Is Higher BMI Associated with Worse Overall Mortality in Hepatocellular Carcinoma Patients? An Evidence Based Case Report

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ABSTRAK

Latar belakang: *saat ini kanker hati adalah kanker paling mematikan kedua di dunia yang umumnya dengan karsinoma hepatocelullar (HCC) - terhitung 90% dari semua kasusnya. Dengan peningkatan obesitas global yang cukup mengkhawatirkan, maka ada peningkatan kasus penyakit hati berlemak, yang merupakan salah satu etiologi utama sirosis virus di dunia. Tujuan dari penelitian ini adalah untuk mengevaluasi apakah pasien HCC obesitas memiliki hasil kelangsungan hidup yang lebih buruk.* ***Metode:*** *PubMed, Cochrane, Scopus, ProQuest, dan EBSCOhost secara komprehensif mencari ulasan sistematis dan penelitian prognostik kohort dengan mempelajari kelangsungan hidup keseluruhan pasien HCC yang kekurangan berat badan dan obesitas menurut indeks massa tubuh (IMT) mereka. Tiga studi dipilih dan dinilai secara kritis. Data kemudian dirangkum secara deskriptif.* ***Hasil:*** *tiga studi terdiri dari satu meta-analisis dan dua studi kohort. Studi meta-analisis menyatakan tidak ada hubungan antara kelebihan berat badan dan status obesitas dengan tingkat kematian yang lebih tinggi pada pasien HCC ras Asia (aHR, 1,10; 95% CI, 0,63-1,92). Sebuah studi kohort dari Jepang melaporkan sementara ada perbedaan yang signifikan dari tingkat kematian pada pasien HCC obesitas dalam analisis bivariat, penyesuaian dengan faktor prognostik penting lainnya berdasarkan analisis multivariat tidak ditemukan korelasi signifikan antara obesitas dan tingkat kematian terkait HCC (aHR, 1,00; 95 % CI, 0,83-1,22). Studi kohort lain dari Cina melaporkan bahwa tingkat kematian terkait HCC pada pasien dengan IMT tinggi, lebih rendah daripada pasien dengan IMT rendah (aHR, 0,347; 95% CI, 0,239-0,302).* ***Kesimpulan:*** *tidak ada hubungan antara BMI yang lebih tinggi dengan mortalitas terkait HCC pada pasien ras Asia.*

Kata kunci: *karsinoma hepatoselular (HCC), mortalitas, indeks massa tubuh (IMT), overweight, obesitas, prognosis.*

ABSTRACT

Background: *liver cancer is currently the second deadliest cancer in the world with hepatocelullar carcinoma (HCC) being the commonest form—accounting 90% of all its cases. With the current global alarming increase of obesity, there is hence an increase of fatty liver disease cases, which is one of the major non-viral etiology of cirrhosis in the world. The objective of this study is to evaluate whether obese HCC patients have worse survival*

outcome. ***Methods:*** *PubMed, Cochrane, Scopus, ProQuest, and EBSCOhost were comprehensively searched for systematic review and cohort prognostic researches studying overall survival of HCC patients who are underweight and obesity according to their BMI. Three studies were selected and critically appraised. Data were then summarized descriptively.* ***Results:*** *the three studies included consist of one meta-analysis and two cohort studies. Meta-analysis study stated no association between overweight and obesity status with higher mortality rate in Asian race HCC patients (aHR, 1.10; 95% CI, 0.63-1.92). A cohort study from Japan reported while there was a significant difference of mortality rate in obese HCC patients in bivariate analysis, adjustment with other important prognostic factors with multivariate analysis found no significant correlation between obesity and HCC-related mortality rate (aHR, 1.00; 95% CI, 0.83-1.22). Another cohort study from China reported that HCC-related mortality rate in patients with higher BMI was lower than in patients with lower BMI (aHR, 0.347; 95% CI, 0.239-0.302).* ***Conclusion:*** *there is no association between higher BMI with HCC-related mortality in Asian race patients.*

Keywords: *hepatocellular carcinoma (HCC), Mortality, body mass index (BMI), overweight, obesity, prognosis.*

INTRODUCTION

Liver cancer, the fifth most common occurring cancer in the world, is currently the second deadliest cancer—weighing more than 800.000 per year globally.[1] Hepatocellular carcinoma (HCC), the most common histological form of liver cancer, accounts 90% of all liver cancer cases in the world.[2] In Indonesia, HCC is the fourth most common occurring cancer with a grave prognosis, where the average life expectancy would usually not reach a period of three months.[3] Of all cases of HCC, 80-90% patients had an underlying condition of cirrhosis.[4] In many low and middle income countries, hepatitis B acts as the most common etiologies and is a major risk factor for liver cirrhosis due to the low coverage of hepatitis B vaccination in newborn babies as one of its major cause, followed by chronic hepatitis C, alcoholic liver disease, and non-alcoholic fatty liver disease.[5,6]

