cirrhosis, there is substantial rise in number of cases of Non-B Non-C related HCC. It can be roughly divided into alcoholic and non-alcoholic.

Non-alcoholic fatty liver disease (NAFLD) has become one of the trending aetiology in Non B Non C HCC. Non-alcoholic fatty liver disease encompasses a wide spectrum of presentations, ranging from isolated hepatic steatosis to Non Alcoholic hepatosteatosis (NASH), which may or may not progress to cirrhosis, and ultimately lead to HCC formation.

1.2 Literature review

The incidence for NonB NonC related HCC has become one of the major topics to be discussed in the Hepatobiliary Unit around the world. Hiroki Nishikawa et al make an observation study on the epidemiology trend, aetiology and risk factors of NBNC HCC in Japan, noted even though Hep C related HCC is still major cause of HCC, but incidence is reducing trend, and found out NBNC HCC in a rising trend in recent year(1). Many latest articles including Fingas et al reported NBNC HCC incidence in United State accounted around 15% to 50%.(2). In Malaysia, after HBV, cryptogenic/NAFLD is the predominant cause of HCC, owing to increase incidence of obesity and diabetes.(3)

Of all the aetiologies of NBNC related HCC, NAFLD/NASH has been extensive studied and has been categorized as one of the most important factor in view of increasing trend of obesity incidence in the whole world(4, 5). However a retrospective study done in Taiwan, stated that Obesity, DM and Metabolic disease are not significant factors for HCC in an HBV and HCV endemic area in southern Taiwan(6).

Diagnosis of NAFLD was achieved based on histology or clinically according to international guidelines. According to European Association for the study of liver, NAFLD defined by the presence of steatosis in >5% of hepatocytes according to histological analysis, excluding both secondary causes and of a daily alcohol consumption >=30 g for men and >=20 g for women (7). This is because of low predictive value for non-invasive test on NAFLD(8). This study focused on detection of fatty liver changes in all resected HCC specimen, in concordance to international diagnostic criteria.

Multiple hypotheses have been implicated over pathogenesis of NAFLD/NASH induced HCC. Most paper demonstrates the natural history of NAFLD progressed to NASH, with liver fibrosis, and conversion to cirrhosis in a few, which lead to development of HCC (9-11). The initial development of NAFLD may be due to insulin resistance even without obesity(11). Other metabolic syndrome like hypertension, DM, dyslipidemia also give rise to hepatic steatosis. The progression from NAFLD to NASH is about 20%-30% of cases, with 20%-25% of NASH progress to cirrhosis(1, 4, 12), NASH progressing to HCC incidence is similar to alcoholic progressing to HCC, around 3%-4% per year(4). Another study showing NASH progressing to cirrhosis is around 9% in short period (2 – 5 years) (11). Looking into data regarding incidence of NASH induced HCC without cirrhosis, Cholankeril G et al found out that NASH related HCC with cirrhosis was lower compared to patient HCV related HCC with cirrhosis, and NASH related HCC without cirrhosis has been observed in few studies, largely related malignant transformation of hepatic adenoma with underlying metabolic

disease(10). Luis Calzadilla Bertot et al reported a 15% - 50% of cases with NASH related HCC without cirrhosis (12). Brazillian survey done in nine unit of hepatobiliary centre across 6 states by Cotrim HP et al showed NASH related HCC without cirrhosis/fibrosis was around 7.7%(13). Genetic predisposition has been implicated in this conversion (9), thus the study of tumour marker to predict the NASH related HCC has been extensively evaluated. This article also suggested that lipodomic analyses may be a useful way to identify NASH patient who may have a higher HCC risk (9).

Treatment of Non B Non C related HCC is similar to other HCC. NASH/NAFLD treatment included regular exercise and controlled calorie intake. However, NASH related HCC using similar preventive measure are doubtful(10). Other measures like dietary antioxidants, Vitamin E, Vitamin D have chemopreventive potential in patient with NASH. Metformin may have role in decreasing incidence of HCC in NASH(10). Statins have shown a protective effect in individuals who are at risk of developing steatohepatitis and fibrosis(10). Surgical treatment including liver resection and liver transplantation in selected HCC patient. NASH related HCC liver transplant patient was the fastest growing indications according to Cholankeril G et al and Luis Calzadilla Bertot et al. (10, 12). These patients have better survival outcome as compare to HCV related HCC transplant patient in 5 year post transplant period.(10)

The mortality of HCC patient is mainly depending on the histopathology characteristic of the tumour. H. Lang et at on liver resection of HCC in non-cirrhotic liver without underlying viral hepatitis, stated that chance of long term survival is better with patients with solitary tumour without vascular invasion(14). Viral or alcoholic related HCC still top the mortality of HCC as the incidence of viral or alcoholic induced cirrhosis still remain the main aetiology, although NASH/NAFLD related HCC in the rising trend(15).

