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**Case Report**

# Wide Sexual Dimorphism of Hepatocellular Carcinoma Presentation in Algeria

Yazid Chikhi<sup>a</sup> Salima Cheraitia<sup>a</sup> Rachid Ould Gougam<sup>a</sup> Fadila Lounes<sup>a</sup>  
Chahrazed Zemmouchi<sup>a</sup> Nassila Belal<sup>b</sup> Maroua Bendaoud<sup>c</sup>  
Sonia Ait Younes<sup>d</sup> Aicha Bensalem<sup>e</sup> Saadi Berkane<sup>f</sup> Hocine Asselah<sup>a</sup>  
Pascal Pineau<sup>g</sup> Mustapha Lahcene<sup>a</sup>

<sup>a</sup>Department of Internal medicine and Gastroenterology, EPH Bologhine, Algiers, Algeria;

<sup>b</sup>Department of Radiology, Hôpital Central de l'Armée, Ain Naadja, Algiers, Algeria;

<sup>c</sup>Department of Radiology, EPH Bologhine, Algiers, Algeria; <sup>d</sup>Department of Pathology, EPH Parnet, Algiers, Algeria; <sup>e</sup>Laboratory of Virology, Institut Pasteur d'Algérie, Sidi Ferruch, Algiers, Algeria; <sup>f</sup>Department of Gastroenterology, CHU Mustapha, Algiers, Algeria; <sup>g</sup>Unité "Organisation nucléaire et oncogénèse", INSERM U993, Institut Pasteur, Paris, France

**Keywords**

Hepatocellular carcinoma · Algeria · Sexes · Risk factors · North Africa · Cholecystectomy

**Abstract**

Hepatocellular carcinoma (HCC) represents a worrying public health problem in North Africa and particularly in Egypt. The situation is unclear in western North Africa where HCC has been rarely submitted to careful scrutiny. We decided to analyze demographic, biochemical, virological, and clinical data of a series of HCC from Algerian patients to establish the landscape of this tumor in the country. In the present work, we described 337 cases of primary liver cancer from Bologhine Hospital in Algiers, the capital of Algeria. The mean age of patients was  $63.8 \pm 11.4$  years with a male:female sex ratio of 1.5. The most prevalent risk factors were hepatitis C, hepatitis B, and metabolic pathologies (type 2 diabetes and obesity). The mean BMI was  $25.6 \pm 4.7$  at tumor diagnosis. A strong duality of risk factors and tumor presentation between male and female patients was apparent. Women tended to be older (mean 65.4 vs. 62.7 years,  $p = 0.039$ ) and either seropositive for anti-HCV (60.0 vs. 41.6%,  $p = 0.0018$ ) resulting primarily from tattoos and/or scarification (47.2 vs. 25.7%,  $p = 1.0 \times 10^{-4}$ ) or more often affected by metabolic disorders (mean BMI  $26.1 \pm 0.7$  vs.  $25.1 \pm 0.5$ ,  $p = 0.0248$ ) commonly associated with personal antecedents of cholecystectomy (21.2 vs. 5.8%,  $p = 4.4 \times 10^{-5}$ ). By contrast, men were younger, poorer survivors (mean 9.3 vs. 13.3 months,  $p = 0.005$ ), more frequently HBsAg carriers (27.8 vs. 10.5%,  $p = 4.8 \times 10^{-5}$ ), and more exposed to lifestyle risk

Pascal Pineau and Mustapha Lahcene should be considered as co-directing authors.

Dr. Yazid Chikhi  
Service de Médecine Interne et Gastroentérologie  
EPH Ibn Ziri, Bologhine  
Algiers 16000 (Algeria)  
E-Mail cyazid2002@yahoo.fr

factors such as smoking (39.4 vs. 3.0%,  $p = 3.9 \times 10^{-16}$ ) or alcohol use (19.1 vs. 0.7%,  $1.5 \times 10^{-8}$ ). Finally, geographic disparities throughout Algeria were reminiscent of the situation of chronic hepatitis C in the country. A significant excess of cases originated from the region of Batna, Eastern Algeria, already known for its high rate of hepatitis C. Our results suggest that due to culture or sex-dependent biological differences, the tumor process affecting the liver is drastically different between sexes in Algeria.

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## Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequent human tumor and the third cause of death from neoplasm worldwide. In North Africa (Egypt, Libya, Tunisia, Algeria, and Morocco), HCC is the first incident tumor type for males with most cases affecting the Egyptian population due to the importance of hepatitis C epidemics and to the large population size of the country [1, 2]. In Egypt, the incident number of HCC cases is still predicted to rise in the next decades [3]. In other nations of the Middle East and North Africa (MENA) region such as Iran or Lebanon, HCC incidence is increasing for both sexes [4, 5]. In addition, authors have indicated that there could be an important underreporting (30–40%) of HCC in the region [5]. The epidemiology of HCC is less clear in the Maghrib, the western part of North Africa (that includes Algeria, Libya, Morocco, and Tunisia), where 90 million habitants with arabo-berberic ancestry are living. In this region, very few series of HCC have been described so far, although studies conducted two decades ago, on North African migrants in France, have shown an excess of liver cancer in these populations when compared to European populations [6, 7]. Algeria is the most populated state of the Maghrib (40 million habitants), but the presentation and cause of HCC in this country have been only superficially described in the literature.

