Gender difference in patients with hepatocellular carcinoma

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Différences entre hommes et femmes ayant un carcinome hépatocellulaire

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R É S U M É

Prérequis : Le carcinome hépatocellulaire représente le 5ème cancer le plus fréquent de part le monde et compte environ pour 90% des cancers primitifs du foie. Les hommes ont une prévalence plus élevée que les femmes, avec un sex-ratio de 2 :1 à 4 :1, en fonction de la répartition géographique de ce cancer.
But : Déterminer l'influence du genre sur les caractéristiques clinico-biologiques et la survie des patients ayant un carcinome hépatocellulaire.
Méthodes : Il s'agissait d'une étude rétrospective incluant 62 patients atteints de carcinome hépatocellulaire. Nous avons comparé les caractéristiques clinico-pathologiques et la survie des patients par le logiciel SPSS version 11.5.
Résultats : Parmi ces patients, 36 étaient des hommes (57,1%) avec un sex ratio de 2:1.5, l'âge moyen chez les femmes était de 59,8ans (p=0.054). L'albuminémie était significativement plus basse chez les femmes (p=0.0061). La taille moyenne de la tumeur était de 45,8mm et la différence n'était pas significative (p=0,638). Le carcinome hépatocellulaire était significativement plus fréquent chez les 16 hommes ayant une cirrhose post virale B (p=0,04). La principale raison à l'abstention thérapeutique était le caractère multifocal du carcinome hépatocellulaire. La médiane de survie (6.52 mois) n'était pas significative entre les 2 groupes
Conclusion : Au moment du diagnostic, les femmes étaient plus âgées que les hommes. L'étiologie virale C était statistiquement plus fréquente chez les femmes. Bien que le carcinome hépatocellulaire fût plus agressif chez les hommes, la survie médiane n'était pas significative entre les 2 groupes. Un dépistage et une prise en charge précoce peuvent limiter ce fléau.

M o t s - c l é s
Sexe, Carcinome hépatocellulaire, Survie.

S U M M A R Y

Background: Hepatocellular carcinoma represents the fifth most common cancer worldwide and account for approximately 90% of primary liver cancer. Men have a higher prevalence than women; the sex ratio varies between 2:1 and 4:1, depending on the geographic region. Aim: To determine the influence of gender on the clinicopathologic characteristics and survival of patients with hepatocellular carcinoma.
Methods: A retrospective analysis of medical records was performed in 63 patients with hepatocellular carcinoma and their clinicopathologic features and survival were compared in relation to gender. The data was summarized by descriptive statistics and analysed with SPSS version 11.5.
Results: Among these patients, 36 were men (57.1%) with male-to female ratio of 2:1.5, the mean female age was 59.8 years (p=0.054). Serum albumin level was significantly lower in women (p=0.0061). The average size of the tumor was 45.8mm and the difference was not significant (p=0.638). Hepatocellular carcinoma was significantly more prevalent among 16 men with post viral B cirrhosis (p=0.04). The main reason for therapeutic abstention was multifocal character of the hepatocellular carcinoma. The median survival time (6.52 months) was not different between the 2 groups.
Conclusion: At diagnosis, men were younger than women. The viral C etiology was statistically more frequent in women than in men. Hepatocellular carcinoma was more aggressive in male but median survival time was not significant between groups. Screening and early treatment can limit this problem.

K e y - w o r d s
Sex, Hepatocellular carcinoma, Survival time.

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, he is a dreaded complication of chronic liver disease that occurs in the setting of risk factor such as hepatitis B (HBV) and hepatitis C (HCV) viral infections, alcohol liver disease, hemochromatosis and nonalcoholic steatohepatitis as well as to genetic and environmental interactions [1-3]. HCC usually occurs in individuals with chronic liver disease: in fact, the risk of developing HCC per year in cirrhosis ranges from 2 to 8%, depending on the different etiologies of the underlying cirrhosis [4]. The incidence of HCC has increased in the last decades worldwide: a number between 500 000 and 1 000 000 of new cases of HCC are reported every year, and HCC is responsible for about 750 000 deaths per year (the 5-year survival rate for patients with HCC is only 7%) [3, 4]. Men are about three of five times more likely to develop HCC than women [1]. A similar or even more pronounced gender disparity is seen in rodent HCC models. HCC is notably more prevalent in males worldwide, with reported male:female ratios ranging from 2:1 to 8:1 in most series, being more marked in high incidence areas, but less different in low incidence regions [2, 5]. Despite the extent of this evidence, the reasons for sex differences in the incidence of HCC remain unclear.