1.3 Study Rationale

The incidence of Non B Non C hepatitis related HCC has been increasing in the world. Most of the aetiologies of Non B Non C hepatitis related HCC are modifiable factors that can be prevented or altered. The study of NAFLD related HCC has been studied here because the underlying causes of NAFLD are modifiable like obesity, diabetes mellitus etc. The aim of this study is to demonstrate resectable NAFLD related HCC trending incidence over 7 years in high volume centre, identified various modifiable factors that caused it, and its survival outcome.

CHAPTER 2.0 - STUDY PROTOCOL

2.1 DOCUMENT SUBMITTED FOR ETHICAL APPROVAL

Jabatan Surgeri

Department of Surgery

Pusat PengajianSains Perubatan,

Kampus Kesihatan

Universiti Sains Malaysia

16150,Kubang Kerian,

Kelantan,Malaysia.

Date: 13 May 2020

Chairperson,

Human Research Ethics Committee USM (HREC)

Health Campus, USM,

Kubang Kerian, Kelantan.

Protocol Title: Non Alcoholic Fatty Liver Disease Related Hepatocellular Carcinoma: A 7 years Retrospective Observation StudyPrincipal

Investigator: Yong Chin Woon

Dear Prof,

Thank you for considering my thesis proposal.

RESEARCH PROPOSAL

Non Alcoholic Fatty Liver Disease Related Hepatocellular Carcinoma: A 7 years Retrospective Observation Study

PRINCIPAL INVESTIGATOR:

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1.1 Title

Non Alcoholic Fatty Liver Disease Related Hepatocellular Carcinoma: A 7 years Retrospective Observation Study.

1.2 Brief Background

NAFLD related HCC is one of the uncommon causes of HCC compare to Hepatitis B, Hepatitis C and alcoholic. Evidence of NAFLD related HCC is in rising trend in view of increase incidence of obesity and metabolic disease among population. Our aim was to study the NAFLD related HCC in one of the high volume hepatobiliary centre in Malaysia to determined its incidence, various factors associated with NAFLD related HCC and survival outcome.

It's a retrospective cross sectional study among the patient underwent liver resection in Hospital Sultanah Bahiyah for HCC in the period of 7 years (2009-2016). Liver resection include anatomical and non-anatomical hemihepatectomy, segmentectomy, bisegmentectomy, multiple segmentectomy, left and right hepatectomy, extended right and left hepatectomy, either in emergency or elective setting. Other surgery or procedure that is not involve in liver resection like excision or incision biopsy, FNAC of liver nodule, are excluded.

Result will be based on the observation of NAFLD related HCC incidence in the past 7 years, and study on various premorbids including diabetes, hypertension, hyperlipidemia, obesity, smoking etc. associated with NAFLD using multivariate analysis. Survival outcome of NAFLD related HCC also been studied and documented using Kaplan Meyer survival analysis.

Conclusion will be drawn from the above result.

2.Introduction

Hepatocellular carcinoma has become a major health issue all over the world. The incidence and cancer related death has risen steadily over the years, render it becoming the Fifth common cancer in the world, and Third leading cause of cancer related death, behind lung cancer and gastric cancer.

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3.Problem statement & Study rationale

The incidence of Non B Non C hepatitis related HCC has been increasing in the world. Most of the aetiologies of Non B Non C hepatitis related HCC are modifiable factors that can be prevented or altered. The study of NAFLD related HCC has been studied here because the underlying causes of NAFLD are modifiable like obesity, diabetes mellitus etc. The aim of this study is to demonstrate resectable NAFLD related HCC trending incidence over 7 years in high volume centre, identified various modifiable factors that caused it, and its survival outcome.

4. Literature Review

The incidence for NonB NonC related HCC has become one of the major topics to be discussed in the Hepatobiliary Unit around the world. Hiroki Nishikawa et al make an observation study on the epidemiology trend, aetiology and risk factors of NBNC HCC in Japan, noted even though Hep C related HCC is still major cause of HCC, but incidence is reducing trend, and found out NBNC HCC in a rising trend in recent year(1). Many latest articles including Fingas et al reported NBNC HCC incidence in United State accounted around 15% to 50%.(2). In Malaysia, after HBV, cryptogenic/NAFLD is the predominant cause of HCC, owing to increase incidence of obesity and diabetes.(3)

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treatment including liver resection and liver transplantation in selected HCC patient. NASH related HCC liver transplant patient was the fastest growing indications according to Cholankeril G et al and Luis Calzadilla Bertot et al. (10, 12). These patients have better survival outcome as compare to HCV related HCC transplant patient in 5 year post transplant period.(10)

