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MINIREVIEWS

Coffee: The magical bean for liver diseases

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Abstract

Coffee has long been recognized as having hepatoprotective properties, however, the extent of any beneficial effect is still being elucidated. Coffee appears to reduce risk of hepatocellular carcinoma, reduce advancement of fibrotic disease in a variety of chronic liver diseases, and perhaps reduce ability of hepatitis C virus to replicate. This review aims to catalog the evidence for coffee as universally beneficial across a spectrum of chronic liver diseases, as well as spotlight opportunities for future investigation into coffee and liver disease.

Key words: Coffee; Hepatocellular carcinoma; Liver; Hepatitis; Fatty liver

Core tip: Coffee is one of the most popular beverages consumed in the United States, with about 75% of the population reporting consuming it. Coffee has also long been associated with hepatoprotective effects, the extent of which there appears to be an ever growing body of benefits as well as a wide variety of etiologies of chronic liver disease it may positively affect. This article reviews recent available literature and summarizes the potential positive or preventive effects of coffee on liver malignancy as well as chronic liver disease secondary to alcohol, viral hepatitis, and fatty infiltration. These studies collectively suggest a simple lifestyle modification patients may be able to incorporate to enhance their own health.

Heath RD, Brahmbhatt M, Tahan AC, Ibdah JA, Tahan V. Coffee: The magical bean for liver diseases. *World J Hepatol* 2017; 9(15): 689-696 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i15/689.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i15.689

INTRODUCTION

With 1.4 billion kilograms of coffee consumed yearly

in the United States alone, coupled with 74.7% of the population being coffee drinkers some may call drinking coffee the national pastime[1,2]. Beyond the taste and stimulating effects, coffee has been associated with improved outcomes with chronic liver disease, hepatocellular cancer (HCC), cirrhosis, colorectal cancer, esophageal cancer, breast cancer, prostate cancer, pancreatic cancer, ovarian cancer, kidney cancer, hepatitis B virus (HBV), hepatitis C virus (HCV), and non-alcoholic fatty liver disease (NAFLD). A recent 2015 meta-analysis of 16 case-control and cohort studies of Western populations demonstrated significantly reduced incidence of cirrhosis amongst coffee drinkers when compared to those who did drink the beverage[3]. As coffee continues to grow in popularity, with daily consumption of coffee-based beverages increasing from 19% to 41% in the 25-39 years old age group from 2008, the documented benefits of increased coffee intake have also grown[4,5]. Furthermore, coffee is generally considered to have a wide safety profile, with the American Food and Drug Administration noting caffeine as a substance generally recognized as safe, not known to be a health hazard[6]. Many countries' health agencies set no upper limit for daily caffeine intake; in 2006 Health Canada did set an upper limit of 450 mg per day as safe[6]. Over 30 million Americans have chronic liver disease and about 31000 deaths have been attributed to it yearly[7]. Studies evaluating coffee's potential hepatoprotective effect on liver disease are important as they may represent a simple lifestyle modification patients can incorporate to enhance their own health.

COFFEE AND AN ASSOCIATION WITH DECREASED LIVER ENZYMES

In numerous studies, it has been noted that coffee consumption has been associated with decreased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), and alkaline phosphatase (ALP). One of the first studies to document consumption of coffee with relatively decreased GGT was in 1985 in the Tromsø Heart Study[8]. That same year, another study noted an inverse relationship between coffee consumption and AST and ALT levels amongst both Korean and Japanese immigrants[9]. These studies began an investigation into elucidating a more direct relationship between coffee and possible hepatoprotective properties. The Tromsø study looked at multiple beverages, notably including green tea. Since 1985 multiple other studies have been performed with similar findings when testing specifically for the possible effect of coffee consumption on liver disease.

One such study, performed in 1993, tested an Italian population of 2240 with findings indicating not only a decrease in GGT but also ALT and ALP in drinkers of three or more cups of coffee daily when compared to groups that drinking less than this amount[10]. Another Japanese study in 1998 of 12687 participants with no history of liver disease or abnormal serum aminotransferases indicated significantly decreased levels of GGT, ALT, and AST in men; however, this finding was unable to replicate in women greater than 50 years of age in the study. Another noteworthy aspect of this study was the lack of similar effect on green tea, suggesting a specific role for coffee in liver disease.

A later 2000 Japanese study of 1353 men demonstrated lower GGT levels in coffee drinkers[11]. A follow-up study by this same group noted lower AST and ALT in Japanese men aged 35-56 years of age[12], noting a decrease in these liver enzymes over a 4 year period with increased coffee consumption. A 1998 amongst Japanese men and women, excluding those with a history of chronically elevated liver enzymes or chronic liver disease, evaluated GGT levels amongst subgroups of alcohol drinkers, body mass index (BMI), and cigarette smoking, and green tea consumption[13]. While coffee consumption was not associated with significantly decreased GGT activity in male non-alcohol drinkers, the response was noted to be significant in male alcohol consumers. Results published in 2014 from the National Health and Nutrition Examination Survey utilized self-reported dietary logs, demonstrating individuals drinking > 3 cups of coffee daily demonstrated significantly lower levels of AST, ALT, ALP and GGT[14]. A 2001 Japanese study evaluated AST and ALT levels amongst 7313 men, excluding former alcohol drinkers or a history of a chronic liver disease, examining for a dose related response by subgrouping men amongst self-reported drinking of < 1, 1-2, 3-4, or > 5 cups of coffee daily[15]. Transaminases were significantly lower in groups reporting increased coffee usage. Of note, men reporting ongoing alcohol use with concurrent coffee consumption exhibited a relatively reduced rise in AST compared to non-coffee drinking alcohol users. A 2010 study in Japan evaluated levels of AST, ALT, and GGT amongst various subgroups of men and women with high BMI, low BMI, and high and low alcohol consumption. Transaminases were noted to be lower amongst men and women with higher coffee consumption, the relationship appearing to be stronger in those with higher alcohol consumption and lower BMI[16].

While studies had been performed previously testing for coffee consumption and its association with liver enzyme levels, one study evaluated effect of coffee in patients with risk factors for chronic liver disease: consumption of greater than two alcoholic beverages daily, positive serum HBV antigen, positive serum HCV antibody, transferrin saturation > 50%, elevated BMI, and uncontrolled diabetics[17]. This study demonstrated relatively reduced levels of ALT amongst these higher

risk groups.

COFFEE AND LIKELY PROTECTIVE EFFECTS AGAINST DEVELOPMENT OF FIBROSIS

Given the above information the association between coffee and relative reduction of liver enzymes appears clear, however, the benefits of coffee appear to extend further. In a 2015 population-based prospective cohort study demonstrated coffee intake with reduced mortality from chronic liver disease[18]. In fact, as little as 1 cup of coffee consumed daily resulted in 15% reduction in risk of death from chronic liver disease; 4 cups daily was associated with 71% reduction, suggesting a dose-dependent response. This study appears to reaffirm findings of an earlier 2005 study noting that consumers of coffee and tea exhibited significantly decreased risk of chronic liver diseases[19]. The study followed 9849 participants for a median of 19 years and a decreased risk of hospitalization or death with a chronic liver disease; a dose-dependent response was seen again in this group, with consumption of 2 or more cups of coffee doubling the relatively reduced risk of complications than those drinking 1 cup. A 2003 Norwegian study found similar findings, noting progressively improved mortality with increasing coffee consumption, though the effect appears to negligible beyond drinking 4 cups of coffee daily[20]. In addition to less frequent complications of liver disease, there is evidence demonstrating coffee has an association with reduced fibrosis. A 2010 study evaluated effect of coffee intake over a six month period in a group of 177 patients with variable degrees of liver fibrosis[12]. In this study, intake of at least 2 cups of coffee daily was associated with the less advanced observed fibrotic disease. A 2011 study echoes these findings, noting that advanced fibrosis in a population of chronic HCV patients was not only seen significantly less frequently in coffee drinkers but that the frequency decreased with increasing reported coffee intake, again suggesting a dose-dependent response[21]. A 2014 Brazilian study reinforces this impression, evaluating 136 patients with biopsy, ultrasound, or endoscopic evidence of fibrotic disease, finding that individuals drinking higher amounts of coffee demonstrated a significantly lower frequency of advanced fibrosis on liver biopsy[22]. A 2015 study of 910 chronic HCV male patients evaluated the association of daily intake of various caffeinated beverages, including coffee, finding a higher percentage of coffee drinking amongst patients without advanced fibrosis than those with demonstrated fibrotic disease[23]. A recent meta-analysis of multiple cohort studies and case-control studies independently demonstrated a significantly reduced risk of cirrhosis with consumption of at least 2 cups of coffee daily[24].

Coffee clearly correlates with reduced frequency of fibrosis, but is coffee itself responsible for these effects, or can its probable protection against fibrosis be seen utilizing any caffeinated beverage? Other studies referenced above seem to suggest hepatoprotection is unique to coffee amongst caffeinated beverages, however, a 2001 study attempted to answer this question head-on[25]. This group noted that caffeine intake from other beverages did not show significant odds ratio along with no evidence of significant trends over the amount of intake whereas with coffee intake there was an inverse association with cirrhosis and coffee consumption with just one cup of coffee daily[15]. A 2012 study found a similar association of reduced observation of advanced in coffee drinkers but not in espresso[26].

