

International

Changes in the Etiologies of Liver Cancer in Upper Egypt over a Decade from 2010 to 2020: A Single Tertiary Care Center Study

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Abstract



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Keywords

- ▶ HCC
- ▶ Egypt
- ▶ MAFLD
- ▶ viral hepatitis
- ▶ trends

The profile of liver diseases in Egypt is changing dramatically and viral hepatitis is declining, while the fatty liver disease is increasing dramatically. However, the impact of these changes on the profile of hepatocellular carcinoma (HCC) remains uncertain. Therefore, we determined the temporal trends in the etiologies of HCC in Egypt over a decade. We retrospectively analyzed data from consecutive patients who were diagnosed with HCC over 10 years (2010–2020) in a large center in Upper Egypt. Standard tests were utilized to diagnose hepatitis C virus (HCV) and hepatitis B virus. In the absence of other liver disorders, the presence of obesity, or diabetes in the absence of other risk factors, metabolic dysfunction-associated fatty liver disease (MAFLD) was diagnosed. A total of 1,368 HCC patients were included, in which 985 (72%) had HCV, 58 (4%) had hepatitis B virus, and 143 (10.5%) had MAFLD, 1 patient had hemochromatosis, 1 had autoimmune liver disease, and 180 (13%) patients were with unknown cause. The annual proportions of MAFLD-related HCC were increased significantly between 8.3% in 2010 and 20.6% in 2020 ($p = 0.001$), while HCV-related HCC declined from 84.8 to 66.7% ($p = 0.001$). Throughout the study period, there were significant increases in the age at diagnosis of HCC, the proportion of female patients, obesity, diabetes, and less severe liver dysfunction at diagnosis ($p < 0.05$ for all). With the decline of HCV, MAFLD is becoming a major cause of HCC in Egypt, which has increased substantially over the past 10 years. This study urges the creation of comprehensive action strategies to address this growing burden.

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Introduction

Hepatocellular carcinoma (HCC) is a major global public health challenge and HCC is the sixth most common form of cancer in the world and the fourth leading cause of cancer death in 2018.¹ Primary liver cancer, which is mostly composed of HCC, has a terrible prognosis, with a 5-year survival rate of only 17%, second only to pancreatic cancer.² From 1990 to 2016, the global incidence of liver cancer grew by 114.0%, the second-highest annual percentage rise in males and the greatest annual percentage increase in women among all primary malignancies in the period from 2008 to 2017.¹

In Egypt, most of this increase has been attributed to hepatitis C virus (HCV), which has been the leading cause of HCC.³ Over the past two decades, Egypt had adopted a wide national program for screening and treating HCV and it is on track for meeting World Health Organization (WHO) targets for elimination of HCV by 2030.⁴ However, the reflection of this program on changing the burden of HCV-related HCC is unknown.

On the other hand, over the past decade, the metabolic dysfunction-associated fatty liver disease (MAFLD) has become the most common chronic liver disease in the world that affects nearly a quarter of the global population, with the highest prevalence in the Middle East and North Africa region, in parallel with the dramatic increase in prevalence of obesity and diabetes.^{5–7} Therefore, it is anticipated that MAFLD will increase the burden of advanced liver disease.⁸ More than any other liver condition, MAFLD is concerning more likely to lead to HCC without cirrhosis.⁹ However, in Egypt, neither the clinical characteristics of MAFLD-related HCC nor the burden of HCC caused by MAFLD is known. This drastic change in the profile of the liver disease in Egypt over the decade from infectious to metabolic dominant pattern provides a unique opportunity to assess the impact of these changes on HCC burden in a real-life context.

As a result, we set out to look at the changing prevalence of HCC caused by MAFLD, hepatitis B virus (HBV), and HCV in a cohort of 1,368 patients diagnosed with HCC between 2010 and 2020 in a well-defined geographical area.

Methods

Study Design

We conducted a hospital-based study between 2010 and 2020, identifying all HCC patients and assessing temporal trends of incidence by etiology in patients identified in a tertiary care center in Minia, Upper Egypt.

Study Participants

All patients with a diagnosis of HCC between December 31st, 2010, to December 31st, 2020, were considered for inclusion in the study. MAFLD was defined as follows: (1) the exclusion of other liver diseases, in particular HCV, HBV, and autoimmune liver disease; (2) either physician documentation of fatty liver disease; or (3) the presence of overweight/obesity, presence of type 2 diabetes mellitus, or signs of metabolic

dysregulation, according to the recent international consensus.¹⁰

The fibrosis 4 (FIB-4) score computation was used to stage liver disease according to fibrosis stage (FIB-4 score over 3.25 suggesting advanced liver disease) or manifest clinical or radiological signs of advanced liver disease such as ascites or gastroesophageal varices. If there were any additional clinical, biochemical, and radiological data; they were registered if present within 1 month of HCC diagnosis.