In this respect, we analyzed the medical records on individuals in whom HCC was diagnosed during five-year period at Mongi Slim University Hospital (La Marsa, Tunisia).

PATIENTS AND METHODS

A total of 63 patients with HCC who were admitted to Mongi Slim University Hospital (department of gastroenterology and department of surgery) between January 2008 and October 2012 were retrospectively analyzed and included in this study. All patients were diagnosed based on liver tumor characteristics detected by ultrasound/CT scan. Of those, there were 36 male (57.1%) and 27 female (42.85%), making a male-to-female ratio of 2:1.5. We compared the difference and the clinicopathologic features, including: age, biochemical liver function test, presence or absence of associated cirrhosis, etiologic factors predisposing towards HCC (hepatitis B or C); degree of tumor differentiation, macroscopic examination of the tumor, tumor size, presence of vascular invasion, evidence of distant metastasis and modalities of therapy of HCC. Biochemical liver function tests were determined by automated chemical analyzer at the Mongi Slim University Hospital. The normal levels are within the range of <40 IU/L for serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and 100-290 IU/L for serum alkaline phoaphatase (AP). Gross pathology, tumor size and localization of HCC as well as presence of portal or hepatic venous involvement, were obtained by abdominal ultrasound or computerized tomography (CT).

The data was summarized by descriptive statistics (means and frequencies) and analysed with SPSS version 11.5. Data are shown as percentage, mean and standard deviation (SD). Differences in proportions were analyzed by chi-square or Fischer test; differences in mean quantitative value were analyzed by student's t-test. P value less than 0.05 was accepted as statistically significant. Survival rate were established using the Kaplan–Meier method and differences between curves were demonstrated using the log-rank test.

RESULTS

The mean age of female patients (59.81 years) was significantly lower from that of male (66.12 years) (p=0.054). Ascitis was noted in 64% of patients with hepatocellular carcinoma. Which ascitis was statistically more frequent in female than in male (p=0.061). There were a significantly differences in positive rates of serum HBsAg and anti-HCV: positive serum HBsAg was significantly more frequent in male than in female (16 male/6 female) p=0.04, whereas positive anti-HCV was significantly more frequent in female than in male (14 male/20 female) p=0.014. However, no significant differences between groups were observed regarding mean serum alpha fetoprotein (AFP) levels and biochemical abnormities, with the exception that female patients had significantly lower serum albumin levels than male patients (p=0.0061). The mean serum albumin rate was respectively 35.37g/dL and 29 g/dL in male and female. Table 1 summarizes the demographic and clinical data of female and male patients with HCC at initial diagnosis. Table 2 demonstrates the clinicopathologic data of the patients at the time of the diagnosis of HCC.

Table 1: Demographic and clinical data of female and male patients with HCC at initial diagnosis

Characteristics	Female (n=27)	Male (n=36)	P
Age (yr)	59.81±9.33	66.12±12.19	0.054
Viral hepatitis marker			
HBs Ag (+/-)	7/20	16/17	0.04
Anti-HCV (+/-)	20/7	14/17	0.014
Ascitis (+/-)	14/11	9/25	0.061
Mean AFP (IU/mL)	963.26±3027.93	10493.62±42370.89	0.83
Biochemical liver function tests			
Total bilirubin (mg/dL)	41.1±41.63	67.37±117.36	0.93
Alkaline phosphatase (IU/L)	234.36±166.37	461.1±687.5	0.17
AST (IU/L)	108.04±73.05	94.47±89.8	0.54
ALT(IU/L)	68.8±48.78	71.3±67.78	0.87
Albumin (g/dL)	29.04±5.78	35.37±5.6	0.0061
Prothrombin time (%)	72.09±17.75	72.56±19.70	0.92

Female patients in this study tended to have less aggressive tumor characteristics than male patients: the mean tumor size in female (41.18 mm) was smaller than of male patients (48.43 mm) but did not reach a significant difference; the nodular type of HCC appeared to be more frequently found among female patients, whereas the massive and diffuse types were more common among males (p=0.71). Nonetheless, no significant

differences between groups were observed as the degree of tumor differentiation, the prevalence of extrahepatic metastasis and portal or hepatic vein invasion.