There is always a concern when findings of a beverage are correlated with health benefits that there may be confounding factors in play. In a case-control study performed in Italy, it was confirmed that the inverse relationship between coffee consumption and cirrhosis across strata of tobacco use, alcohol consumption, age, and sex. A consistent inverse relationship was still noted in moderate alcohol drinking indicating the relationship between coffee consumption and cirrhosis is not restricted to alcohol-related cirrhosis[27].

The variety of different liver diseases, as well as a variety of ethnicities, involved in the aforementioned studies, suggests a possibly universal effect of coffee on this disease spectrum, however, further studies have been done in populations with more homogenous liver pathology. As one can glean from the above information, chronic viral hepatitis etiologies appear to be most heavily represented population in liver disease literature related to coffee.

COFFEE AND EVIDENCE OF HEPATOPROTECTION IN PATIENTS WITH VIRAL HEPATITIS

In the United States, the most predisposing factors to hepatocellular cancer are alcohol abuse, HBV, and HCV. The aforementioned case-control study in Italy determined that the inverse relationship exists between coffee consumption and cirrhosis across varying degrees of alcohol consumption it is documented that hepato-cellular carcinoma risk is also decreased with the intake of coffee[27].

A similar Italian case-control study performed a few years later also demonstrated a substantial decrease in hepatocellular carcinoma risk in drinkers of coffee of 3 or more cups of coffee daily, going on to note a decreased risk of hepatocellular carcinoma regardless of etiology of chronic liver disease[28]. A large prospective study of 776 participants with advanced HCV-related liver disease was also exhibited lower rates of disease progression with regular coffee consumption. This prospective study noted that drinkers of 3 or more cups

of coffee per day had 53% lower risk of liver disease progression than non-coffee drinkers with advanced HCV-related liver disease[29]. A 2014 study evaluated levels of AST and ALT levels in HCV-HIV co-infected patients, with those self-reporting higher levels of coffee (> 3 cups/d) demonstrating lower levels of liver enzymes[30]. A 2013 cohort study amongst 229 HCV patients with normal baseline ALT levels found that 189 retained normal ALT levels one year after being followed; daily coffee drinks were three times more likely to maintain their baseline ALT level than non-coffee drinkers[31]. Another 2013 study evaluated 40 HCV patients, splitting them into two groups; one drank 4 cups of coffee/day, the other drank no coffee. HCV viral loads were significantly higher in the non coffee drinking group, as well as oxidative damage *via* telomere length and measured 8-hydroxydeoxyguanosine levels[32]. Studies demonstrating a dose-dependent response in patients specific for HCV mediated disease are lacking, however, the previously presented data suggests direction for future studies. A common thread one may note amongst these and aforementioned studies is a large number of studies of HCV infected population. One 2011 cross-sectional study of Asian populations with HBV did not demonstrate any correlation between caffeine drinking and liver fibrosis using elastography as a tool for evaluating severity of disease[33]. While this evidence does not demonstrate that coffee intake in this population may not be associated with decreased risk of HCC, it does suggest that coffee's protective mechanism may be unrelated to prevention of fibrosis.

Beyond demonstrating an association with decreased fibrotic disease, studies are beginning to emerge suggesting a more specific hepatoprotective role for coffee in patients with HCV. A 2015 study utilizing human hepatoma cell line infected with HCV demonstrated significantly decreased HCV viral load in lines introduced to caffeic acid, an organic acid found in coffee, compared to control lines infected with HCV[34]. Another study done in 2015 yielded similar results, with caffeine inhibiting HCV replication a hepatic cell line infected with the virus[35].

COFFEE, METABOLIC SYNDROME, AND NAFLD

While alcohol has been noted to be hepatotoxic, it has long been observed not all alcohol abusers develop cirrhosis. Development and progression of fibrosis appear to involve multiple factors at play in the disease process. Metabolic syndrome appears to be linked to increased risk of fibrosis, though the relationship has not been fully described at this juncture. Research involving coffee and liver disease appears to demonstrate a close relationship between these disease states. In a mortality follow-up study of 51036 individuals, it was noted that coffee drinking had an inverse association with cirrhosis risk in the setting of four or more cups of coffee consumed daily[20]. A fair question, again, concerns whether coffee is a confounding variable; are individuals consuming this much coffee are generally avoiding other foods and beverages which would predispose one to liver disease? Two 2008 Japanese studies appear to reinforce this belief, noting that metabolic syndrome appears to be associated with increased risk of HCC, whilst coffee drinkers appear to be less likely to have metabolic syndrome[36,37]. Given that metabolic syndrome appears to be a risk factor HCC, perhaps due to steatosis, this would imply an indirect benefit of coffee. It is worth noting the second study was done in exclusively HCV patients, suggesting again that coffee is hepatoprotective against a large spectrum of liver disease[37]. Studies have also indicated an association between coffee consumption and NAFLD and liver fibrosis. An inverse relationship between NAFLD patients and fibrosis was noted in a 2011 cross-sectional study[38]. Another two studies was performed using bright liver score as a method to gauge the advancement of NAFLD, noting again an inverse relationship between progression of fibrosis and coffee consumption[39,40]. A 2003 study noted relatively decreased fibrosis in obese women drinking coffee compared to those that did not[25]. The mechanism of possible hepatoprotection in NAFLD is unclear. One 2015 cross-sectional study of a random German patients demonstrated expected correlations between NAFLD and obesity, however, saw no significant difference in either levels of ALT nor sonographic evidence of NAFLD when comparing coffee drinkers *vs* those who did not drink coffee, though is unable to comment on coffee's effect on rate of disease[41]. An earlier noted meta-analysis, it should be stated, did note its protective effect in coffee drinkers significant for HCV and alcoholic liver disease populations, though not in NAFLD[6]. While the NAFLD population is not heavily represented in this study, one must consider the possibility that coffee's potential protective effect on NAFLD may be due to disease modifying effects on metabolic syndrome. Taken together, however, these studies suggest evidence for a positive influence of coffee consumption on NAFLD.

COFFEE AND DECREASED RISK OF HEPATOCELLULAR CARCINOMA

There have been numerous studies performed which have indicated the association between coffee consumption and risk of HCC. We have previously presented information suggesting protective effects of coffee in patients with viral hepatitis, a known risk factor for HCC. Further studies demonstrate broad support for the hypothesis that coffee protects again HCC in general. An earlier referenced population-based prospective cohort study performed involving > 215000 men and women found that when compared with non-coffee drinkers that consumption of 2-3 cups per day had 38% reduction in

Table 1 Summary of findings from studies evaluating coffee consumption and reduced risk of hepatocellular cancer

Studies	Year	Study type	Summary
Setiawan *et al*[18]	2015	Prospective cohort	2-3 cups/d noted to have 38% HCC reduction risk 4 cups/d noted to have 41% risk reduction
Yu *et al*[45]	2013	Prospective cohort	Significantly decreased risk of HCC noted among coffee drinkers
Bravi *et al*[44]	2013	Meta-analysis (14 studies)	40% HCC risk reduction with 1-3 cups coffee/day
Bravi *et al*[43]	2007	Meta-analysis (10 studies)	Inverse association noted between coffee consumption and HCC
Larsson *et al*[42]	2007	Meta-analysis (9 studies)	43% HCC risk reduction
Gelatti *et al*[28]	2005	Case control	Inverse relationship noted between coffee and HCC

HCC: Hepatocellular cancer.

risk for HCC and with 4 cups per day found to have 41% reduction in HCC[18]. Yet another hospital-based case control study found that regardless of the etiology of HCC, there was an inverse relationship of observed HCC with coffee consumption[28]. According to a meta-analysis done involving relevant studies from 1966 to 2007 indicated a 43% reduced risk of liver cancer with the consumption of two cups of coffee[42]. Yet another meta-analysis performed involving ten studies with 2260 HCC cases and six case-control studies from southern Europe and Japan with 1551 cases and four cohort studies from Japan accounting for 709 cases also confirmed an association with decreased risk of liver cancer and coffee consumption[43]. A 2013 meta-analysis of studies through 1966 to 2012 found 14 studies demonstrating a pooled reduced risk of HCC by 40%, suggesting strong evidence that coffee consumption is associated with decreased risk of HCC, though the necessary minimum appears to be anywhere from 1 cups daily to 3 cups[44]. Another 2013 study of Western populations who recorded their consumption of coffee for 24 years, stratifying for age, BMI, as well as smoking and alcohol use with a decreased risk of HCC demonstrated amongst this group of people[45]. These studies together (Table 1) suggest a universally decreased risk of HCC amongst people of all ethnicities with potentially a variety of different risk factors to develop HCC.

COFFEE AND EVIDENCE OF DECREASED RISK OF OTHER GI TRACT MALIGNANCIES

As though the already stated benefits of coffee consumption were not enough there has been emerging data of other malignancies that may also be affected by coffee consumption. In a hospital based case-control study conducted in Italy and Switzerland, it was noted that with greater than three cups of coffee consumed daily was associated with an odds ratio of 0.6 when compared to drinkers of one or less cups of coffee daily in relation to pharyngeal cancer. The same study also noted an odds ratio of 0.6 for esophageal cancer; indicating a decreased risk of pharyngeal and esophageal cancer with greater than three cups of coffee[46]. One case-control study performed earlier indicated an inverse relationship with coffee consumption and colon cancer along with rectal cancer. However, the same study was unable to find a significant association with cancers of the mouth, stomach, or pancreas[47]. Ultimately; coffee consumption appears to have an association with decreased risk of colon, rectal, esophageal, and pharyngeal cancer.