Statistical Analysis

For continuous data, medians, and interquartile ranges are displayed. Categorical and dichotomous data are expressed using total numbers and percentages. To determine whether there were any differences between groups, the Mann-Whitney *U*-test, chi-squared test, and analysis of variance tests were utilized. A body mass index (BMI) of more than 25 kg/m² was regarded as being overweight or obese. The statistics were all run with SPSS. A *p*-value of less than 0.05 was used to indicate statistical significance.

Ethical Considerations

Due to the low risk to participants and the disproportionate difficulty in obtaining informed consent due to the high mortality of HCC, the ethics committee in Minia, Egypt, approved this study, which includes a general authorization to collect nominative data and analyze anonymized data with a waiver of informed consent.

Results

The study included 1,368 patients who were diagnosed with HCC between 2010 and 2020. Their mean age at the time of diagnosis was 62.7 years (standard deviation [SD]: 9.25 years), and the majority were men (73.6%). Diabetes mellitus, hypertension, and smoking were reported in 23, 21.6, and 39.4%, respectively. The mean BMI was 27.5 kg/m² (SD: 3.37).

Changes of Etiologies of HCC over a Decade

Overall, 985 (72%) of all HCC cases had HCV, 58 (4%) had HBV, 143 (10.5%) had MAFLD, 1 patient had hemochromatosis, 1 with autoimmune liver disease, and 180 (13%) were with unknown cause. The annual percentage of MAFLD-related HCC has dramatically grown between 8.3% in 2010 and 20.6% in 2020 ($p = 0.001$; **–Fig. 1**). Similarly, MAFLD-related HCC increased significantly in the duration between 2010 and 2015 compared to 2016 to 2020 between 9 and 15.9% ($p = 0.001$). In addition, the annual proportion of HBV-related HCC increased significantly from 2.6% in 2010 to 6% in 2020 ($p = 0.01$; **–Fig. 1**). Similarly, HBV-related HCC increased significantly from 1.7% in the duration between 2010 and 2015 to 5.4% in the duration between 2016 and 2020 ($p = 0.001$).

In contrast, the annual proportion of HCV-related HCC declined from 84.8% in 2010 to 66.7% in 2020