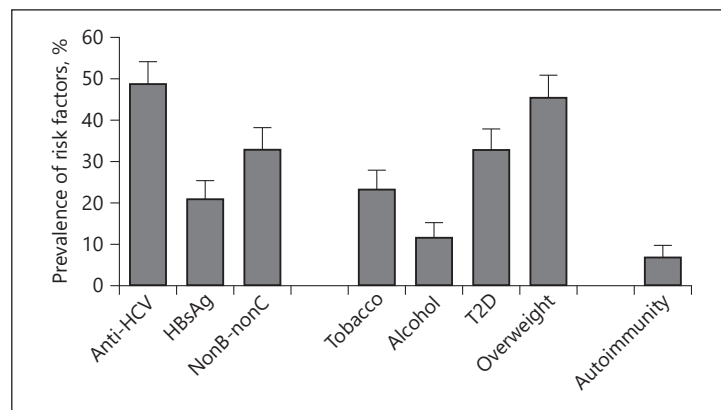
Major etiological factors of HCC include chronic infections with hepatitis B, C, and Delta viruses. The two former conditions represent significant public health problems in Algeria with 2–3% of the population chronically infected with these viruses [8, 9]. By contrast, heavy alcohol consumption, another major risk factor worldwide, is considered as only marginally involved in HCC epidemiology in the country due to the cultural temperance of predominantly Muslim populations. The roles of mutagenic factors such as aflatoxin B1 or tobacco in the liver cancers are unknown due primarily to the absence of molecular studies aiming to define the mutation pattern in tumors [10]. Finally, the toll assigned in HCC epidemiology to metabolic diseases such as overweight-obesity, type 2 diabetes (T2D) or metabolic syndrome is suspected to be significant due to the importance of these morbidities in North-African populations [11, 12].

In the present report, we describe the distribution and connections of the different risk factors in a series of 337 HCC cases diagnosed in Algiers between January 2008 and December 2016.

## Patients and Methods

### *Patients*

A series of 337 consecutive records of primary liver cancer were recovered at Ibn Ziri Bologhine Hospital of Algiers from a period covering January 2008 to December 2016. Medical records included sociodemographic data, risk factors, medical antecedents, survival length, biochemistry including serum alpha-feto-protein (AFP) levels, serological data concerning hepatitis B and C viruses, autoantibodies, blood formula, prothrombin time, etc... The diagnosis of cirrhosis was based on clinical and laboratory findings associated with signs of portal hypertension on endoscopy and/or US, and/or the finding of an irregular liver margin on



**Fig. 1.** Prevalence of the principal risk factors of hepatocellular carcinoma in the 337 patients.

US. Pathological confirmation of tumor type by hematoxylin-eosin staining was possible in 89 cases (26.3%). A single case of cholangiocarcinoma (0.3%) was identified together with two fibrolamellar variants (0.6%) and a mixed hepato-cholangiocellular tumor (0.3%). Therefore, despite the absence of systematic histopathological characterization of tumor cases, we assume that the great majority of patients ( $\approx 98\%$ ) were affected by a bona fide HCC. According to Edmonson-Steiner classification, a minor subset of tumor was graded as poorly differentiated (III–IV, 25%). In 326 cases (98%), the diagnosis of HCC was established after positive imaging findings (US, CT scan) and AFP level measurement. Circulating AFP levels were considered as normal when  $<20$  ng/mL. Exclusion criteria were patients who were found to have liver metastases from ectopic tumors, when the diagnosis of HCC was not reasonably certain, and where patients could not be followed up for social, psychological, or geographical reasons.

#### Statistical Analyses

All statistical analyses were performed using the Prism 6.0 statistical package. Numerical variables were summarized by their median, mean, and range according to their distribution types. They were compared either by a Student *t* test or by a Mann-Whitney test as appropriate. Categorical variables were summarized as frequencies that were compared by the Fisher exact test. All tests were two-sided and the level of significance was set at  $p = 0.05$ . Overall survival was defined as the time between diagnosis and death due to any causes.

## Results

### General Features

The clinicopathological features of the series are summarized in Table 1. Briefly, the mean age of patients was  $63.8 \pm 11.4$  years with a low male:female (M:F) sex ratio (1.5). Men were significantly younger than women ( $62.7 \pm 12.2$  vs.  $65.4 \pm 9.9$  years,  $p = 0.036$ ).

Regarding infectious risk factors, anti-HCV seroreactivity, proxy for a current or past infection with hepatitis C virus (HCV), was the most prevalent (48.7%) (see Fig. 1). Chronic hepatitis B (HBsAg carriage) was more than twice less frequent (21.8% of cases) but previous contact with hepatitis B virus (HBV) (anti-HBc seroreactivity) was frequent (61.9%), suggesting that occult B infection might be found in a significant number of cases in this series. An absence of persistent hepatitis B or C (nonB-nonC cases) was found in 28.1% ( $n = 106$ ) of cases (Fig. 1).

Noninfectious risk factors of HCC were found at a very high level in this series, either alone or in association with the viruses. Among the behavioral risks, tobacco smoking was the most frequent (23.4%) while any kind of alcohol consumption (going from moderate to excessive) was, as expected, rather marginal (11.8%). By contrast, metabolic affections were far more prevalent. Indeed, more than 45% of patients were affected by a BMI  $>25$  at tumor diagnosis and 32.8% of the whole series was previously diagnosed for T2D. The mean BMI at

**Table 1.** Baseline demographic and disease characteristics

<i>Age, years</i>	
Mean ± SD	63.78±11.4
Median (range)	63.7 (11–87)
<i>Sex ratio (M:F)</i>	
Undeserved	1.5 (204/133)
Liver cirrhosis	74.4 (251/337)
	81.5 (265/325)
<i>Risk factors of cancer</i>	
Tobacco smoking	23.4 (79/331)
Coffee drinking	43.2 (115/266)
Alcohol consumption	11.8 (40/337)
Type 2 Diabetes	32.8 (101/308)
Overweight (25 < BMI < 30)	28.1 (83/295)
Obesity (BMI >30)	17.3 (51/295)
Autoimmunity	7.1 (24/337)
Previous cholecystectomy	11.8 (40/337)
<i>Viral features</i>	
HBsAg	21.0 (67/318)
HBeAg	21.8 (12/55)
anti-HBc	61.9 (88/142)
anti-HBe	54.4 (37/68)
anti-HBs	16.3 (17/104)
anti-HCV	48.7 (155/318)
nonB-nonC	33.0 (106/321)
HBV DNA load	
Mean	51 × 10 <sup>6</sup>
Median	1.8 × 10 <sup>4</sup>
HCV RNA	
Mean	2 × 10 <sup>6</sup>
Median	4.5 × 10 <sup>5</sup>
Genotype 1	95.7 (67/70)
Genotype 2	2.8 (2/70)
Genotype 5	1.4 (1/70)
<i>Risk factors of infection</i>	
Transfusion	10.9 (36/331)
Dental care	91.6 (291/323)
Tattoos-scarifications	34.1 (111/325)
Therapeutic injections	3.9 (13/327)
<i>ECOG OMS</i>	
0	34.5 (115/333)
1	45.9 (153/333)
2	15.0 (50/333)
3 and 4	4.2 (14/333)
<i>Symptoms</i>	
Pain	48.2 (161/334)
Asthenia	27.4 (92/335)
Wasting	21.8 (73/335)
Hemorrhage	5.0 (17/335)
Collateral venous circulation	27.9 (92/330)
Jaundice	27.3 (91/333)
Ascites	33.9 (113/333)
Hepatomegaly	29.8 (99/332)
Lower extremity edema	14.5 (48/330)
Splenomegaly	17.8 (69/331)