DISCUSSION

With coffee growing in popularity its documented health benefits are also growing. With the benefits of coffee consumption ranging from liver enzyme laboratory test improvement to improved mortality from cirrhosis, HCC, as well as other malignancies, and chronic liver diseases secondary to HBV, HCV and NAFLD.

In summary, the etiology of coffee's apparent beneficial effects have been greatly debated. One hypothesis involves the observation that coffee consumption is associated with better lifestyle choices, confounding the positive effects that had been associated with coffee consumption. One previously discussed cohort study argues against this hypothesis, demonstrating subjects that were prone to increased coffee consumption actually had higher median consumption of cigarettes, lower education levels, and higher median intake of alcohol than those with decreased coffee consumption[16].

An additional question regarding coffee consumption's benefits relates to the attribution of the caffeine content than the coffee itself. In a study involving inpatient cirrhotics, it was noted that caffeine intake from beverages other than coffee did not show significant odds ratio at least in relation to liver cirrhosis[15] Multiple studies referenced above demonstrate beneficial effects related to coffee that are generally not reproducible when testing against other caffeinated beverages. Regardless, as a biologic mechanism has not been proposed, the link is still unclear.

A few hypotheses exist to possibly demonstrate a physiologic basis of coffee's beneficial effects. One hypothesis is that coffee activates enzymes that detoxify the liver *via* activation of uridine 5'-diphospho-glucuronosyltransferases[48]. A 2002 study demonstrates increased expression of such enzymes in mice fed coffee specific compounds known as diterpenes, kahweol and cafestol,

conferring protection against toxins associated with colon cancer[48]. A 2007 study demonstrated that kahweol and cafestole administered to hepatocytes subsequently treated with carbon tetrachloride significantly prevented markers of liver injury as compared to control *via* measured ALT and AST levels, reduced glutathione content and lipid peroxidation[49]. Another hypothesis suggests the anti-oxidant properties of polyphenols present in coffee mediate its hepatoprotective effects[25,50]. As for the mechanism with which coffee prevents worsening of hepatic fibrosis, one thought involves caffeine decreasing transforming growth factor-β (TGF-β), a mediator of fibrogenesis[51]. Hepatic stellate cells are induced by TGF-β for differentiation to myofibroblasts, synthesizing connective tissue involved in fibrogenesis. A study in rat hepatocytes demonstrated caffeine inhibited TGF-β signaling by upregulating peroxisome proliferator activated receptor γ (PPAR-γ)[52]. As noted above, not all studies reviewed suggest a modifying effect of fibrogenesis as the protective etiology conferred in what appears to be a generally positive outcome effect on chronic liver disease, however, further studies appear warranted to evaluate for any possible delayed onset of fibrosis amongst coffee drinkers *vs* non coffee drinkers in comparable populations at risk for cirrhosis. In addition, the studies demonstrating the potential effects of caffeic acid on HCV replication suggest a possible mechanism for the apparent positive affects of coffee in this population. Further studies need to be done to verify these and others noted above, such as coffee potentially preventing HCV replication. Regardless, with the wealth of evidence suggesting a positive disease modifying effect of coffee on chronic liver diseases in a multitude of patient populations, there is clearly a strong basis with which to move forward with studies evaluating the potential causative agent. To conclude, while the reason why coffee is good for you is not yet completely clear, these studies should encourage the vast number of patients with chronic liver disease to enjoy the beverage as many others already do.

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MINIREVIEWS

Cardiovascular assessment in liver transplant for non-alcoholic steatohepatitis patients: What we do, what we should do

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is increasing considerably due to the current lifestyle, which means that it is becoming one of the main indications for liver transplantation. On the other hand, there is a strong association between NAFLD and cardiovascular disease. This has been evidenced in many studies revealing a higher presence of carotid plaques or carotid intima-media thickness, leading to cardiovascular events and, ultimately, mortality. According to the liver transplant guidelines, screening for heart disease in transplant candidates should be performed by electrocardiogram and transthoracic echocardiography while a stress echocardiogram should be reserved for those with more than two cardiovascular risk factors or greater than 50 years old. However, there are no specific recommendations in NAFLD patients requiring a liver transplantation, despite its well-known cardiovascular risk association. Many studies have shown that these patients probably require a more exhaustive assessment and a global approach including other specialists such as cardiologists or nutritionists. Also, the incidence of cardiovascular disease is also increased in NAFLD patients in the post-transplantation period in comparison with other etiologies, because of the pre-existent risk factors together with the immunosuppressive therapy. Therefore, an early intervention on the lifestyle and the individualized selection of the immunosuppressive regimen could lead to a modification of the cardiovascular risk factors in NAFLD patients requiring a liver transplantation.

Key words: Cardiovascular risk; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Pre-transplant assessment; Liver transplantation

Core tip: Non-alcoholic fatty liver disease is a growing condition due to the current lifestyle. It is considered the liver manifestation of the metabolic syndrome, so it is

strongly related to cardiovascular disease. Given that is one of the main indications of liver transplantation, it is essential to carry out an adequate assessment of the pre-transplant cardiovascular risk, as well as an individualized management of the patient in the post-transplantation period (due to the pre-existent cardiovascular risk factors and the immunosuppressive therapy).

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a clinical-pathological condition that encompasses a wide range of liver damage not caused by chronic alcohol consumption, including steatosis, non-alcoholic steatohepatitis (NASH) and cirrhosis[1]. NAFLD is considered a hepatic manifestation of metabolic syndrome. Its prevalence has increased considerably over last years, especially in Western countries, due to the current lifestyle (diet, sedentary lifestyle, obesity)[2,3]. It has been calculated that up to 30% of the population shows NAFLD, representing up to the 70% in patients with type 2 diabetes mellitus (DM)[4]. On the other hand, the prevalence of NASH (characterized by the presence of inflammation) is around 3%-5%. In NASH patients, cardiovascular (CV) risk represents one of the leading causes of mortality due to the frequent association with dyslipidemia, DM and other features of metabolic syndrome[5]. In fact, NASH patients suffer more subclinical atherosclerosis, heart disease, and CV clinical events than those without it[6]. This latter, together with NASH has become the second cause of liver transplantation (LT) in the United States and Europe[7], makes especially relevant the adequate cardiovascular assessment in LT setting.

CV RISK IN NAFLD PATIENTS

Several studies have clearly demonstrated the link between NAFLD and CV risk. It is not surprising, considering that they share many risk factors derived from metabolic syndrome (such as obesity, insulin resistance, DM, sedentary lifestyle, hypertension, dyslipidemia) and genetics (PNPLA3, TM6SF2)[8]. Gut microbiota also plays an important role. In both mice and humans, a high-fat diet results in an increase of lipopolysaccharides in plasma (a cellular component of Gram-negative bacteria) by modifying the microbiota and, therefore, the intestinal permeability. That is the reason to increase TLR4 receptor expression, stimulating liver cells to produce inflammatory cytokines and creating a systemic pro-inflammatory status, which favors atherosclerosis[9,10]. According to CV risk, we can classify it in three steps: Subclinical atherosclerosis, clinical events, and mortality.

Firstly, a higher prevalence of subclinical atherosclerosis has been well-documented (Table 1). In 2005, Brea *et al*[11] published that NAFLD patients showed an increased carotid artery intima-media thickness (CIMT) and a higher prevalence of carotid plaques (50% *vs* 25%) compared to healthy controls. Regarding NAFLD subjects, NASH patients showed greater subclinical atherosclerosis in comparison with those with simple steatosis and the CV risk was progressively increased according to liver fibrosis[11]. Later, Kim *et al*[12] identified that patients with NAFLD had a higher percentage of coronary artery calcification (by computerized tomography) independently of other known factors. More recently, Puchner *et al*[13] again assessed the link between NAFLD and advanced coronary arterial disease. After performing a coronariography by computerized tomography, they found that the presence of significant coronary stenosis (16% *vs* 5%), global carotid plaques (78% *vs* 24%) and high-risk carotid plaques (59% *vs* 19%) were more prevalent in individuals with NAFLD. All of these findings have been confirmed in a recent meta-analysis, as NAFLD patients showed a greater link with subclinical atherosclerosis regarding CIMT [OR 2.04 (95%CI: 1.65-2.51)] and the presence of carotid plaques [OR 2.82 (95%CI: 1.87-4.27)][14]. Secondly, NAFLD patients suffer more CV events than the overall population. In 2016, Fracanzani *et al*[15] aimed to evaluate the incidence of CV and cerebrovascular events in patients with NAFLD, who had been monitored for 10 years. Patients presented a higher number of CV events than the control group (19% *vs* 10%), being the presence of carotid plaques [OR 5.08 (95%CI: 2.56-10.95)] and liver steatosis [OR 1.99 (95CI: 1.01-3.94)] the main risk factors[15]. As a consequence of the higher prevalence of subclinical atherosclerosis and clinical events, CV mortality is ultimately increased as well. In fact, CV-related death appears to be one of the leading causes of death in most of the studies in NASH patients (Table 2). Ekstedt *et al*[16] followed-up 229 patients during more than 30 years, concluding that CV disease was the first cause of mortality for NASH patients without cirrhosis.

Taking all together, the European Association for the Study of the Liver recommend screening for CV disease in patients with NAFLD, irrespective of the presence of other traditional risk factors[17].

CV EVALUATION PRE-LT

CV disease is a major cause of death in post-LT knowing that this risk is bigger in patients showing pre-LT risk factors (irrespective of the etiology). For example, coronary artery disease has been observed in as many as 60% of potential LT candidates and, obviously, its presence increases the CV morbi-mortality pre and post-surgery[18]. Therefore, it is essential an adequate CV assessment to prevent these complications and increase post-LT survival rates.