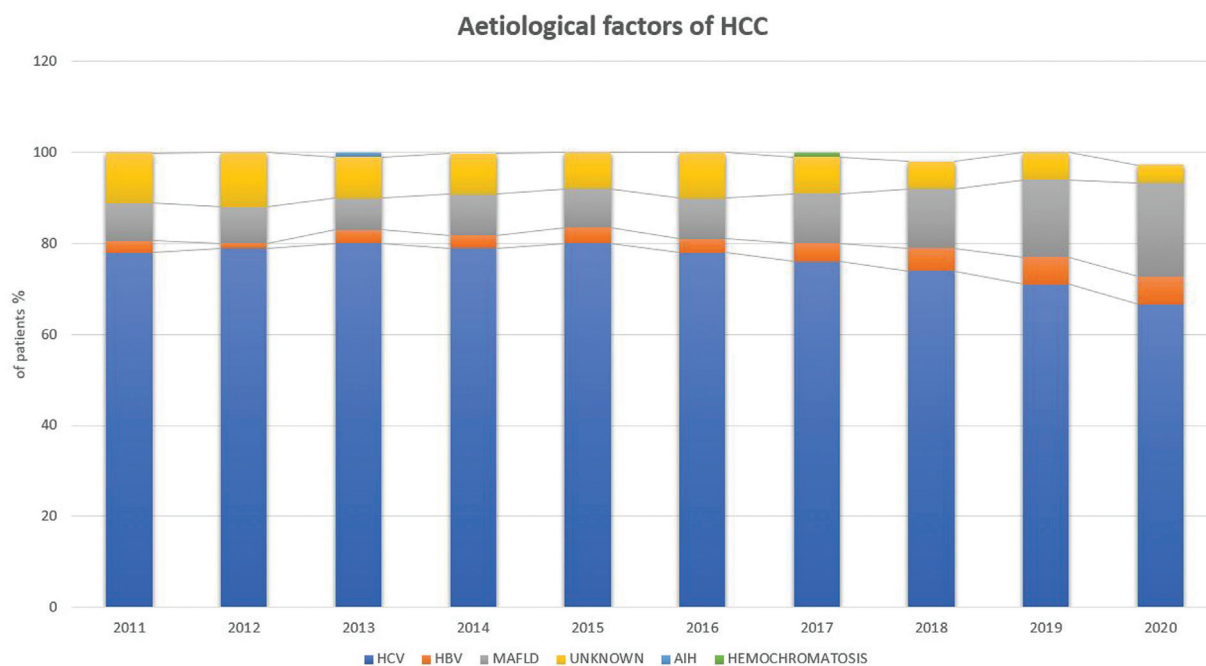


Fig. 1 Different hepatocellular carcinoma (HCC) etiologies through a decade (2010–2020). AIH, Autoimmune hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic-dysfunction-associated fatty liver disease.

($p = 0.001$; **Fig. 1**). Similarly, HCV-related HCC significantly decreased in the duration between 2010 and 2015 compared to 2016 to 2020 between 82.5 and 67.8% ($p = 0.001$). Then, we examined the difference in the characteristics of HCC patients caused by specific etiologies. As would be expected, when compared to patients with HCV- or HBV-related HCC, MAFLD-related HCC patients were considerably more likely to have metabolic comorbidities such as diabetes, hypertension, elevated BMI, blood glucose, and white blood cells (**Table 1**). No differences were noticed regarding age, gender, or other characteristics. No difference in the proportion of portal vein thrombosis or metastasis was observed between the three groups. In a subset of 675 patients with available FIB-4 data, there was no difference in FIB-4 score of more than 3.25 indicates advanced liver disease, between the three groups ($p = 0.5$).

Changes of Characteristics of HCC over a Decade

Finally, we examined the changes of characteristics of HCC patients over the study period, by comparing the characteristics of patients diagnosed with HCC in the duration between 2010 to 2015 and 2016 to 2020. We demonstrated an increase in the age (from 61.5 ± 8.9 to 64.2 ± 9.3 years, $p = 0.0001$), the proportion of female (from 21 to 31%, $p = 0.01$), proportion of overweight and obese (from 71.5 to 80.4%, $p = 0.001$), proportion of diabetes (from 17.4 to 31%, $p = 0.0001$), and they exhibited a high mean of blood sugar (from 112 to 122 mg/dL, $p = 0.01$). While patients who are smoking declined from 43.1% to 35.2%, $p = 0.04$, and those who had hypertension declined from 24.9% to 17.8%,

$p = 0.03$. The alpha-fetoprotein was found to be not significantly different in the duration between 2016 and 2020 compared to 2010 to 2015 (**Table 2**).

Discussion

According to our data, MAFLD was responsible for 10.8% of HCC cases in the Egyptian population. This percentage significantly rose from 4.3 to 20.6% during the study period. Patients with MAFLD-related HCC have a distinct phenotype when compared to those with HCC brought on by other factors; they are older and more likely to have metabolic comorbidities such as diabetes, hypertension, and overweight and obesity when they are first diagnosed. HCC patients (12%) had no discernible risk factors, according to a previous cross-sectional investigation of HCC risk variables in an Egyptian population from 2006 to 2016; however, MAFLD and the dynamic of changes over time were not considered in that study.³

Egypt has launched a widespread national program for HCV testing and treatment over the past 10 years,¹¹ which should have an impact on the decline of problems associated to HCV. Here, HCC caused by HCV significantly dropped from 94.8% in 2010 to 76.7% in 2020, according to our data. Although only 3.9% of patients with HCC had HBV-HCC, their annual proportion has rapidly increased from 2.6% in 2010 to 7% in 2020.

There are three key consequences of our findings. First, the percentage of HCC linked to MAFLD is increasing quickly, supporting earlier modelling studies conducted in other nations.^{12,13} Egypt-specific modelling research would be necessary. These results imply that in order to address this mounting load, an urgent action plan is required. Second,