The alarming increase of obesity which currently happening across many parts of the world including in developing countries, has been regarded to be one of the major cause of the increase of non-alcoholic fatty liver disease incidence in recent years. The known pathophysiology of which is through the accumulation of triglycerides in the liver that leads to the inflammation and the forming of fibrosis that may later develop into cirrhosis and HCC.[7] This situation is becoming more common in patients and have been considered to negatively impact the prognosis of cirrhosis and at the same time complicate the judgement of performing liver transplantation—particularly in the setting of living donor liver transplantation where the negative ratio of low graft to recipient may affects survival. On the other hand, treatment of obesity tends to be more arduous in these patients due to difficulty in implementing lifestyle measures, safety of orally consumed anti-obesity drugs and high risk of surgery.[8]

Obesity epidemic had emerged as a major factor underlying the increasing burden of liver disease in the United States and many other countries—yet there is no evidence based case report which studied the prognosis of HCC patients who are underweight and obesity.[9] This evidence-based case report is meant to comprehensively review the overall survival rate of HCC patients with an underlying condition of overweight and obesity from available studies.

CASE ILLUSTRATION

A 52 years old woman suffering from fatigue, swelling in the legs, and loss of appetite who had previously been diagnosed with hepatocellular carcinoma (HCC) with the etiology of fatty liver disease went to the doctor as a part of her routine check-up. The woman is currently obese and is wondering whether her weight could contribute to a higher mortality rate in the upcoming years. Therefore, the doctor is curious if the condition of overweight and obesity in people with HCC could worsen their survival rate.

CLINICAL QUESTION

Based on the case illustration, the clinical question is "Is higher BMI associated with worsened overall survival rate in hepatocellular carcinoma patients?"

Table 1. Clinical question formulation

Population	Patients with HCC
Exposure	Overweight and obesity
Comparison	-
Outcome	Death
Type of question	Prognosis
Type of relevant studies	Systematic Review-Meta Analysis of Cohort Studies and Cohort Studies

METHODS

Literature searching was conducted using the keywords shown in **Table 2** from five different journal databases of which are Pubmed, ProQuest, Cochrane, Scopus, and EBSCOhost. The studies obtained from the search were screened by title and abstract. They were filtered through the inclusion criteria which are in accordance with prognostic studies design (cohort, systematic review, and meta-analysis). Relevant articles were then further studied by reading their full article. Articles not in accordance with the objective of this study are separated by the exclusion criteria. Searching strategy, searching results, inclusion and exclusion criteria are shown in **Figure 1**. Exclusion criteria of subjects with age under 50 years old were made to study the natural history of obesity.[10]

RESULTS

Based on the process of article selection, 3 relevant studies were collected to be analyzed further in our evidence-based case report. The studies consist of two cohort studies and one meta-analysis study.

Critical Appraisal

We divided the critical appraisal process and results into two tables based on the studies' design. Critical appraisal of the studies conducted by Li Q, et al.[11] and Fujiwara N, et al.[12] which are both retrospective cohort studies, is evaluated in **Table 4**. Study conducted by Gupta A, et al.[13] is a meta-analysis study and therefore evaluated in **Table 5**.

Cohort Studies

HCC patients analyzed in the study of Fujiwara, et al.[12] were included in the study after being diagnosed with hepatocellular carcinoma (HCC). Based from **Table 4**, weaknesses were found on each aspect of validity, importance, and