To be included on the liver transplant list, comprehensive evaluation must be performed to evaluate the

Table 1 Methods to detect subclinical atherosclerosis[8]

Carotid ultrasound	CIMT	> 0.9 mm
CT coronary angiography	No. of calcifications in coronary arteries	⩾ 1
Endothelial function	Flow-mediated vasodilation brachial artery	
	Carotid-femoral pulse wave velocity	> 12 m/s
Morpho-structural alteration	Electrocardiogram (left ventricular hypertrophy)	Sokolov-Lyon > 38 mm; cornell > 2444 mm*ms
Renal function	Slight increase in plasmatic creatinine	M: 1.3-1.5 mg/dL F: 1.2-1.4 mg/dL
	Low glomerular filtration	Creatinine clearance < 60 mL/min
	Microalbuminuria	30-300 mg/24 h Alb/Cr ⩾ 22 (M) or ⩾ 31 (F) mg/g Cr
Inflammatory biomarkers	TNF, IL-6, C-reactive protein	
Thrombogenic biomarkers	PAI-1, fibrinogen, factor VII	

CIMT: Carotid intima-media thickness; CT: Computerized tomography; M: Male; F: Female; TNF: Tumor necrosis factor; IL: Interleukin; PAI-1: Plasminogen activator inhibitor type 1.

Table 2 Cardiovascular mortality in non-alcoholic fatty liver disease patients

Ref.	Year	NAFLD diagnosis	Follow-up	CV mortality	Cause of mortality
Dam-Larsen *et al*[48]	2004	Histology	20 yr	38%	1st
Adams *et al*[49]	2005	Histology	8 yr	25%	2nd
Ong *et al*[50]	2008	Ultrasound	9 yr	25%	1st
Rafiq *et al*[51]	2009	Histology	29 yr	13%	1st
Söderberg *et al*[52]	2010	Histology	28 yr	35%	1st
Angulo *et al*[53]	2013	Histology	9 yr	38%	1st
Stepanova *et al*[54]	2013	Histology	12 yr	28%	1st
Ekstedt *et al*[16]	2015	Histology	26 yr	43%	1st

CV: Cardiovascular; NAFLD: Non-alcoholic fatty liver disease.

peri-surgery risk that could prevent from good long-term results. Regarding to CV assessment, current recommendations include[19]: (1) to carry out an electrocardiogram and a trans-thoracic echocardiography to rule out underlying heart disease; (2) in patients with > 2 CV risk factors or those older than 50 years old, an ergometry or a stress echocardiogram with dobutamine to detect subclinical ischemic cardiopathy; and (3) whether a significant coronary artery disease is detected during the usual evaluation, a coronariography must be performed (if this latter results effective, the survival rate after LT is similar to those who do not have previous CV disease[20,21]). Sometimes, non-invasive methods to screen for CV disease have low sensitivity and specificity compared to other tests (*i.e.*, angiography)[22]. However, there is no sufficient evidence to recommend invasive tests to evaluate CV risk before LT in asymptomatic patients. Therefore, the American Heart Association and the American College of Cardiology Foundation[23] propose to perform a coronariography in CV high-risk candidates, defined as those who have > 2 CV risk factors (DM, age > 60 years, smokers, AHT, and dyslipidemia). On the other hand, they recommend non-invasive stress tests in those patients with low risk of CV disease[24].

Given that CV risk factors before LT have a great impact, it has been proposed that the Framingham Risk Score (an algorithm to predict CV risk at 10 years including age, sex, smoking, DM, arterial hypertension, and dyslipidemia) could be useful for predicting post-LT CV risk in candidate patients. This strategy could lead to performing individualized diagnostic and therapeutic tests depending on the score[25].

Clinical guidelines for NAFLD patients recommend that CV risk must be carefully evaluated in LT setting because theoretically these subjects have more risk factors to suffer CV-related clinical events and mortality. Even more, some of them probably would require invasive tests but the best method remains unclear. The British guideline[26] proposes the evaluation of the functional capacity of the patient measured by the MET unit (energy expenditure during physical activity), guiding the following tests according to the result. Consequently, patients able to climb at least two flights of stairs (equivalent to 4 METs) and those who do not present CV risk factors, may not require further tests. On the other hand, those with a MET < 4 or showing at least one CV risk factors (myocardial infarction, heart failure, stroke/transient ischaemic attack, renal dysfunction, DM requiring insulin therapy) will need a stress echocardiogram or cardiopulmonary exercise test. Likewise, they recommend the simultaneous evaluation with a cardiologist in CV high-risk patients, especially those who have suffered a CV disease before LT[23]. Despite all this, pre-LT CV assessment in NAFLD patients is not routinely different to those patients who have cirrhosis for other etiologies.

CV RISK IN NAFLD POST-LT

Post-LT survival rates have been increasing over time,

Table 3 Immunosuppressive drugs and metabolic side effects affecting post-liver transplantation cardiovascular risk[33]

Drug	Group	Side effects
Corticosteroids		Dyslipidemia ++ AHT +++ DM +++ Renal impairment -
Mycophenolate mofetil	*De novo* purine synthesis inhibitor	Dyslipidemia - AHT - DM - Renal impairment -
Cyclosporine Tacrolimus	Calcineurin inhibitors	Dyslipidemia ++ AHT +++ DM ++ Renal impairment ++
Sirolimus Everolimus	mTOR inhibitors	Dyslipidemia +++ AHT - DM - Renal impairment -

(+): Positive association; (-): No association; AHT: Arterial Hypertension; DM: Diabetes mellitus.

due to the loss of the liver graft is less common and the short-term mortality is lower[27]. After the transplant, patients usually gain weight, and the incidence of metabolic syndrome is greater (as much as two-thirds of patients at 5 years) probably related to the lifestyle and the immunosuppressive treatment, respectively[28,29]. In this scenario, metabolic and CV complications are currently the main responsible for affecting the mid- and long-term survival.

Among non-liver-related 1-year mortality after the LT, CV disease is the second cause after tumors, followed by infections and kidney failure[30]. Madhwal *et al*[31], based on a meta-analysis including twelve observational studies, observed that CV events were present in 13.6% (95%CI: 9%-18%) of NAFLD patients within 10 years. Also, they noted that the incidence of CV disease was especially relevant in those who had additionally metabolic syndrome (four times higher of suffering a CV event)[31]. Precisely, NAFLD patients who required LT are older and have more prevalence of DM and obesity (as well as chronic kidney failure or previous CV disease) in opposition to the rest of etiologies[32].

The prevalence of metabolic syndrome is around 50%-60% of the post-LT population[28,33], influenced by the appearance of several risk factors. Obesity (BMI > 30 kg/m^2) is approximately 24%-64% after LT[27], due to the fact that the weight increases after the operation (reversion of cirrhosis and its hypercatabolic state, increase in appetite, absence of the chronic disease, effects of steroids) which means an increase in DM and dyslipidemia, as well as in vascular events and kidney disease[34]. On the other hand, DM (the most important risk factor of NAFLD) is diagnosed in 10%-64% of post-LT patients[28,35], and is being considered more and more the main complication after LT. Its appearance is multifactorial, but the main modifiable factor (apart from lifestyle) is the choice and dose of the immunosuppressive therapy. Corticoids have diabetogenic effects producing resistance to insulin and increasing the gluconeogenesis, while the calcineurin inhibitors can directly damage the pancreatic cells (tacrolimus has a significantly higher risk than cyclosporine[36]). The immunosuppressive therapy is also responsible, at least in part, of the appearance of post-transplant AHT (40%-85%) and dyslipidemia (40%-66%)[37] (Table 3). All of this means that the liver disease can return after the LT (*de novo* NAFLD). Out of NASH patients who are transplanted, this entity reappears in 75%, being the post-LT hypertriglyceridemia, BMI and steroid treatment, the main risk factors[38] (causing a positive feedback for post-LT CV risk).

In this scenario, several studies have evaluated whether patients with NAFLD show a higher risk of post-LT CV disease in comparison with other etiologies. Yalamanchili *et al*[39] evaluated 2152 patients with liver cirrhosis, of which 12% had NAFLD or cryptogenic cirrhosis. Survival rate at 10 years after the LT was similar regardless of the etiology, but a significant increase was observed in CV mortality in NAFLD patients (21% *vs* 14%)[39]. VanWagner *et al*[40] compared the incidence of CV events between NAFLD and alcohol after the LT. Authors observed an increase in CV-related 1-year mortality after LT in NAFLD group (26% *vs* 8%) and, more interestingly, the most of the CV events occurred in the peri-surgery period (70%)[40]. The same research group has recently determined a group of risk factors clearly associated with post-LT CV mortality: Age > 55 years old, male sex, DM, and kidney failure[32]. Wang *et al*[41] performed a meta-analysis in NAFLD patients to estimate post-LT results regarding overall survival, CV mortality, sepsis and liver graft failure. Authors concluded that survival rates were similar in patients with or without NAFLD, as far as 5 years after LT. However, it was found that NAFLD patients were more likely to die because of CV complications [OR 1.65 (95%CI: 1.01-2.70)][41].

RECOMMENDATIONS IN NAFLD LIVER TRANSPLANT

Pre-liver-transplantation recommendations

Taking into account the information exposed before, the pre-LT CV assessment in patients with NAFLD should be more exhaustive than in the rest of etiologies. However, there are no specific recommendations probably due to there is no an ideal procedure regarding cost, availability, and reliability.