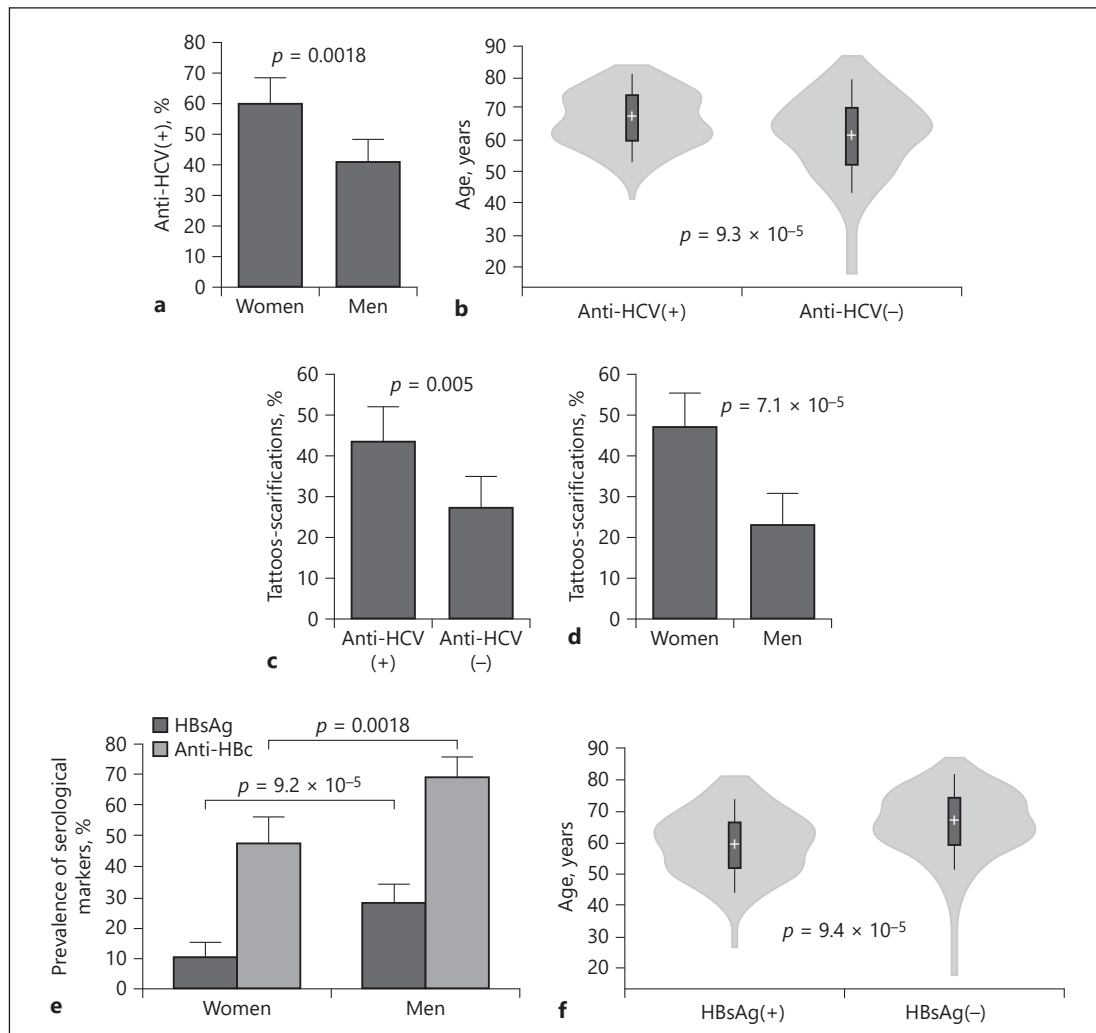
**Table 1** (continued)

<i>Hematology</i>	
Group A	35.0 (105/300)
Group B	19.3 (58/300)
Group O	49.9 (149/300)
Rhesus +	92.0 (276/300)
Leucopenia	27.7 (92/332)
Anemia	45.9 (154/335)
Thrombopenia	58.5 (196/335)
Sedimentation rate >20F/30H	67.5 (123/182)
<i>Biochemistry</i>	
Bilirubin total >10	61.7 (192/311)
Prothrombin time <70	49.0 (160/326)
ASAT	69.8 (229/328)
ALAT	53.0 (174/328)
γ-Glutamyltransferase	69.0 (195/280)
Alkaline phosphatases	71.6 (215/300)
Hypoproteinemia	27.7 (65/234)
Hypoalbuminemia	63.1 (183/290)
AFP	
<20 ng/mL	37.9 (121/319)
20 < AFP < 350 ng/mL	28.8 (92/319)
>350 ng/mL	32.9 (105/319)
Urea	11.4 (36/314)
Hypercreatininemia	10.0 (32/318)
Hypercholesterolemia	5.8 (16/275)
Hypertriglyceridemia	10.3 (28/271)
Fasting hyperglycemia	42.6 (134/314)
Hypocalcemia	64.9 (115/177)
Values are % (n/N) unless otherwise indicated.	

diagnosis was  $25.6 \pm 4.8$  ( $25.1 \pm 0.5$  for men and  $26.5 \pm 0.7$  for women,  $p = 0.023$ ). Overall, a metabolic component of liver disease (e.g., BMI >25 or diabetes) was found in 65% of the cases without viral hepatitis ( $n = 62/95$ ). An autoimmune origin of the disease was suspected in around 7.1% of cases due to the presence of autoantibodies (anti-nucleus, anti-smooth muscles, anti-mitochondria, anti-LKM1) or to a primary biliary cirrhosis. Other potential risk factors such as a previous cholecystectomy or antecedents of tumors were also found in 11.8 and 8.9% of cases, respectively.