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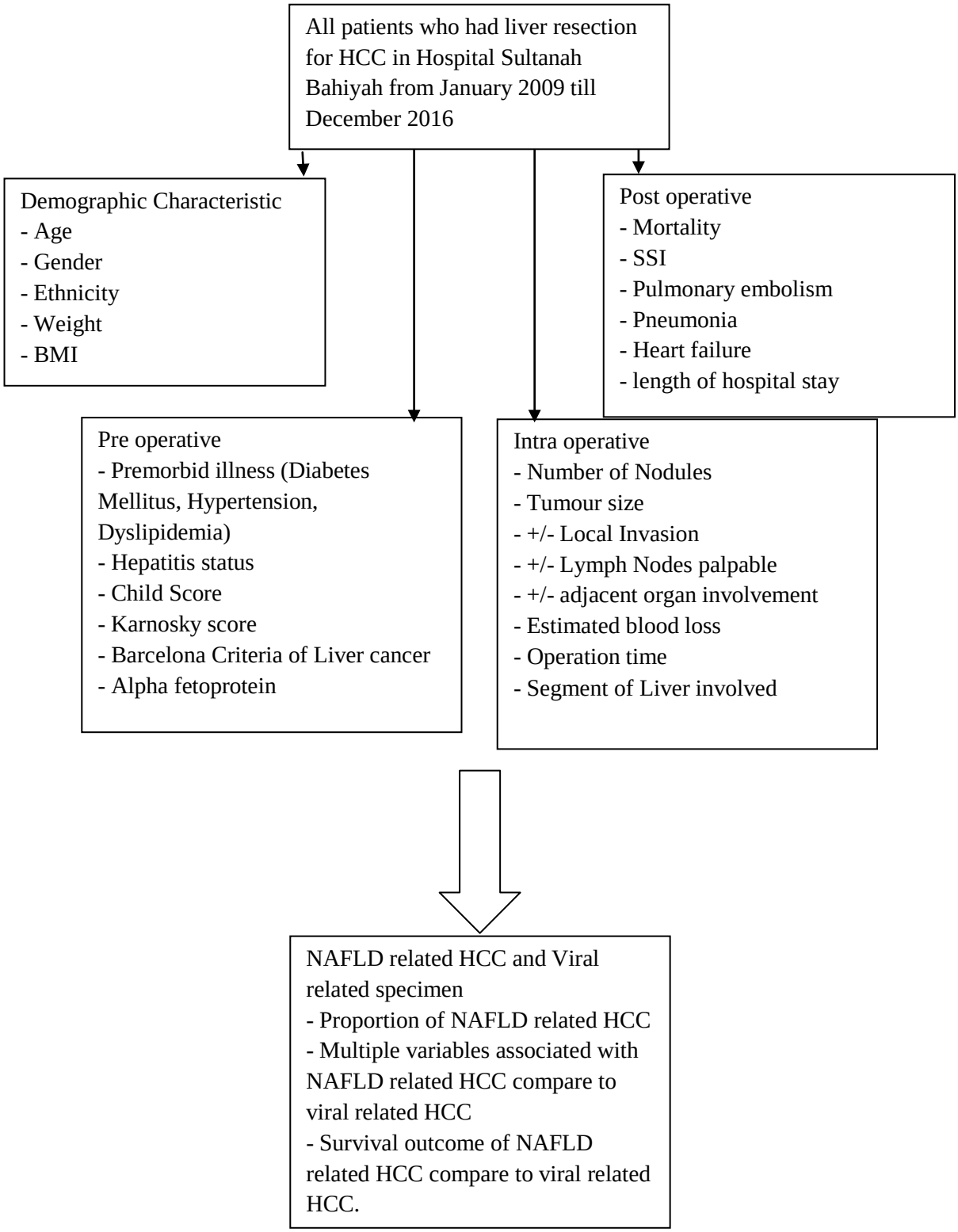
5. Conceptual framework



6. Objective

1. To determine the proportion of NAFLD in the resected HCC for past 7 years in hepatobiliary tertiary centre.

2. To study demography and post-operative outcomes associated with resected NAFLD related HCC with viral associated HCC:

    a. Comorbidity including diabetes, hypertension, dyslipidemia, liver cirrhosis, obesity.

    b. Post-operative complications like SSI, bleeding, liver failure, pulmonary embolism, length of hospital stay.

3. To determine 2 years survival rate of resected NAFLD related HCC in this study in compare to resected viral related HCC:

    a. Variables like post resection histopathological findings include tumour size, tumour number, margin clearance and lymphovascular were compared between viral related HCC and NAFLD related HCC.