NAFLD is not considered a CV risk criterion to influence the decision of the selection of the CV evaluation in the pre-LT assessment. Consequently, many NAFLD patients only undergo a trans-thoracic echocardiogram or a computerized coronary tomography with calico-score. Some authors have proposed the stress echo-cardiography with dobutamine as an initial test in NAFLD candidates for LT because it shows a high negative predictive value to detect low-risk patients[42]. In high CV

risk patients (age > 55 years, male gender, DM, kidney failure), it probably should be the initial test.

NAFLD is a condition that, more than a specific treatment, needs a multidisciplinary approach whose aim is a dramatic change in the lifestyle[43]. Thus, it is crucial to have a systematic intervention of a nutritionist during the LT evaluation in NAFLD patients (overweight, obesity, unhealthy diet) to reinforce and maintain a healthy lifestyle after the LT[44].

Post-liver-transplantation recommendations

Given that liver transplant recipients have an increased risk of CV disease, an early and effective treatment is required, as well as changing of the other risk factors (lifestyle, treatment of co-morbidities, immunosuppressive therapy). One example is the obligation of starting the treatment to control AHT, dyslipidemia or DM as soon as possible[44].

Regarding the immunosuppressive drugs, most of them can cause and enhance various CV risk factors. Mycophenolate mofetil is associated with an increased risk of CV disease in post-LT patients[45]. More recently, the use of mTOR inhibitors (sirolimus, everolimus) was associated to lower CV risk than calcineurin inhibitors[46]. Therefore, mTOR inhibitors could be considered for patients with metabolic syndrome and multiple CV risk factors, such as NAFLD patients. Nevertheless, these findings must be confirmed and validated in prospective cohorts. On the other hand, we should use a steroid-free regimen (or an early steroid withdrawal) preferably considering an, for example, a basiliximab-based induction therapy[26].

A healthy diet and regular exercise are effective and complementary therapies[47]. Exercise is effective to lower the CV risk in non-transplant patients, but the connection between the benefits and the possible damage of regular exercise after LT has not been established. Also, there are no data concerning the impact of these exercise programs on the prevalence of metabolic syndrome or its individual components after LT.

CONCLUSION

The increased CV risk in patients with NAFLD, compared to other etiologies of liver disease, has important implications both in pre- and post-LT. An adequate stratification of CV risk and an early detection of the different features of metabolic syndrome is required to prevent or decrease CV-related morbi-mortality. In this scenario, an active intervention on lifestyle and an individualized management of immunosuppression could be the most suitable strategies to maintain an adequate balance between risks and benefits.

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ORIGINAL ARTICLE

Observational Study

Trend of hepatocellular carcinoma incidence after Bayesian correction for misclassified data in Iranian provinces

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Abstract

AIM

To study the trend of hepatocellular carcinoma incidence after correcting the misclassification in registering cancer incidence across Iranian provinces in cancer registry data.

METHODS

Incidence data of hepatocellular carcinoma were extracted from Iranian annual of national cancer registration reports 2004 to 2008. A Bayesian method was implemented to estimate the rate of misclassification in registering cancer incidence in neighboring province. A

beta prior is considered for misclassification parameter. Each time two neighboring provinces were selected to be entered in the Bayesian model based on their expected coverage of cancer cases which is reported by medical university of the province. It is assumed that some cancer cases from a province that has an expected coverage of cancer cases lower than 100% are registered in their neighboring facilitate province with more than 100% expected coverage.

RESULTS

There is an increase in the rate of hepatocellular carcinoma in Iran. Among total of 30 provinces of Iran, 21 provinces were selected to be entered to the Bayesian model for correcting the existed misclassification. Provinces with more medical facilities of Iran are Tehran (capital of the country), Razavi Khorasan in north-east of Iran, East Azerbaijan in north-west of the country, Isfahan in central part and near to Tehran, Khozestan and Fars in south and Mazandaran in north of the Iran, had an expected coverage more than their expectation. Those provinces had significantly higher rates of hepatocellular carcinoma than their neighboring provinces. In years 2004 to 2008, it was estimated to be on average 34% misclassification between North Khorasan province and Razavi Khorasan, 43% between South Khorasan province and Razavi Khorasan, 47% between Sistan and balochestan province and Razavi Khorasan, 23% between West Azerbaijan province and East Azerbaijan province, 25% between Ardebil province and East Azerbaijan province, 41% between Hormozgan province and Fars province, 22% betweenChaharmahal and bakhtyari province and Isfahan province, 22% between Kogiloye and boyerahmad province and Isfahan, 22% between Golestan province and Mazandaran province, 43% between Bushehr province and Khozestan province, 41% between Ilam province and Khuzestan province, 42% between Qazvin province and Tehran province, 44% between Markazi province and Tehran, and 30% between Qom province and Tehran.

CONCLUSION

Accounting and correcting the regional misclassification is necessary for identifying high risk areas and planning for reducing the cancer incidence.

Key words: Trend of hepatocellular carcinoma; Cancer incidence registry; Misclassification; Bayesian correction

Core tip: In many developing countries and even in some developed countries some errors occur in disease registry system. Since registered data is used for planning at the national and sub-national level, correcting the existed errors has a great importance. One of these errors is misclassification in registering cancer incidence. It occurs because some patients from divested provinces prefer to get more qualified diagnostic and treatment services at their adjacent provinces with more medical facilities without mentioning their permanent residence. The aim of this study is to investigate the trend of hepatocellular carcinoma after correcting for misclassification error in Iran's cancer registry using Bayesian method.

Hajizadeh N, Baghestani AR, Pourhoseingholi MA, Ashtari S, Fazeli Z, Vahedi M, Zali MR. Trend of hepatocellular carcinoma incidence after Bayesian correction for misclassified data in Iranian provinces. *World J Hepatol* 2017; 9(15): 704-710 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i15/704.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i15.704

INTRODUCTION

Hepatocellular carcinoma (HCC) is the 5th most common cancer worldwide[1]. It is the fifth most common cancer in men (7.5% of the total, 554000 cases) and the ninth most common cancer in women (3.4% of the total, 228000 cases). Eighty-three percent of the estimated new cancer cases worldwide occurred in less developed regions in 2012 that 50% of that belongs to China alone[2]. HCC is the second most common cause of cancer death in the world[1] and it is estimated to be responsible for nearly 746000 deaths based on Globocan report 2012[2]. The major risk factors for HCC, are infection with the hepatitis B virus (HBV) and hepatitis C virus[3]. The most common cause of HCC in Iran is HBV and 80% of HCC cases are positive for at least one of the markers of HBV[4-6]. It is estimated that approximately 1.5 million people in the country are infected with this virus and 15% to 40% of them are at risk of developing cirrhosis or HCC[7,8]. The other known risk factors are Gender (HCC is more common in males than in females), Race (Pacific Islanders and Asian Americans have the highest rates of HCC, followed by American Indians and Hispanics, African Americans, and whites), Cirrhosis, Non-alcoholic fatty liver disease, Heavy alcohol use, Obesity, Aflatoxins and Tobacco use[9]. Overall mortality to incidence ratio of HCC is 0.95, so the geographical patterns of incidence and mortality are similar[2,3]. The regions of high incidence are Eastern Asia and South-Eastern Asia, the regions of intermediate incidence are Southern Europe and Northern America (9.3) and the lowest rates are occur in South-Central Asia and Northern Europe[2]. Iran is located in Middle East, an area with low risk for HCC[1,10] with an annual incidence much less than 5 per 100000 populations[4,11] but, while prognosis for HCC is very poor, the true prevalence of HCC in Iran is unknown and up to 40% of its death statistics are underreported; so it is not considered as an uncommon malignancy[2-4].

Nowadays having a thorough information of geographic distribution of cancers has become so important[12]. Cancer registries are known as the main resource of epidemiologic data by registering the mortality, incidence, prevalence and survival for different disease in a systematic manner that is used by health policy makers for cancer control planning and evaluation of cancer

screening programs, detecting the impact of treatments and interventions, and allocating of resources to various provinces based on their need to healthcare facilities[13]. In addition to poor diagnosis of HCC, some patients want to get healthcare in facilitate neighboring provinces outside their resident without reporting their permanent address. It causes misclassification error in cancer registry system. Misclassification error is the disagreement between the observed and the true value. The expected coverage of cancer incidence in different provinces is the evidence of existence of misclassification error; that the observed rate of incidence is more than expected rate in some of the provinces, but then, it is much less than expected rate in their neighboring provinces[14], while it is expected that the rate of cancer incidence be about the same in neighboring provinces that are similar in lifestyle and environmental conditions. Misclassification error in registered data leads to erroneous estimates of the incidence rates of cancer in different provinces and consequently affects need assessments. There are two methods to correct for misclassification error. The first is using a valid data that usually is not available or it is so time consuming and costly to valid a sample data and generalizing the results to the population[15]. The second is implementing Bayesian method. This is a statistical method that can be used to import the researcher's prior knowledge about the rate of misclassification to the analysis and updating prior information with observed data to estimate the misclassification rate[16].

The aim of this study is to assess the trend of HCC incidence after correcting for misclassification error in registering cancer incidence in neighboring provinces of Iran, using a Bayesian method.