We examined thereafter tumor features. An overwhelming proportion of patients (81.5%) developed the tumor on a cirrhotic liver. Regarding biomarkers, almost one third of cases ( $n = 105$ , 32.9%) presented with a frankly elevated AFP (>350 ng/mL), but another 28.8% of patients displayed AFP values within a “grey zone” (20–350 ng/mL), legitimating the suspicion of an ongoing liver cancer process in the frame of an otherwise evocative clinical context. HCC was already multinodular or diffuse at diagnosis in 54% of cases. The median size of the main nodule was 56 mm (range 13–242). Finally, the median overall survival was 8 months (range 1–84).

Given the large country size and the diversity of living conditions of the populations, we next wondered whether some heterogeneity prevails according to the birthplaces or place of residence of the patients. Origins of patients were scattered throughout Algeria with 33 administrative regions (out of 48) represented. Some of them were significantly overrepresented though. The most important contingent was born in Algiers (24% of cases,  $p = 1.4 \times 10^{-7}$ ), a situation most plausibly due the proximity of health care facilities. More importantly, significantly increased proportions of patients were born in the remote regions of Batna ( $n =$



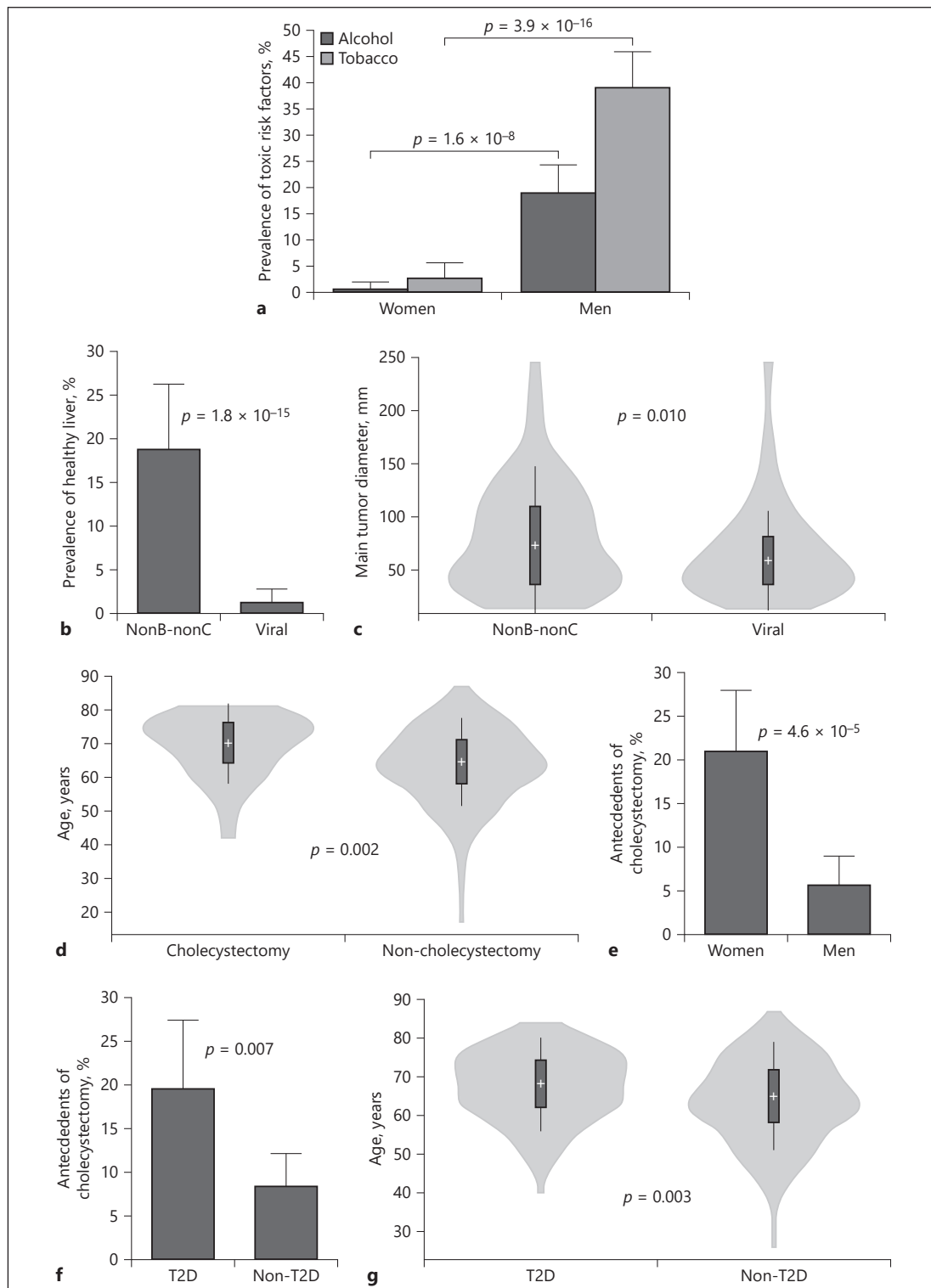
**Fig. 2.** Features of viral risk factors. **a** Prevalence of anti-HCV in female ( $n = 133$ ) and male ( $n = 204$ ) HCC patients. **b** Age of anti-HCV(+) and anti-HCV(-) patients. Violin plot produced with BoxPlotR (<http://shiny.chemgrid.org/boxplotr/>). **c** Prevalence of tattoo and/or scarification risk factor in anti-HCV(+) ( $n = 155$ ) and anti-HCV(-) ( $n = 163$ ) patients. **d** Different prevalence of tattoo and/or scarification risk factor according to sex. **e** Prevalence of serological markers of hepatitis B virus (HBV) infection according to sex. **f** Age of patients according to the presence ( $n = 67$ ) or the lack ( $n = 251$ ) of HBV surface antigen (HBsAg).