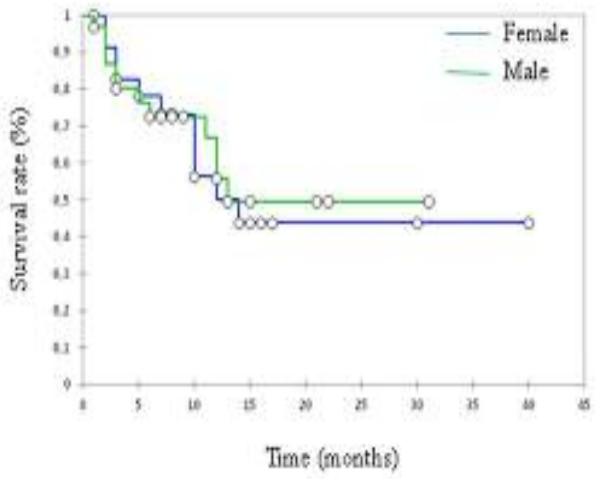
Table 2: Clinicopathologic data of female and male patients with HCC at initial diagnosis

Characteristics	Female (n=27)	Male (n=36)	P
Mean tumor size (cm)	41.18±29.37	48.43±43.73	0.69
Tumor size			
≤5cm/>5cm	16/11	18/18	0.64
Gross appearance of HCC			
Nodular/Multinodular/ Diffuse	15/8/4	18/12/6	0.71
Tumor cell differentiation			
Well/Moderately/Poorly	2/2/0	5/4/2	0.57
Portal or hepatic vein invasion (+/-)	3/24	10/26	0.096
Extrahepatic metastasis (+/-)	0/27	2/34	0.5
Therapy of HCC (+/-)	23/4	28/8	1
Modality of therapy			
Surgical resection (+/-)	9/18	5/31	0.64
Percutaneous treatment	6/21	5/31	0.91
Chemoembolization (+/-)	11/16	10/26	0.73

There was no statistically significant difference between groups in term of the number of patients treated with specific therapeutic modalities. However, female patients were more likely than male patients to undergo surgical resection, which included segmental and lobar resection, percutaneous treatment or treated with transcatheter arterial chemoembolization (TACE), but there was no significance.

The median survival time in this study regardless of their gender, was 6.52 months. The Kaplan-Meier survival curves demonstrated that the overall median survival for female and male patients were 7.09 and 6 months, respectively (p=0.627) (Figure 1).

Figure 1: Overall survival of male and female patients with hepatocellular carcinoma



Survival at 6 months in female and male was respectively 45.5% and 50%, survival at 12 months was 9% and 0% respectively in female and male. For treated patients, the median survival for the male and female group was 6 and 5 months, respectively and there was no significance. In the untreated patients, the median survival of the male group was shorter than that of the female group: 3 and 7 months respectively, however, this difference did not achieve statistical significance.

DISCUSSION

In our study as in the literature, there are differences between genders. Indeed, men are more affected by HCC, with advanced age, a chronic hepatitis B etiology and especially a more aggressive character of the tumor compared to women. However, the median survival time was not different between genders probably related to the size of the studied population and the short follow-up period. HCC represents the fifth most common cancer worldwide and account for approximately 90% of primary liver cancers. Its incidence rate, however, has been increasing over the last two decades of the 20th century. In the United States, the reported incidence has increased to 4.7/100,000 [6]. In both cases, the male population, both black and white, is primarily affected. However, the incidence of HCC in eastern Asia and middle Africa is more than five times that of North America. Furthermore, from 1981 to 1985 the peak incidence of HCC occurred in patients 80 to 84 years of age, whereas from 1991 to 1995 the peak was noted in persons 74 to 79 years of age. This shift in incidence toward younger persons seen over the last two decades coincides with the prevalence of the hepatitis C infection.

The large majority of cases occur in patients with chronic infection with hepatitis B virus (HVB) or hepatitis C virus (HCV). In our study, 16 male within 36 were infected by chronic hepatitis B virus, and 20 female within 27 were infected by chronic hepatitis C virus. The relative risk of hepatocellular carcinoma in patients with chronic HBV or HCV infection is about 25 to 30 times than of those without infection [7]. Huang et al, concluded in their study that there is an inverse association between HBV and HCV viral load, and the effect of dual infection on HCC is higher than, that of monoinfection, although in a submultiplicative pattern. Risk of HBV-associated HCC decreases with age in men, and HCV-associated HCC risk increases with age in women [8]. In our study, at the diagnosis of HCC male were younger than female (the mean male age was 59.8 and 65.33 years old in female).