MATERIALS AND METHODS

Incidence data of HCC was extracted from Iranian annual of national cancer registration report from 2004 to 2008[14]. Annual of 2008 was the last available data to use. The Age Standardized Rate (ASR) for HCC [coded based on the 10th revision of the International Classification of Diseases (ICD-10; C22)] was calculated for all provinces of Iran in each year with direct standardization method and using the standard population reported by Word Health Organization for both genders and four age groups (0-14 years, 15-49 years, 50-69 years and over than 70 years old). Age standardized rate was used to achieve comparative statistics on cancer in Iran with those for other countries[17].

The expected coverage of cancer cases was calculated for medical universities of each province that is considered to be 113 per 100000 population. In the process of cancer incidence registry, all new diagnosed cancer cases by diagnostic centers are reported to the medical university. Reported data are entered to software which is made by ministry of health. Medical university of each province sends its temporary data bank to the ministry of health. Ministry of health after removing duplicates and coding the recorded cancers based on 10th revision of international coding of disease provides a permanent data bank of cancer cases and sends it back to medical university of each province. So medical universities have an observed number of cancer cases in addition to the expected rate. Percent of expected coverage for each province is calculated by dividing the observed number to the expected number of cancer cases.

The data were entered to the Bayesian model in the form of two vectors y_1 and y_2. Vector $y_1 = (y_{11}, y_{21}, ..., y_{r1})'$ contained the data of the province that has an expected coverage less than 100% and vector $y_2 = (y_{12}, y_{22}, ..., y_{r2})'$ contained the data of a neighboring province with more than 100% expected coverage. Subscript r is the indicator of covariate patterns that is made by age-sex group combinations. A Poisson distribution was considered for y_1 and y_2 that are count data[18,19]. An informative beta prior distribution was assumed for the misclassified parameter θ as the probability of registering a data in misclassified group; so $\theta \sim beta\ (a,b)$[20-22]. In order to the expectation of beta distribution which is $a/(a + b)$ get converged to the misclassified rate, prior values for b were selected based on the calculated expected coverage of the medical university with lower than 100% expected coverage and a was calculated with subtracting b from 100. Since misclassified parameter is unknown, a latent variable approach was employed to correct the misclassification effect[18,19]. The latent variable U was considered as the number of events from the first group that are incorrectly registered in the misclassified group with binomial distribution, *i.e.*, $U_i|\theta,y_1,y_2 \sim Binomial\ (y_{i2},P_i)$ that $P_i=(\lambda_{i1}\theta)/(\lambda_{i1}\theta + \lambda_{i2})$.

Finally by multiplying likelihood function in prior distribution, posterior distribution obtained in the following form; $\theta|U_i,y_1,y_2 \sim Beta\ (\sum_i U_i + a, \sum_i y_{i1} + b)$[18,23-25]. Misclassified parameter was estimated by using a Gibbs sampling algorithm and averaging the generated posteriors. After estimating the misclassification rate between each two neighboring provinces, the rates of HCC incidence for each province were re-estimated and the trend of HCC were checked out during 2004 to 2008. Analyses were carried out using R software version 3.2.0.

RESULTS

All registered HCC cases from 2004 to 2008 in Iran were included in the study. The ASR of HCC for female increases from 0.43 per 100000 population (103 cases) in 2004, to 1.56 per 100000 (376 cases) in 2008. Also ASR of HCC for male increases from 0.66 per 100000 population (180 cases) in 2004, to 2.03 per 100000 (574 cases) in 2008. The trend of HCC from 2004 to 2008 for Iranian male and female is shown in Figure 1.

Among 30 provinces of Iran, 21 ones were selected for correcting the misclassification error in registering HCC incidence in neighboring provinces based on their expected coverage percent of cancer cases. In the other nine provinces, the number of cancer cases was about the same as their expected number; so the cancer

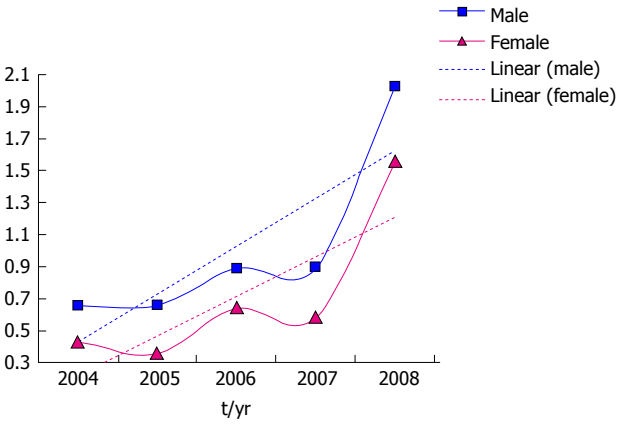

Figure 1 Age standardized rate of hepatocellular carcinoma and its trend for male and female in Iran (2004-2008).

Table 1 Expected coverage of cancer cases in provinces of Iran (2004-2008)

	2004	2005	2006	2007	2008
South khorasan		30.30	45.16	41.02	41.40
Razavi khorasan	106.50	106.50	101.81	117.54	143.74
Tehran	157.11	157.11	162.25	145.74	155.63
Markazi	43.35	43.35	53.07	57.46	69.60
Sistan	25.24	25.24	18.78	18.83	18.44
Qom	53.09	53.09	62.76	60.98	53.90
Ghazvin	65.07	65.07	71.44	72.84	66.30
Khozesta	61.09	61.09	62.68	69.81	101.19
Ilam	28.42	28.42	32.97	41.27	39.40
Bushehr	28.46	28.46	29.10	26.00	25.00
Golestan	50.65	50.65	58.61	58.20	50.80
Mazandaran	148.13	148.13	161.78	163.83	338.45
North khorasan		30.76	40.47	44.87	34.80
Chaharmahal	40.67	40.67	34.39	40.76	37.00
Isfahan	111.51	111.51	114.09	116.93	106.98
Kohgilouye	23.90	23.90	29.00	29.60	25.10
Hormozgan	25.44	25.44	25.11	25.31	19.00
Fars	98.07	98.07	112.01	134.53	127.65
Ardebil	63.73	63.73	72.71	64.99	63.00
East azarbaijan	108.22	108.22	110.98	138.52	123.60
West azarbaijan	81.96	81.96	75.32	82.53	69.00

rates of them remained unchanged. Each time the data of two neighboring provinces that one of them had a more than 100% expected coverage and the other one had a less than 100% of its expected coverage were candidates for entering the Bayesian model for estimating the existed misclassification between them.

For example the reported percent of expected coverage of cancer incidence for East Azerbayjan which is a province with more medical facilities in north-west of Iran, was 123.6% in 2008. It means that East Azerbaijan province have covered 23.6% more cancer cases than its expectation, whereas the West Azerbaijan and Ardebil provinces that are in neighborhood of East Azerbaijan, have just covered 69% and 63% of their expected coverage of cancer incidence respectively; which is a clear indication of existence of misclassification error in registering cancer cases. The expected coverage for the provinces for years 2004 to 2008 are reported in Table 1. After implementing the Bayesian method it was estimated to be 0.13% misclassification between East Azerbaijan and Ardebil and 0.42% misclassification between East Azerbaijan and West Azerbaijan in 2008. The estimated misclassification rate among other provinces for years 2004 to 2008 are reported in Table 2. The rate of HCC incidence, before and after Bayesian correction of misclassification for years 2004 to 2008 are reported in Table 3.

Table 2 Bayesian estimated from misclassification rate between provinces

		Estimated misclassification rate				
		2004	2005	2006	2007	2008
Razavi khorasan	South khorasan		0.2	0.51	0.44	0.58
Tehran	Markazi	0.31	0.41	0.39	0.38	0.73
Razavi khorasan	Sistan	0.39	0.39	0.65	0.41	0.51
Tehran	Qom	0.18	0.22	0.18	0.28	0.65
Tehran	Ghazvin	0.2	0.25	0.5	0.4	0.74
Khozesta	Ilam	0.19	0.21	0.42	0.5	0.73
Khozesta	Bushehr	0.38	0.4	0.31	0.36	0.72
Mazandaran	Golestan	0.08	0.28	0.21	0.14	0.38
Razavi khorasan	North khorasan		0.16	0.43	0.34	0.42
Isfahan	Chaharmahal	0.16	0.16	0.18	0.39	0.23
Isfahan	Kohgilouye	0.18	0.43	0.16	0.18	0.16
Fars	Hormozgan	0.3	0.34	0.4	0.38	0.64
East azarbaijan	Ardebil	0.36	0.17	0.13	0.46	0.13
East azarbaijan	West azarbaijan	0.28	0.15	0.05	0.25	0.42

DISCUSSION

There was a non-ignorable misclassification in registering cancer incidence between neighboring provinces in Iran. An increase is observed in trend of HCC during 2004 to 2008. The rate of HCC is even gets higher in some provinces after correcting for misclassification. Higher rates of estimated misclassifications are belonging to provinces with lower facilities like Hormozgan, Bushehr, Ilam, Qom, Markazi, Qazvin, Sistan and South Khorasan. Meanwhile it seems that misclassification rate is increasing during the period under study. It shows that not enough attention is paid to equip low-facilitate provinces.

The incidence of this cancer in many countries such as the United States, Central America and Europe is on the rise[7]. The findings of a study on incidence of HCC in Iran, showed that the incidence of this cancer is increasing in the country, especially in males and higher age groups[1]. A study on HCC indicated that little is known about the incidence of HCC in Iran, particularly in southeast of the country. Some provinces such as Ardebil, Guilan, Kerman, Fars, Razavi Khorasan, and most notably Tehran as the capital of Iran, have a low but significantly higher incidence proportional to other provinces[26]. It is also indicates the presence of misclassification error between neighboring provinces that are expected to have similar incidence rates of cancer.