62,  $p = 1.6 \times 10^{-11}$ ) in Eastern Algeria and in the coastal region of Tipaza ( $n = 25$ ,  $p = 6.6 \times 10^{-4}$ ), west of Algiers.

#### Clinicopathological Correlations

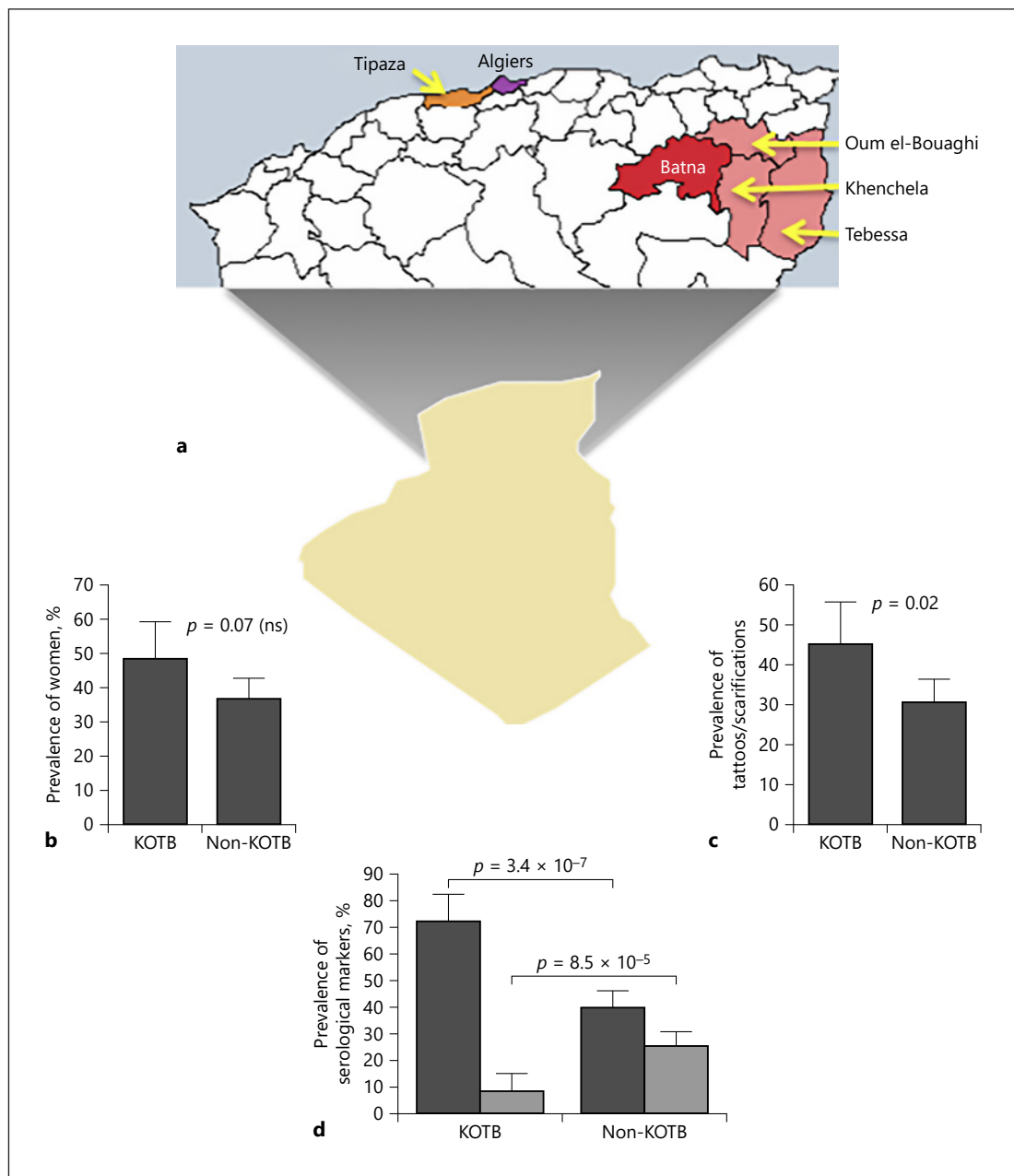
We subsequently decided to explore the putative connections between risk factors responsible for incident HCC cases in Algeria between 2008 and 2016.

As mentioned above, the most important risk factor of HCC in the present series is the seroreactivity against HCV found in almost half of the cases (Fig. 2). Infections with HCV tended to predominantly affect women more than men (60.0 vs. 41.6%, OR = 2.0, 95% CI = 1.3–3.4,  $p = 0.0018$ ) and older patients (66.3 vs. 61.2 years,  $p = 9.3 \times 10^{-5}$ ). The presence of anti-HCV seroreactivity was significantly associated with tattoos and/or scarifications (43.7 vs. 27.7%, OR = 2.0, 95% CI = 1.2–3.4,  $p = 0.005$ ), but this was not the case for some other



**Fig. 3.** Characteristics of nonviral risk factors. **a** Prevalence of toxic risk factors according to sex. **b** Prevalence of healthy liver in nonB-nonC cases. **c** Main tumor diameter in nonB-nonC patients and patients with serological markers of viral infections. **d** Age of patients according to the presence of the lack of antecedents of cholecystectomy. **e** Antecedents of cholecystectomy according to sex in patients with HCC. **f** Antecedents of cholecystectomy in patients with ( $n = 101$ ) or without ( $n = 207$ ) type 2 diabetes (T2D). **g** Age difference between HCC patients with or without T2D.





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**Fig. 4.** Features of the patients originating from the Khenchela, Oum-el-Bouaghi, Tebessa, and Batna (KOTB) regions. **a** Location of the KOTB area in Algeria. **b** Prevalence of women in patients with HCC from the KOTB region ( $n = 83$ ) or from elsewhere in Algeria ( $n = 254$ ). **c** Prevalence of tattoos and/or scarification in patients originating from KOTB or from elsewhere in Algeria. **d** Prevalence of serological markers of HCV and HBV infection in patients from KOTB or from elsewhere in Algeria.

putative risk factors such as dental care, past surgery, or even medical injections. In accordance with this observation, tattoos and/or scarifications, two traditional feminine esthetic and ritual practices in some Algerian regions, were primarily found in women (47.2 vs. 25.7%, OR = 2.6, 95% CI = 1.6–4.3,  $p = 7.1 \times 10^{-5}$ ).