Table 2. Searching strategy

Database	Searching Strategy	Hits	Selected
Pubmed	(((((((Obesity[Title/Abstract]) OR Obesity[MeSH Terms]) OR Obese[Title/Abstract]) OR Obese[MeSH Terms]) OR Overweight[Title/Abstract]) OR Overweight[MeSH Terms])) AND ((((Hepatocellular carcinoma[Title/Abstract]) OR Hepatocellular carcinoma[MeSH Terms]) OR HCC[Title/Abstract]) OR HCC[MeSH Terms])) AND ((((((mortality[Title/Abstract]) OR mortality[MeSH Terms]) OR death[Title/Abstract]) OR death[MeSH Terms]) OR survival rate[Title/Abstract]) OR survival rate[MeSH Terms])	316	3
ProQuest	(TI(hepatocellular carcinoma OR liver cancer OR cancer of liver OR hepatoma) OR AB(hepatocellular carcinoma OR liver cancer OR cancer of liver OR hepatoma)) AND (TI(obesity OR (obese OR overweight)) OR AB(obesity OR (obese OR overweight))) AND (TI(mortality OR death) OR AB(mortality OR death)) AND stype.exact("Conference Papers & Proceedings" OR "Scholarly Journals" OR "Dissertations & Theses") AND at.exact("Dissertation/Thesis" OR "Conference Proceeding" OR "Conference Paper" OR "Conference" OR "Article") AND la.exact("English") AND subt.exact("humans" NOT ("animals" OR "mice"))	296	8
Cochrane	"hepatocellular carcinoma" OR "liver cancer" OR hepatoma in Title Abstract Keyword AND obesity OR (obese OR overweight) in Title Abstract Keyword AND mortality OR death in Title Abstract Keyword - (Word variations have been searched)	4	0
Scopus	(TITLE-ABS-KEY (hepatocellular AND carcinoma OR hcc) AND TITLE-ABS-KEY (obesity OR overweight OR obese) AND TITLE-ABS-KEY (mortality OR death OR survival AND rate))	186	1
EBSCOhost	("hepatocellular carcinoma" OR "liver cancer" OR hepatoma) AND (obesity OR (obese OR overweight)) AND (mortality OR death) Human; Human	285	9