Knowledge of geographic pattern of diseases is useful to identify the influencing factors on disease incidence and planning for disease control and prevention[27,28].

Table 3 Age standardized rate of hepatocellular carcinoma

	ASR before Bayesian correction					ASR after Bayesian correction				
	2004	2005	2006	2007	2008	2004	2005	2006	2007	2008
South khorasan		0.50	0.46	0.46	0.47		0.83	0.98	0.95	1.12
Razavi khorasan	0.74	0.35	1.18	0.91	1.57	0.54	0.17	0.61	0.25	0.64
Tehran	0.43	0.44	0.57	0.46	2.23	0.37	0.37	0.51	0.41	2.12
Markazi	0.37	0.25	0.35	0.30	0.32	0.63	0.48	0.61	0.49	0.66
Sistan	0.44	0.21	0.26	0.52	0.63	1.07	0.50	1.14	1.65	1.90
Qom	0.67	0.55	0.95	0.45	0.48	0.90	0.78	1.22	0.65	1.05
Ghazvin	0.62	0.47	0.24	0.27	0.32	0.80	0.65	0.40	0.42	0.67
Khozesta	0.79	0.65	1.00	1.23	5.09	0.62	0.46	0.73	0.93	4.47
Ilam	1.13	0.86	0.54	0.49	0.78	1.88	1.50	1.23	1.07	2.23
Bushehr	0.45	0.36	0.85	0.83	0.82	1.05	0.87	1.75	1.97	3.16
Golestan	0.76	0.40	0.83	0.55	0.66	0.88	0.62	1.13	0.68	1.14
Mazandaran	0.22	0.46	0.61	0.28	1.04	0.18	0.35	0.43	0.20	0.80
North khorasan		0.62	0.62	0.76	0.86		0.94	1.28	1.34	1.89
Chaharmahal	0.84	1.13	1.02	0.52	1.01	1.17	1.57	1.55	1.01	1.62
Isfahan	0.41	0.61	0.64	0.85	0.83	0.27	0.40	0.44	0.68	0.52
Kohgilouye	0.39	0.32	1.15	1.36	1.54	0.68	0.90	1.78	2.18	2.51
Hormozgan	0.26	0.25	0.69	0.68	0.51	0.56	0.57	1.78	1.70	2.23
Fars	0.30	0.35	1.12	0.80	2.21	0.22	0.27	0.67	0.54	1.56
Ardebil	0.47	0.49	0.41	0.41	2.20	0.74	0.61	0.48	0.69	2.65
East azarbaijan	0.69	0.30	0.19	0.92	0.97	0.44	0.16	0.12	0.57	0.61
West azarbaijan	0.64	0.55	0.91	0.98	0.53	0.86	0.64	0.97	1.27	0.84

When a cluster with high incidence is not occurred by chance, this question comes to mind that what could be the underlying causal mechanism. It is natural to initially get focused on risk factors of the disease[29]. But major differences in incidence rate of HCC in neighboring provinces that are almost identical in exposure with risk factors, is justifiable with existence of misclassification error in registering patient permanent residence, that are diagnosed and registered in facilitate provinces of the country.

In conclusion there is misclassification error in cancer registry system despite international efforts to standardize cancer incidence data collection processes and elimination of deficiencies in personal and demographic information, especially in developing countries such as Iran[30]. So the true incidence rate of HCC is higher than the reported rate in some provinces and consequently lower in some other provinces. Since cancer registry data is used by health policy makers to allocate the facilities and resources to different provinces. To help for making the right decisions, it is necessary to correct for misclassification in cancer incidence between provinces. Otherwise again fewer resources will be assigned to low facility provinces based on the low incidence rate, while they are in need of more healthcare facilities and the true cancer incidence rate is more than taught in that provinces.

Iran is located in Middle East, a region where majority of HCC cases presents with intermediate or advanced stages of the disease[4,31]. In most Asian countries, early detection and treatment services are limited. There are many people who have no health insurance and many of them are too poor to go for screening tests or medical treatments. Therefore, it is important for the health organizations and governments in each country to recognize these groups in order to reduce the incidence and mortality of cancers[5].

The dramatic increase in the forecasted number of deaths due to HCC in the United States is a warning to the research and healthcare systems since it projected to be one of the top three cancer killers in 2030[32-34].

So whereas deaths from liver are projected to increase, changes in treatment and prevention strategies, using screening tests, vaccination, and informing about risk factors and early symptoms of HCC can alter both the incidence and death rates. It requires an unisonant effort by search and health care organizations now for a substantial change in the future[7,9,34]. Also employing and training more motivated and educated staff in all sectors of cancer registry program in order to complete the cancer case registry forms accurately and remit them to the appropriate center, Enhancing hardware and software resources, expert researchers in medicine, biostatistics and computer science are needed to qualify the cancer registry program and increasing its completeness; specially in address-related information[35,36].

In the absence of valid data, statistical methods are good alternatives for correcting the existed errors in data. Of course it should be noted that there is always some uncertainty as a potential weakness in statistical models and the statistical model which was used in this study is also not an exception. Thus a small cluster of HCC cases could be misattributed as patients registering in a neighboring province. But the low cost, high speed and efficiency of this model can compensate small errors.

COMMENTS

Background

Some patients from deprived provinces prefer to get medical treatment in their

neighboring provinces with more medical facilities without mentioning their permanent residence. It makes misclassification error in cancer registry data. Consequently health policy makers who use cancer registry data for resource allocation and cancer control programs will make mistakes in their decisions. The aim of this study is to investigate the trend of hepatocellular carcinoma incidence after correcting for misclassification between neighboring provinces by means of a Bayesian method.

Research frontiers

Knowing about geographic spread of cancers is so important for identification the risk factors of cancers for control and prevention purposes. There is misclassification in patient's permanent residence in Iran's cancer registry data that leads to under-estimating the rate of cancer in some provinces and consequently over-estimating in other provinces. While those cancer rates are used in spatial analysis to determine the high risk areas, the existence of misclassification error is usually ignored. The hotspot of this study is accounting and correcting for misclassification in registering cancer incidence using the Bayesian method.

Innovations and breakthroughs

By using the Bayesian method for estimating the rate of misclassification, that's enough to have prior information about the misclassification rate and there is no need for validating data to explore the misclassification rate which is costly and time consuming. Bayesian method for correcting the misclassification is a faster and more cost effective method in comparison to data validation which in many cases is not achievable.

Applications

Cancer incidence rates are used for allocating medical resources to different provinces. So to have more accurate estimates from the rates of cancer incidence in each province misclassification error in registering patient's permanent residence should be corrected. Consequently better planning and decisions will be made for interventions for cancer control and prevention.

Terminology

Bayesian method is a statistical method that assigns a prior distribution to parameters or events, according to expert's idea or previous knowledge from previous studies and updates those distributions with combining prior knowledge by observed data by using Bayes' theorem. Misclassification is one of the measurement error which is defined as disagreement between the observed value and the true value in categorical data.

Peer-review

This is a very interesting study from Iran aimed at estimating the rate of regional misclassification in registering the incidence of hepatocellular carcinoma in cancer registry system using a Bayesian method. The study is original and very well written. The statistical analysis is well done. The results are consistent.

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LETTERS TO THE EDITOR

Usefulness of the MESH score in a European hepatocellular carcinoma cohort

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Abstract

The Barcelona Clinic Liver Cancer classification is the most widely - used hepatocellular carcinoma (HCC) staging system because it is simple, precise and linked to a treatment algorithm based on randomized studies. But each group includes a broad spectrum of tumors, with limited therapeutic options, particularly for intermediate and advanced stages. Consequently, different additional scoring systems have been proposed to refine the prognosis and/or to improve the management. But until now, there is no consensus. Liu *et al* proposes a new scoring system, based on a large HCC cohort, with patients at different stages, treated using diverse modalities. This score includes six parameters used in current practice. It is simple to calculate, reliable, with an ability to predict survival superior to other systems, which also works with our European HCC cohort. The MESH score may be especially useful to differentiate subgroups with different prognosis for each treatment modality.

Key words: Hepatocellular carcinoma; Barcelona Clinic Liver Cancer; Scoring system; MESH; NIACE

Core tip: The Barcelona Clinic Liver Cancer system has become the reference classification for hepatocellular carcinoma (HCC). But it has been criticized; each group includes a broad spectrum of tumors with limited therapeutic options. For this reason, different additional scoring systems have been proposed to improve the management. Liu *et al* proposes the MESH score, based on a large HCC cohort. It includes six parameters used in current practice, and in a European HCC cohort, this new score appears to be simple, reliable and useful to differentiate subgroups with different prognosis for each treatment modality.

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TO THE EDITOR

Hepatocellular carcinoma (HCC) staging system is still a controversial issue, and we have read with interest the article by Hsu *et al*[1] who proposed a new survival prognostic score for HCC called MESH. This score has been determined by multivariate analysis within a large HCC cohort (n = 1591) mainly related to viral B hepatitis, mostly treated (44%) with curative strategy (surgery or radiofrequency ablation). The MESH score demonstrated a good predictive survival value, superior to other known staging and scoring systems [Barcelona Clinic Liver Cancer (BCLC), Hong Kong Liver Cancer (HKLC), Cancer of the Liver Italian Program (CLIP), Taipei Integrated Scoring system] within a large validation cohort (n = 1591), with a lower Akaike information criterion (AIC) value, a higher homogeneity; within each BCLC stage and whatever treatment strategy (curative or palliative).