The second viral risk factor by order of importance, HBV surface antigen (HBsAg) carriage, was, as previously mentioned, found in 21.0% of cases. It was mostly present in men (28.3 vs.

10.4%, OR = 3.3, 95% CI = 1.2–6.8,  $p = 9.2 \times 10^{-5}$ ) and younger patients ( $59.2 \pm 10.2$  vs.  $64.8 \pm 11.6$  years,  $p = 9.3 \times 10^{-5}$ ). Male patients were also significantly more often anti-HBc carriers than women (69.7 vs. 47.6%, OR = 2.7, 95% CI = 1.2–6.0,  $p = 0.0018$ ). Among HBsAg carriers, active HBV replication (characterized by HBeAg presence) was present in a subset of patients for whom we had this annotation ( $n = 12/55$ , 21.8%, i.e., only 3.5% of the whole series). Co-infections with HBV and HCV were particularly rare in the present series ( $n = 7$ , 2.0%) and as a consequence carriage of HBsAg or anti-HCV were inversely correlated (OR = 0.18, 95% CI = 0.06–0.44,  $p = 2.3 \times 10^{-5}$ ). Such observation implies that B and C viruses are transmitted through drastically different routes in Algerian HCC patients.

Examining the group of patients ( $n = 95$ ) defined as nonB-nonC, we found it predictably heterogeneous and segmented by few significant characters such as the presence of steatohepatitis (8.4% of cases,  $p = 3.6 \times 10^{-5}$ ), a healthy liver (19.8 vs. 1.3%, OR = 2.3, 95% CI = 1.3–4.0,  $p = 1.8 \times 10^{-15}$ ), or a lower prevalence of anti-HBc seropositivity (27.7 vs. 76.3%, OR = 0.12, 95% CI = 0.04–0.30,  $p = 4.7 \times 10^{-7}$ ). This latter observation indicates that occult B infection might not represent the primary explanation to the tumor development in this subset of patients and that we are rather facing that most of them are genuine nonviral HCC cases.

The various nonviral risk factors were diversely interacting between each other and with viruses to modulate the final presentation of the disease (Fig. 3). Contrasting for obvious cultural reasons with what is generally observed in many developed countries, alcohol consumption plays only a marginal role on the epidemiology of HCC in Algeria. Occasional or heavy consumption was observed, of course, more often in men (19.1%,  $n = 39/204$ ) than in women (0.75%,  $n = 1/133$ , OR = 31.0, 95% CI = 5.1–1265,  $p = 1.6 \times 10^{-8}$ ). Another toxicant commonly involved in liver tumorigenesis, tobacco, was also the hallmark of HCC in males (39.4 vs. 3.0%, OR = 20.8, 95% CI = 7.4–80.9,  $p = 3.9 \times 10^{-16}$ ) in Algeria. As expected, tobacco consumption was strongly associated with alcohol use (40.5 vs. 3.1%, OR = 20.5, 95% CI = 8.5–54.8,  $p = 7.6 \times 10^{-16}$ ) in the present series. Overall, we observed that HCC developed in a context of chronic lifestyle-associated intoxication (alcohol and/or tobacco) was a hallmark of the male population in Algeria.

Metabolic disorders were highly prevalent in the current series of HCC. T2D, diagnosed in more than 32% of the patients ( $n = 101$ ), was characterized by a late presentation of HCC ( $67.2 \pm 9.0$  vs.  $63.5 \pm 12.4$  years,  $p = 0.003$ ) and a history of cholecystectomy (19.7 vs. 8.4%, OR = 2.6, 95% CI = 1.2–5.6,  $p = 0.007$ ).

In addition, overweight and obesity were found in more than 45% of patients. Cholecystectomy is frequently the consequence of the presence of cholesterol gallstones and is sometimes considered as predictive of HCC development. As mentioned above, a history of cholecystectomy was surprisingly high in the present series ( $n = 40/337$ , 11.8%). As expected, this surgical antecedent was significantly more frequent among women than men (21.2 vs. 5.8%, OR = 4.2, 95% CI = 1.9–9.5,  $p = 4.6 \times 10^{-5}$ ) and was associated with a later presentation of the liver tumor ( $69.5 \pm 7.9$  vs.  $63.9 \pm 12.5$  years,  $p = 0.002$ ). Contrasting with previous reports from patients with European ancestry, or even Algerian patients, chronic hepatitis C was not associated with T2D or overweight/obesity [13].

We observed that main tumor diameter was significantly lower in virus-induced HCC than in nonB-nonC cases ( $64 \pm 36$  vs.  $79 \pm 52$  mm,  $p = 0.010$ ), a situation plausibly due to the better tumor screening in patients with virus-induced chronic liver diseases, a more rapid and aggressive course of the disease, or the significantly better condition of the liver in nonB-nonC patients (less liver cirrhosis, more healthy liver; data not shown). As a consequence, overall survival of virus-infected HCC patients tends to be longer than for nonB-nonC patients, albeit without reaching the level of significance ( $14.9 \pm 1.6$  vs.  $9.9 \pm 1.7$  months,  $p = 0.059$ , ns).