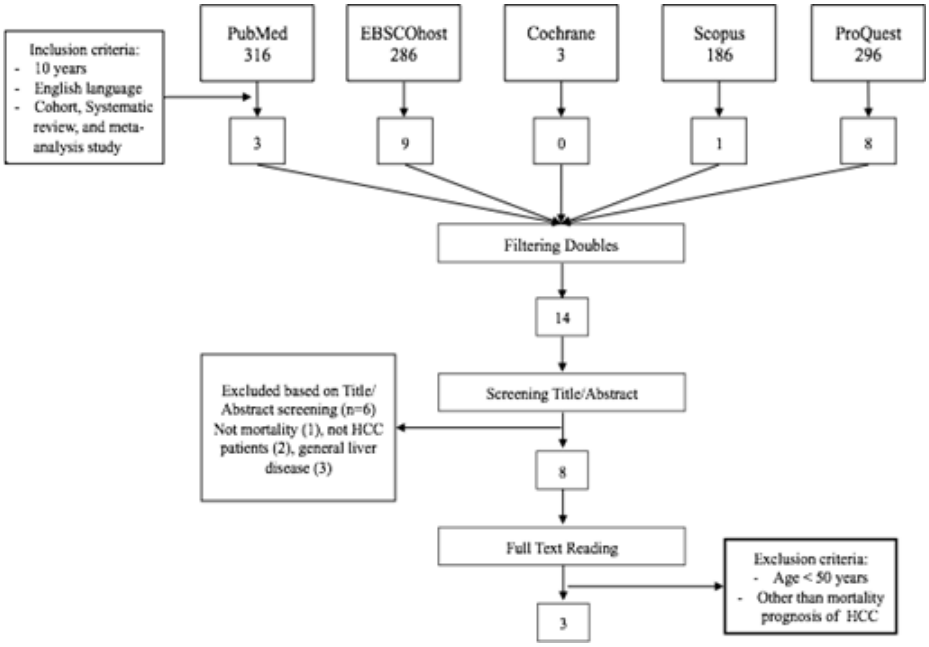

Figure 1. Literature searching procedure

Table 3. Summary of studies

Study	Fujiwara N, et al.	Li Q, et al.	Gupta A, et al.
Type	Retrospective cohort	Retrospective cohort	Systematic Review and Meta-Analysis
Subject	1257 patients with different stages of Hepatocellular Carcinoma in the Department of Gastroenterology, University of Tokyo Hospital.	379 patients who were diagnosed with HCC at the First Affiliated Hospital of Harbin Medical University between June 2012 and August 2014	HCC patients with Obesity, 9 studies in pooled analysis Systematic review from 6 databases; Medline In Process, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, dan Cochrane Database of Reviews of Effect
Control	No control was used	No control was used	No control was used
Results	BMI did not have significant effect on HCC mortality HR = 1.00 [95% CI 0.83-1.22, p= 0.97]	Higher BMI has significant correlation with lower HCC-related mortality rate after adjustment with other prognostic factors (aHR, 0.347; 95% CI, 0.239-0.502). The absolute reduction risk (ARR) is 37,9%.	Obese HCC patients have higher rate of mortality compared to HCC patients with normal BMI in Caucasian patients, while there's no difference in mortality rate of Asian obese and non-obese patients
Other results	Factors such as low SMI (called sarcopenia), low MA (called intramuscular fat [IMF] deposition), and high VSR (called visceral adiposity) were significantly associated with mortality, independently of cancer stage or Child-Pugh classification. A multivariate analysis revealed that sarcopenia (hazard ratio [HR], 1.52; 95% confidence interval [CI], 1.18–1.96; p = 0.001), IMF deposition (HR, 1.34; 95% CI, 1.05–1.71; p = 0.020), and visceral adiposity (HR, 1.35; 95% CI, 1.09–1.66; p = 0.005) were significant predictors of survival	Multivariate analysis found, that besides BMI, Child-Pugh staging, treatment strategy, and extrahepatic metastases has significant correlation with HCC-related mortality rate	On subgroup analysis, magnitude of increased mortality was higher in obese men (aHR, 2.50; 95% CI, 2.02-3.09; 3 studies) as compared with obese women (aHR, 1.45; 95% CI, 1.08-1.97; 2 studies). The impact of premorbid obesity on HCC-related mortality was observed only in western populations (aHR, 2.10; 95% CI, 1.77-2.48; 4 studies), but not Asian populations (aHR, 1.10; 95% CI, 0.63-1.92; 1 study)

Table 4. Critical appraisal for cohort studies

	Appraised Aspects	Studies	
		Fujiwara, et al.	Li Q, et al.
Validity	A defined, representative sample of patients was assembled at a common point in the course of the disease	+	+
	Patient follow-up was sufficiently long and complete	+	+
	Objective outcome criteria were applied in a "blind" fashion	-	-
	There was adjustment for important prognostic factors, if subgroups with different prognoses are identified	+	+
Importance	Likely outcome	-	-
	Precise prognostic estimation	+	+
Applicability	Patients of the study were similar	+	+
	This evidence will make a clinically important impact	-	+

+ = stated in the article; - = not stated in the article

applicability of a critical appraisal. By evaluating the validity, we found no blinding of researchers in both studies—although this is not an issue due to the objective outcome of mortality. Even though blinding was not performed, to minimize selection bias and potential finding, Fujiwara, et al.[12] utilized propensity score. Propensity score is a statistical matching technique using logistic regression which attempt to estimate the conditional probability of exposed subjects by accounting for their confounding factors. Moreover, in the study conducted by Fujiwara, et al.[12] the subjects of research were assembled in the same timeline point of the disease. All patients were followed up for 3 to 8 years. This study also conducted adjustments for significant factors i.e. patients' tumor stage and liver functional status.

The study by Fujiwara, et al.[12] showed a non-statistically significant correlation between BMI and HCC-related mortality with the hazard ratio (HR) of 1.00 [95% confidence interval [CI] 0.83-1.22; p = 0.97]. However, the study found a higher prevalence of poor prognosis in HCC patients with obese and underweight compared to patients with normal BMI. This study also highlighted variety of other body composition measurement such as sarcopenia, IMF deposition and visceral obesity as better predictors of survival. Hazard ratio and confidence interval of each body composition measurement are; Sarcopenia, HR 1.52 [95% CI 1.18-1.96; p = 0.001]; visceral adiposity, HR 1.35 [95% CI 1.09-1.66; p = 0.005], and IMF deposition, HR 1.34 [95% CI 1.05-1.71; p = 0.020]. By utilizing the BMI Guideline for Asia Pacific populations—of which include Indonesia—the patients enrolled in the study conducted by Fujiwara, et al.[12] is identical to our patient in the terms of BMI, although there is no significant effect of BMI found on HCC-related mortality (HR = 1.01) in patients with higher BMI (obesity patients) compared to those who had normal BMI (non-obese patients).

Table 5. Critical appraisal for meta-analysis study

	Appraised Aspects	Study Gupta, et al.
Validity	Clear clinical question in the study	+
	Good study selection	+
	Appropriate criteria for inclusion	+
	Sufficient validity of included studies	+
	Similarity of results from study to study	-
Importance	Clinically important HR/ OR/RR	HR: 1.95
	Precise study result	95% CI: 1.46-2.46
Applicability	Patients of the study were similar	+
	This evidence will make a clinically important impact	+

+ = stated in the article; - = not stated in the article

The study conducted by Li Q, et al.[11] included representative subjects from patients with HCC in Harbin Medical School Hospital. The diagnosis for HCC was also made in the

same hospital, enabling all the patients in the cohort study to be followed simultaneously. This cohort study was conducted with the median follow-up period of 296 days (with a range of 15 until 720 days). The follow-up in this study is considered sufficient because of the mean life expectancy of HCC patients is around 134 days.[3] In the study, Li Q, et al.[11] did not specify whether the outcome was blinded or not. However, considering the outcome of the study is the number of patients with HCC-related mortality, which is an objective outcome, we deem that outcome blinding in this study is unnecessary. Li Q, et al.[11] had also adjusted other important prognostic factors by performing a multivariate analysis which included said factors.