7. Research design

7.1 Study Design

It's a quantitative research, using descriptive retrospective cohort study among the patient underwent liver resection in Hospital Sultanah Bahiyah for NAFLD related HCC in the period of 7 years (2009-2016). Various associated confounding factors were studied and compared for NAFLD related HCC and viral related HCC.

Survival analysis were used to study 2 years mortality associated with resected NAFLD related HCC and compare with resected viral related HCC specimen.

7.2 Study Area

Hospital Sultanah Bahiyah, Alor Setar, Kedah

7.3 Study Population

7.3.1 Reference population

All patients who had underwentliver resection for HCC at Hospital Sultanah Bahiyah, Kedah.

7.3.2 Source population

All patients that underwent liver resection for NAFLD related or viral related HCC in Hospital Sultanah Bahiyah, Kedah

7.4 Study duration

All cases that had underwent liver resection for HCC from January 2009 until December 2016.

7.5 Subject criteria

7.5.1 Inclusion criteria

1. Data encoded with A documented ICD-10 diagnosis of Hepatocellular carcinoma with NAFLD or viral related were collected from the Medical Record Unit.

2. All cases of liver resection surgery done for NAFLD related or viral related Hepatocellular carcinoma during the study period were included in the study.

3. Contactable patient or patient family for collection of data through phone call/messenger. Uncontactable patients' information will be traced from National Registration Department with regards to registration of death.

4. Traceable record from the data bank using computer system(eHis) in hospital Sultanah Bahiyah, Kedah.

7.5.2 Exclusion criteria

1. Liver resection was not performed for any reasons, however, incision or excision biopsy or fine needle aspiration cytology of liver nodule that confirmed HCC.

2. Indications of surgery other than HCC, include traumatic liver injury, rupture liver cyst, and rupture liver hematoma, or HCC cases not related to viral of NAFLD.

3. Case with missing case notes, incomplete data or duplicated entries from records

7.6 Sample size estimation

Raosoft® calculator for sample size calculation:

For objective 1, using single proportion estimation for resected NAFLD related HCC among all resected HCC .

- Confidence interval 95%, Z = 1.96
- P = 0.11 (Pinero F et al for changing etiologies in liver cancers in Argentina)
- Precision = 8%
- N =55, considering 10% dropout = 60

For objective 2, using means and proportions estimation respectively for both categorical and numerical variables between two groups.

Comorbids: Diabetes Mellitus between NAFLD group and viral group

- Z = 1.96, Power = 80%
- P0 = 0.61 (Pinero F et al for changing etiologies in liver cancers in Argentina)
- P1 = 0.8
- N = 43, considering 10% dropout = 47 in each group

Comorbids: Dyslipidemia between NAFLD group and viral group

- Z = 1.96, Power = 80%
- P0 = 0.06 (Page & Harrison: NASH and HCC)
- P1 = 0.40
- N = 20 considering 10% dropout = 22 in each group

Comorbids: BMI>30 between NAFLD group and viral group

- Z = 1.96, Power = 80%
- P0 = 0.13 (Page & Harrison: NASH and HCC)
- P1 = 0.45
- N = 28 considering 10% dropout = 31 in each group

Comorbids: Hypertension between NAFLD group and viral group

- Z = 1.96, Power = 80%
- P0 = 0.38 (Rahman R et al. Liver cancer and metabolic syndrome)
- P1 = 0.70

- N = 34 considering 10% dropout = 37 in each group

Comorbids: Cirrhosis between NAFLD group and viral group

- Z = 1.96, Power = 80%
- P0 = 0.25 (Page & Harrison: NASH and HCC)
- P1 = 0.50
- N = 54 considering 10% dropout = 61 in each group

Post-op complications: Surgical site infection between NAFLD group and viral group

- Z = 1.96, Power = 80%
- P0 = 0.11 (Koh et al Liver Resection for Hepatocellular Carcinoma)
- P1 = 0.30
- N = 66 considering 10% dropout = 72 in each group

Post-op complications: Liver failure between NAFLD group and viral group

- Z = 1.96, Power = 80%
- P0 = 0.29 (Koh et al Liver Resection for Hepatocellular Carcinoma)
- P1 = 0.55
- N = 52 considering 10% dropout = 57 in each group

Post-op complications: Bleeding between NAFLD group and viral group

- Z = 1.96, Power = 80%
- P0 = 0.03 (Koh et al Liver Resection for Hepatocellular Carcinoma)
- P1 = 0.40
- N = 15 considering 10% dropout = 16 in each group

Post-op complications: Pulmonary embolism between NAFLD group and viral group

- Z = 1.96, Power = 80%