We have evaluated the prognostic value of the MESH score and compared it to other known staging and scoring systems [BCLC, HKLC, CLIP and NIACE: Tumor Nodularity, Infiltrative nature of the tumor, serum Alpha-fetoprotein (AFP) level, Child-Pugh stage, Eastern Cooperative Oncology Group Performance Status (ECOG PS)[2]] within a French HCC cohort including 581 patients. Demographic and clinical characteristics of the 581 patients with HCC are shown in Table 1. Our patients were mostly male (82%), with a mean age of 67 years. Cirrhosis was present in 87% of our patients, CP A (64%), CP B (36%). Underlying liver disease was mostly related to alcohol abuse (37%) or viral C hepatitis (36%). HCC were multinodular in 61% of cases and vascular invasion or distant metastasis was found in 37% and 10% of patients, respectively. Baseline ECOG PS of our population (as expression of symptomatic tumor) was as follows: PS 0 (48%), PS 1 (23%), PS 2 (24%), PS 3-4 (5%). BCLC distribution was similar to the Liu cohorts: BCLC A 31%, B 16%, C 41% and D 12%. Treatment modalities were as follows: 23% were treated by surgery or radiofrequency ablation (RFA), 30% by transarterial chemoembolization, 26% by Sorafenib and 21% have received supportive care. Mean overall survival for the entire cohort was 26.0 ± 1.3 mo, consistent with the median follow-up duration: 18.3 ± 20.3 mo. Seventy-one percent of patients died. The discriminatory ability (linear trend χ^2 score), homogeneity ability (likelihood ratio test), prognostic stratification ability (AIC) and C-index were compared among scoring systems. Survivals between groups were compared using log-rank test in case of proportionality of hazards across time; generalized Wilcoxon test was used in case of non-proportionality of hazards.

Table 1 Baseline characteristics in European hepatocellular carcinoma cohort (n = 581) n (%)

Patients characteristics	Cohort (n = 581)
Age, yr, mean ± SD	67.4 ± 11.7
Male	475 (82)
Etiology - HCV/HBV/Alcohol/MS/others	209 (36)/41 (7)/215 (37)/87 (15)/29 (5)
Cirrhosis	505 (87)
Child - Pugh stage[1] A/B	323 (64)/182 (36)
Maximal tumor diameter, mean ± SD	60.9 ± 39.1
Tumor nodularities (1/2/≥ 3), n (%)	227 (39%)/76 (13%)/278 (48)
Infiltrative tumor	235 (40)
Extrahepatic metastasis	59 (10)
Vascular invasion	213 (37)
Performance status 0/1/2-4	276 (48)/136 (23)/169 (29)
Laboratory values (mean ± SD)	
Alkaline phosphatase (IU/L) > 200	112 (19)
PT (%), mean ± SD	78.0 ± 15.8
Albumin (g/L), mean ± SD	34.7 ± 6.1
Aspartate transaminase (IU/L), mean ± SD	68.7 ± 60.7
Alpha-fetoprotein (ng/mL), mean ± SD	5680 ± 31332
Tumor stages	
BCLC (A/B/C/D), n (%)	181 (31)/92 (16)/241 (41)/67 (12)
Treatment allocation	
Resection or RFA, n (%)	131 (23)
TACE, n (%)	175 (30)
Sorafenib, n (%)	152 (26)
Supportive care, n (%)	123 (21)
Follow-up Time, mo, mean ± SD	18.3 ± 20.3
Deaths, n (%)	413 (71)
Overall Survival, mo, mean ± SD	26.0 ± 1.3

[1]Cirrhotic patients. HCV: Hepatitis C virus; HBV: Hepatitis B virus; MS: Metabolic syndrom; PT: Prothrombin time; BCLC: Barcelona Clinic Liver Cancer; RFA: Radiofrequency ablation; TACE: Trans arterial chemoembolization.

Each staging system showed a significant difference in the probability of survival across the stages (P < 0.0001). The MESH score determined subgroups of different survival prognosis in our cohort: MESH 0: 66 (40-68) mo, MESH 1: 37 (22-80) mo, MESH 2: 21 (13-49) mo, MESH 3: 10 (6-20) mo, MESH 4: 5 (4-9) mo, MESH 5 and 6: 4 (2-6) mo; P (Wilcoxon) < 0.0001. Its predictive value on survival was higher than other scores or classifications (BCLC, HKLC and CLIP) within this cohort with a lower AIC, a higher homogeneity, a higher c-Index (Table 2). However the NIACE score obtained the best prognostic information.

The BCLC system has become the reference classification by its simplicity, its prognostic value and a treatment algorithm based on randomized clinical trials. But each BCLC stage includes a broad spectrum of tumors of different prognosis[2-5], with one therapeutic option for stages B and C. Some stage B HCC patients could be good candidates for surgery[6,7], unlike other BCLC B

Table 2 Comparison of performances of each scoring systems in the entire cohort

Score	Discriminatory ability linear trend test		Homogeneity likelihood ratio test		Akaike Information Criterion	C-index (95%CI)
	LT (χ^2)	*P* value	LR (χ^2)	*P* value		
MESH	145.125	< 0.0001	372.4846	< 0.0001	4145.284	0.830
BCLC	137.845	< 0.0001	327.5024	< 0.0001	4194.266	0.806
HKLC	104.966	< 0.0001	387.2755	< 0.0001	4146.493	0.811
CLIP	108.423	< 0.0001	341.3485	< 0.0001	4101.288	0.816
NIACE	144.998	< 0.0001	425.6698	< 0.0001	4092.099	0.853

MESH: Model to estimate survival for HCC; BCLC: Barcelona Clinic Liver Cancer; HKLC: Hong Kong Liver Cancer; CLIP: Cancer of the Liver Italian Program; NIACE: Tumor Nodularity, Infiltrative nature of the tumor, Serum Alpha-fetoprotein level, Child-Pugh stage, Eastern Cooperative Oncology Group Performance Status; LT: Linear trend; LR: Likelihood ratio.

Table 3 Comparison of performances of each scoring systems in patients treated by surgery/radiofrequency ablation

Score	Discriminatory ability linear trend test		Homogeneity likelihood ratio test		Akaike Information Criterion	C-index (95%CI)
	LT (χ^2)	*P* value	LR (χ^2)	*P* value		
MESH	21.5588	< 0.0001	23.3342	< 0.0001	346.508	0.719
BCLC	15.5560	< 0.0001	12.4538	0.0020	359.388	0.644
HKLC	5.9647	0.0146	18.9510	0.0020	358.891	0.629
CLIP	9.9391	0.0016	13.1460	0.0003	356.696	0.642
NIACE	19.1701	< 0.0001	23.1937	< 0.0001	346.648	0.672

MESH: Model to estimate survival for HCC; BCLC: Barcelona Clinic Liver Cancer; HKLC: Hong Kong Liver Cancer; CLIP: Cancer of the Liver Italian Program; NIACE: Tumor Nodularity, Infiltrative nature of the tumor, serum Alpha-fetoprotein level, Child-Pugh stage, Eastern Cooperative Oncology Group Performance Status.

HCC patients who do not benefit from the recommended treatment namely the chemoembolization[8]. Consequently, different staging or scoring systems have been proposed in the last years, in order to improve its prognostic value[1] and/or the decision making process[8,9]. A prognostic score needs to be easy to use, reliable and useful, and the MESH score fulfills these conditions. It has a good prognostic value, especially for HCC patients treated by surgery/RFA (Table 3); it is easy to use by adding up the points of each variable, and it includes six parameters used in daily clinical practice, an essential part of HCC management. Actually, it incorporates tumor-related characteristics, general conditions and liver function, as well as two easily available biological variables (AFP, alkaline phosphatase) correlated to the HCC patients' survival, absent from the BCLC and HKLC classifications.

The MESH score could be useful for HCC management. It distinguishes two different prognostic groups within BCLC A HCC patients treated by surgery/RFA in our cohort [MESH $\leqslant$ 2: 68 (44-74) mo *vs* MESH > 2: 7 (5-7) mo, *P* (Wilcoxon) = 0.0292], within BCLC B HCC patients treated by TACE [MESH $\leqslant$ 2: 20 (15-50) mo *vs* MESH > 2: 14 (7-20) mo, *P* (Log-Rank) = 0.0078], or within BCLC C HCC patients treated by Sorafenib [MESH $\leqslant$ 3: 10 (6-26) mo *vs* MESH > 3: 5 (3-8) mo, *P* (Log-Rank) < 0.0001]. Thus, it could help clinicians in the treatment decision. We observed the same findings with the NIACE score whatever HCC stages and treatment modalities[10].

The BCLC treatment recommendations are seldom followed[11,12], related to a strict treatment algorithm and great prognosis heterogeneity within each BCLC stage. In our cohort, 65% of patients have been treated according to the BCLC recommendations and for some authors other options are possible[13,14].

We have checked that the MESH score provides good prognostic information within a European HCC cohort, whatever the treatment modalities, including HCC patients treated according to the BCLC guidelines. But these findings show once again that additional variables such as AFP and/or tumor morphology may influence HCC prognosis and its therapeutic management[15]. If the BCLC system is unavoidable, there are sufficient arguments for a prospective clinical trial to validate the usefulness of this new strategy based on a combination of BCLC system and scores[16] such as NIACE or MESH, and to determine which one to use.

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