Meta-Analysis Study

The systematic review conducted by Gupta, et al.[13] included 9 different cohort studies from 5 databases which discusses the relationship between premorbid obesity and HCC-related mortality. The systematic review has fulfilled almost all of the validity, importance, and applicability criteria in this case report. However, several weaknesses were found in this review such as a moderate degree of heterogeneity in the review which can be explained due to difference in the population studied by the cohorts included (1 cohort studied Asian population while 4 cohorts studied Western population). While the review did state an existing relationship between premorbid obesity and HCC-related mortality (i.e. premorbid obesity increases HCC-related mortality rate), this relationship is only found in Western population studies—hence the results may not be fully applicable in the Asian population.

DISCUSSION

The ceaseless increase of mortality rate due to hepatocellular carcinoma have been a continuous concern for health-care workers in many parts of the world. In the year of 2012, hepatocellular carcinoma rose to be the second most common cause of death due to cancer worldwide[14]—this is suspected due to the current limited therapeutic options and the increase cases of non-viral hepatocellular carcinoma etiologies such as fatty liver disease with metabolic risk factors of obesity and diabetes.[15-17]

Obesity is one of the major health problems associated with the occurrence of non-alcoholic fatty liver disease (NAFLD).[15] Several studies have shown that NAFLD is currently the most influential factor in the increase of liver-health problems including hepatocellular carcinoma. Studies in the United States found that there are as many as 59% of hepatocellular carcinoma cases associated with NAFLD, while hepatitis C virus infection and alcoholic liver disease (ALD) were only associated with the incidence of hepatocellular carcinoma in 22% and 12% of cases.[18] An increase in NAFLD-related cases of hepatocellular carcinoma was also found in various other studies.[19,20] Meanwhile, other studies found that the increase risk of death due to cancer may be correlated with the value of patients' body mass index (BMI). In the study, patients with a BMI of more than 35 kg/m^2 had a ratio of deaths due to cancer 4.52 times than those who had normal BMI.[21]

In this evidence-based case report, we included three studies that were in accordance with the aforementioned clinical question. The three studies provide different statements regarding whether the condition of obesity may predict mortality in hepatocellular carcinoma patients. Stated in the meta-analysis conducted by Gupta, et al.[13] is that obese patients had a higher mortality rate from hepatocellular carcinoma (aHR, 1.95; 95% CI, 1.46-2.46) compared to patients with normal body weight. Different statement was made by Fujiwara, et al.[12], showing that neither overweight nor underweight condition had a significant effect on hepatocellular carcinoma related deaths. Li Q, et al.,[11] on the other hand, found a higher mortality rate in hepatocellular carcinoma patients with less weight (BMI <23 kg/m^2). With three conflicting findings, the answer whether obesity can predict death in hepatocellular carcinoma patients may be inconclusive.

Of the three studies we analyzed, study conducted by Gupta, et al.[13] based on the results of our critical appraisal, is considered to be the most valid—with all aspects of validity were well fulfilled. Both cohort studies included

did not assess output with the blinding, but considering the outcome of interest being the mortality, blinding was eventually not required. In terms of applicability, Gupta, et al.[13] found that the predictive ability of obesity in cancer deaths was only found in Caucasian race patients. Meanwhile, Asian race patients who were obese are found to have no difference in death due to HCC compared to those who are not obese. This finding was confirmed by Fujiwara, et al.,[12] who found no difference in HCC deaths in obese patients compared with non-obese patients in patients at Tokyo University Hospital. However, study of Li Q, et al.,[11] conducted at the Harbin Medical School Hospital, found that BMI levels can predict deaths from hepatocellular carcinoma, although worse outcomes were found in patients with less weight.

CONCLUSION

This evidence-based case report concluded that according to included studies, there are stronger evidence that there is no association between higher BMI with HCC-related mortality in Asian race patients.

RECOMMENDATION

Although BMI is the most common body measurement in assessing patients' body weight, existing literature recommended to use different body composition measurement in predicting HCC-related death due to obesity. These body composition measurements may include IMF deposition and visceral adiposity status.

Despite the inconclusive statement between studies, obese patients with HCC should still control their diet to improve overall health condition. Medications targeted to reduce obesity must be given by considering its metabolism pathway and liver function.

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