### Geographical Distribution of Risk Factors

The major outcome of the geographical analysis of this patient series pointed to the region of Batna as the siege of a specific epidemiological process (Fig. 4). We have recently shown that the number of newly diagnosed hepatitis C cases is significantly higher in an eastern cluster of Wilaya (Khenchela, Tebessa, Oum-el-Bouaghi, and Batna). Likewise, we show in the present study that birth in these regions of East Central Algeria is associated with a specific pattern of HCC. Indeed, patients from this group of regions are more often, albeit nonsignificantly, women (48.2 vs. 36.7%, OR = 1.6, 95% CI = 0.93–2.7,  $p = 0.070$ , ns), present more often with tattoos or scarifications (45.0 vs. 30.6%, OR = 1.9, 95% CI = 1.1–3.8,  $p = 0.020$ ), and exhibit a significantly greater risk of seroreactivity for anti-HCV(+) (72.2 vs. 40.1%, OR = 3.7, 95% CI = 2.2–7.4,  $p = 3.4 \times 10^{-7}$ ) but a lesser seropositivity for HBsAg (8.8 vs. 25.2%, OR = 0.22, 95% CI = 0.08–0.52,  $p = 8.5 \times 10^{-5}$ ).

### Discussion

The epidemiology of HCC is far from being homogeneous in the MENA region (Middle East and North Africa) according to the WHO as there exists, indeed, a strong divide between Middle East and North Africa. The present analysis of this first large series of HCC from Algeria illustrates some peculiarities of the Maghribian epidemiology, at the western end of North Africa.

Overall, the current series is in keeping with a seminal work analyzing primarily cases from Tunisia and Morocco with a minor component of Algerian patients [6]. In this initial article that recruited patients from 2002 to 2005, the mean age was  $62.0 \pm 10$  years and the M:F sex ratio was 1.5, i.e., in very close range from the values of the present series ( $63.8 \pm 11$  years and 1.5, respectively). Likewise, the prevalence of certain risk factors published in this previous survey were highly similar to the present one with chronic hepatitis C (60.0 vs. 48.7%), chronic hepatitis B (17.9 vs. 21.8%), and T2D (18.0 vs. 32.8%) ranking as the main hepatocarcinogenic agents. The respective weights of the main risk factors of HCC are, thus, apparently consistent throughout Maghribian North Africa. By contrast, on the Eastern part of the MENA, risk factor distribution is still commonly dominated by HBV. In Lebanon, it was shown that HBV is present in two third of cases (67%), whereas HCV infection was diagnosed in only 19% of the patients. A similar situation was reported in Yemen or Saudi Arabia where HBV still prevails on HCV (48–67 vs. 4–38%) [14–16]. It is possible, however, that these proportions started to shift in the Arabian peninsula as a recent report indicated a predominance of HCV in HCC cases from Riyadh [17]. In Iran, hepatitis B infection remains the primary etiology of HCC found in more than half of the cases whereas HCV is present in merely 8% of patients [18–20]. In Turkey, HBV is still the first etiological agent of HCC (44–65%) with HCV, although ranking in second position, currently significantly contributing to the disease as well (15–28%) [21–24]. HBV remains, thus, the major risk factor of primary liver cancer in the Near and Middle East. By contrast, HCV infection was the first reported risk factor in Qatar according to the only available report, but the population of patients described in the only available paper is composed mostly of foreigners (62%). To the notable exception of Saudi Arabia, it is, thus, difficult to make a consistent estimation of the risk factors affecting the autochthonous population of the Persian Gulf countries [25]. In the Western part of MENA, once crossed the peninsula of the Sinai, are found countries where chronic hepatitis C is the major contributor to HCC with Egypt representing a dismal paradigm of this situation. In that country, seroprevalence of anti-HCV ranges from 71 to 86% in patients with HCC. By contrast, HBsAg prevalence in HCC patients is only 7–35% of cases [26–30]. There is, thus, for some reason a dramatic difference between North African and Middle Eastern countries regarding

the respective roles played by HBV and HCV in HCC incidence. The origin of Egyptian epidemics of hepatitis C is well known and is to be found in massive anti-bilharzial prophylactic campaigns conducted without precautions on populations where central African genotype 4 of HCV was presumably already seeded by the 19th century slave trade [31, 32]. In the Maghrib, however, the causes of HCV predominance are less clear. It is probable that HCV was already present at low levels in the populations of North Africa before the advent of modern medicine that includes injectable medications, transfusion, etc... Large prophylactic campaigns did not happen in the dryer Maghrib where HCV was most probably continuously spread through traditional esthetic practices of tattooing, notably in East Algeria as suggested in our work.

The values of sex ratio in the MENA region are illustrative as well. In a single country, Qatar, the reported M:F value was close to 1.0 in a very small series of patients ( $n = 42$ ). Overall, sex ratio commonly ranges between 2.5 and 4.5 in most of the Middle Eastern countries (Yemen, Iran, most Saudi Arabian studies, and Lebanon) where HBV still occupies the first rank of risk factors among risks in HCC [14, 17, 20–22, 33–37]. Recently, an epidemiological study conducted in Morocco indicated that liver cancer risk in women was twice that observed in men. Data included in the paper were, however, not supported by a pathological assessment of cases [38]. A recent publication from Sana'a (Yemen) reports a M:F sex ratio of 0.57 with equivalent proportions of HBV- and HCV-infected patients (28–30%). This observation clearly deserves replication in other countries to know whether it represents an early warning of a new epidemiological trend [39]. The M:F sex ratio in Egypt was shown to range between 4.0 and 7.0 and seems therefore the highest of the whole MENA [27, 40, 41]. It suggests that a high M:F ratio is not the hallmark of HBV only. Overall, it seems that in the Maghrib area the M:F ratio is genuinely lower than in the rest of the MENA. Such a situation is obviously a powerful incentive to analyze causative factors of HCC affecting women.

The age at diagnosis of HCC is very close to the Algerian situation (62 years) in many countries including Lebanon (60.5 years), Saudi Arabia (58–66 years), Turkey (61.5 years), and Iran (63 years) [14, 15, 17, 20, 21, 24, 34, 36, 42]. In other countries, such as Yemen, the age of HCC appearance seems to widely depend on the series considered, with one report describing it as early (53.5 years) whereas others are more in keeping with the general situation observed in the MENA region (61.5 years) [16, 39]. By contrast, in Egypt, HCC is diagnosed consistently earlier (mean 43–56 years) than elsewhere in the region [30, 41, 43]. It suggests, therefore, that the Algerian population is not exposed to an additional causative agent, such as aflatoxin B1, suspected to accelerate the liver tumorigenic process [44].