The inflammatory immune response of the host to viral antigens induces hepatocyte damage, which is followed by the regeneration of hepatocytes and the development of fibrosis and cirrhosis; represent the important feature in the pathogenesis of hepatocellular carcinoma. HCC represents a classic case of inflammation-linked cancer and chemically or genetically induced HCC depends on inflammatory signalling [1].

A general characteristic of HCC is the striking male predominance ranking from 2:1 up to 5:1 [6, 7]. As in our study,

sex ratio was 2:1.5. Marked male predominance in HCC incidence is observed in both high and low-risk areas, regardless of ethnic and geographic diversity [5]. HCC is 3-5 times more common in men than in women and in experimental hepatocarcinogenesis, it develops more frequently in male than in females [9]. Earlier hypotheses suspected higher exposition of men to HCC risk factors due to a different socialization. The reasons for disparity between men and women remain obscure, but they may include environmental factors such as a higher prevalence of persistent HBV or HVC infection, alcohol abuse and smoking in men than in women. It has been suggested that the effect of sex hormones may contribute, at least in part, to the greater incidence of HCC observed in male patients [5]. Genetic and hormonal factors such as estrogen and testosterone may also be important as has been underscored in recent studies by Naugler et al [1, 10].

The high prevalence of HCC in men is considered to be due to the high number of androgen receptors, both in HCC cells and surrounding parenchyma, in men than in women, and DNA synthesis in cirrhotic tissues is higher in men than in women [11]. Tanaka et al. reported that an elevated serum estrogen level, may promote the development of HCC in cirrhosis [12]. Jonas et al, reported that estrogen receptor (ER)-positive HCC had lower survival rate compared to (ER)-negative HCC after curative resection of advanced HCC [13]. Estogens seem to play a role in IL6 production and modulation of gene expression through FOXA transcription factors, what prevents HCC development in experimental models of HCC [14, 15]. Kalra et al, demonstrated that studies on hepatoma cell lines, HCC tissues and animal models of hepatocarcinogenesis, highlight the importance of sex hormones and their receptors in HCC pathogenesis [16].

Some studies have suggested that a better prognosis in female patients with HCC was related to a high incidence of tumor encapsulation and less invasion tumors, lower tumor recurrence rates and a lower number of androgen receptors in HCC cells [11]. In our series, tumor size was smaller in female than in male, and the nodular character was frequent in female. Well tumor cell differentiation was more seen in female than in male. It can be suspected, however, that the different HCC prognosis between the gender is simply because females are more compliant with surveillance and, consequently, the tumor is detected at an early stage, offering more therapeutic opportunities and increasing the impact of the lead-time bias [17]. In the Tangkijvanich et al, study a stepwise Cox regression multivariate analysis revealed that high serum AFP, venous invasion, extrahepatic metastasis and absence of specific therapy were significantly and independently predictive for unfavourable prognosis [5]. Female patients with HCC had a much lower prevalence of venous involvement than males. In our series, vascular invasion was significantly more present in male than in female (p=0.096), but female were more often treated curatively than male and the difference was not significant between groups. It seems, therefore, that this is probably one of the main factors contributing to different survival rates between the two sexes in Tangkijvanich et al study [5]. Dohmen et al, showed in their study, that an early detection of HCC, irrespective of gender, contributes to prolonged survival [11]. Generally, the development of HCC in females may be slower than in male, therefore, the four month interval with an ultrasound examination in order to detect HCC lesions does not need to be changed to a shorter interval [12]. In our study, even if the HCC was less aggressive in female than male, median survival time was not significant between groups.

CONCLUSION

Thus, our study showed, as in the literature, that female patients with HCC had certain clinicopathologic features different from those in male patients. However, in our data, there were no significant in the survival rate between groups. Female patients were more likely than male patients to undergo curative treatment or to be treated with TACE. Ideally, to reduce gender disparity in outcomes, more frequent follow-up surveillance programs, in particular male patients at high risk of HCC, must be establish.

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