Some differences with the seminal and still only available publication of Bahri et al. [6] were, however, conspicuous in the current work. The case of liver cirrhosis (94%) was much higher than in the current report (81%, OR = 3.5,  $p = 0.001$ ). Overall, reported rates of cirrhosis in patients with HCC in the MENA countries are generally lower than in Algeria, as illustrated by reports from Saudi Arabia (76%), Iran (42–43%), Turkey (69%), and Egypt (45%) [15, 18, 20, 21, 29, 43]. This observation suggests that risk factors contributing to HCC in Algeria are not potent direct tumorigenic agents but rather proinflammatory conditions leading after a protracted disease to tumor development in a heavily altered liver tissue.

Another major finding of the present report is the striking contrast of the prevalence of risk factors between genders. A typical male patient is characterized in Algeria by HBV infection, consumption of toxic compounds, and diagnosed at younger age, whereas Algerian women are older, more frequently exposed to esthetic/traditional risk factors such as tattoos and scarifications, as a consequence more HCV-infected, and finally display more often dysmetabolic disorders (high BMI). Such striking dichotomy was not apparent in the previous series of Bahri et al. [6]. Reports from Turkey are, however, reminiscent of the observations made on the present Algerian series of HCC. Multicenter studies of HCC in Turkey found a

male predominance among HBV-associated HCC cases and a female majority in HCV-infected patients [22, 37]. With regard to metabolism-associated liver disease, it is known that women are in general more susceptible to develop overweight/obesity than men in the MENA area, [45–47]. As a consequence, in western North Africa, dysmetabolic liver diseases, and foremost steatohepatitis, have been shown to affect primarily women, as reported recently in Morocco [48]. An opposite situation is reported from Iran where male predominance is commonly observed [49, 50]. In the currently available literature, the consequences of dysmetabolic conditions on regional HCC epidemiology have been only partially investigated. A high prevalence of T2D in HCC, described in Saudi Arabia, was neither found to be associated with HCV infection nor with female sex [15]. In another Middle Eastern country, such as Iran, T2D prevalence among HCC patients is apparently very low (3%) [18]. In Egypt, it has been reported that anti-HCV(+) HCC patients present a clear metabolic disruption of the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [41]. In this series, the mean BMI was measured at  $24.9 \pm 2.5$ , i.e., below that measured in the present Algerian one ( $25.4 \pm 5.1$ ). We were unable, however, to consistently associate metabolic alterations and hepatitis C in the present series. Our work indicates that an HCV-independent metabolic component, sometimes leading to gallstones and cholecystectomy, affecting primarily women, plays a major role in the liver tumorigenesis of Algerian patients. Interestingly, a recent report associated multiple pregnancy with HCC in Egypt. Unfortunately, the parity of patients was not available in our survey. Given the strong dichotomous distribution of risk factors between genders in Algeria, hormonal changes induced by multiple pregnancies might turn out to be important in this country as well [51].

Regarding personal habits such as alcohol drinking or tobacco consumption, the drastic difference observed according to patient genders is most probably the result of the important societal disparity between genders in the country. Surveys conducted in Europe have clearly shown that gender differences in addictive behavior are decreasing with societal equality [52]. In the present series as in most of those of the MENA region, alcohol as a risk factor (4–6%) does not seem to play an important role in liver tumorigenesis [21, 22, 26, 39]. The only apparent exceptions to this situation are observed either in western Turkey or in Lebanon where it is found in 15–24% of cases, although very rarely as the only consistent risk factor [22, 23, 37, 42]. The other toxic agent contributing to HCC in Algeria, tobacco smoking, found in 28.8% of cases, has already been associated with an increased risk of HCC in Egyptian and Yemeni populations [39, 43]. Frequently overlooked, this factor may require more careful attention in the MENA region. More specifically, the types and brands of consumed tobacco products should come under scrutiny.

Finally, we regret the unavailability of the occupational data of the patients. Algeria is indeed a great agricultural country with a significant subset of habitants still employed in this sector. It has been suggested both in ancient and recent literature from Iran, Egypt, and Yemen that farming as an occupation, and most plausibly the use of pesticides, could be associated with an increased risk of HCC development [16, 33, 43, 53].

Variations of HCC presentation according to the regional or interregional levels have been well described in countries of MENA. Many of the national states are indeed huge with populations characterized by drastically different living conditions and/or cultural practices [22, 33, 37, 40]. Our current findings confirm a previous work conducted on hepatitis C in Algeria where the burden of hepatitis C was mostly affecting women from Eastern regions.

In conclusion, we provide herein the first epidemiological description of HCC in Algeria and the largest clinical epidemiology description of this tumor in the Maghrib (with a population of 90 million habitants). We confirmed our previous work on chronic hepatitis C that showed a worrying epidemiological situation affecting primarily women in Eastern Algeria. We suggest that a systematic screening of hepatitis C should be conducted on middle-aged

habitants of these regions in order to give them a timely access to direct-acting antivirals and prevent the occurrence of HCC. Among striking features found by our work were the dichotomous risk factor distribution and tumor presentation between men and women as well as the peculiar female vulnerability to some risk factors such as HCV infection or metabolic conditions due to cultural or biological specificities of local populations. Further investigations both in clinics and at a basic science level are now warranted to explain the compound tumor process affecting women in this country.

### Statement of Ethics

Due to the retrospective design of our work no informed consent was obtained. This study protocol was approved by the committee on human research of the School of Medicine of Algiers (Approval No. CEB 00801).

### Disclosure Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

Yazid Chikhi, Pascal Pineau, Saadi Berkane, and Mustapha Lahcene designed the study. Yazid Chikhi, Salima Cheraitia, Rachid Ould Gougam, Fadila Lounes, Chahrazed Zemmouchi, Nassila Belal, Maroua Bendaoud, Sonia Ait Younes, Hocine Asselah, and Aicha Bensalem collected and completed clinical information about patients. Yazid Chikhi built and maintained the database. Yazid Chikhi and Pascal Pineau analyzed the data. Pascal Pineau drafted the manuscript. Yazid Chikhi, Pascal Pineau, Saadi Berkane, and Mustapha Lahcene edited and corrected the manuscript.

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