Table 1 Characteristics of main HCC etiologies

Variables	HCV (n = 985)	HBV (n = 58)	MAFLD (n = 143)	p-Value
Age (years)	63 (56–69)	65 (61–68)	65 (58–71)	0.3 ^a 0.2 ^b 0.9 ^c
Male, n (%)	729 (74.6)	39 (66.7)	97 (68)	0.2 ^a 0.1 ^b 0.8 ^c
Diabetes, n (%)	207 (21)	13 (23)	69 (48)	0.7 ^a 0.0001 ^b 0.003 ^c
Hypertension, n (%)	197 (20)	7 (12)	43 (30)	0.2 ^a 0.01 ^b 0.02 ^c
Smoking, n (%)	394 (40)	23 (40)	54 (38)	1.0 ^a 0.7 ^b 0.8 ^c
BMI (kg/m ²)	27 (24–30)	26 (25–30)	31 (27–32)	0.9 ^a 0.0001 ^b 0.0001 ^c
Hemoglobin (g/dL)	11 (10–12)	11 (9–12)	11 (1–12)	0.9 ^a 0.1 ^b 0.5 ^c
Leucocyte (x10 ⁹ /L)	5 (4–7)	5 (3–6)	6 (4–8)	0.8 ^a 0.0001 ^b 0.02 ^c
Platelets (x10 ⁹ /L)	134 (102–208)	166 (129–240)	168 (123–222)	0.07 ^a 0.019 ^b 0.9 ^c
AFP (IU/mL)	368 (15–17,268)	484 (22–7,534)	313 (34–11,903)	0.8 ^a 0.9 ^b 0.8 ^c
Creatinine (mg/dL)	1 (0.9–1.1)	0.9 (0.9–1.4)	0.9 (0.9–1.1)	0.2 ^a 0.8 ^b 0.2 ^c
Blood glucose (mg/dL)	121 (110–126)	122 (114–141)	121 (111–150)	0.4 ^a 0.0001 ^b 0.3 ^c
ALT (IU/L)	42 (29–54)	42 (32–56)	44 (33–58)	0.9 ^a 0.2 ^b 0.6 ^c
AST (IU/L)	56 (36–76)	62 (56–88)	62 (46–98)	0.7 ^a 0.06 ^b 0.8 ^c
Albumin (g/dL)	3 (3–3.6)	3.5 (3–3.8)	3.5 (3–3.8)	0.2 ^a 0.1 ^b 0.9 ^c
Total bilirubin (mg/dL)	1.4 (1–2)	1.4 (1.2–2)	1.3 (1–1.8)	0.9 ^a 0.9 ^b 0.9 ^c

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; MAFLD, metabolic-dysfunction-associated fatty liver disease. Statistically significant values are in bold.

Data are presented as either the median (IQR) or number (%).

^ap-Value between HCV and HBV.

^bp-Value between HCV and MAFLD.

^cp-Value between HBV and MAFLD.

Table 2 Change of HCC characteristics over a decade (2010–2015 to 2016–2020)

	2010–2015 (n = 774)	2016–2020 (n = 594)	p-Value
Age (years)	61.5 (55–68)	64 (58–70)	0.0001
Gender, n (%)			0.01
Male	588 (79)	410 (69)	
Female	186 (21)	184 (31)	
Diabetes, n (%)	134 (17.4)	184 (31)	0.001
Hypertension, n (%)	186 (24.9)	106 (17.8)	0.03
Smoking, n (%)	333 (43.1)	208 (35.2)	0.04
Overweight or obesity (%)	71.5	80.4	0.001
BMI (kg/m ²)	27 (24–31)	28 (25–30)	0.5
Hemoglobin (g/dL)	11 (10–12)	11 (10–12)	0.07
Leucocyte (x10 ⁹ /L)	5 (4–8)	5 (4–6)	0.01
Platelets (x10 ⁹ /L)	123 (97–188)	166 (121–216)	0.01
AFP (IU/mL)	344 (15–20,278)	332 (22–17,234)	0.1
Creatinine (mg/dL)	1 (1–1.1)	0.9 (0.8–1.1)	0.1
Blood glucose (mg/dL)	112 (100–123)	122 (112–134)	0.01
ALT (IU/L)	42 (27–55)	42 (32–54)	0.2
AST (IU/L)	52 (34–74)	60 (45–78)	0.01
Albumin (g/dL)	3 (2.5–3.3)	3.2 (2.8–3.8)	0.1
Total bilirubin (mg/dL)	1.6 (1–2.6)	1.4 (1–1.8)	0.1

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HCC, hepatocellular carcinoma; IQR, interquartile range. Statistically significant values are in bold. Data are presented as either the median (IQR) or number (%).

over the course of the study period, HCC linked to HCV continued to drop.

Recent research in Egypt revealed a decreasing incidence of HCV¹⁴ and Egypt is on track to achieve the WHO targets for the eradication of HCV by 2030.¹¹ This is undoubtedly responsible for the decline in HCC linked to HCV that we noticed. It should be emphasized, nonetheless that recent studies have shown that over half of HCV patients have MAFLD and that those with dual etiologies had much more severe fibrosis than those with HCV alone.^{15,16} Therefore, the presence of MAFLD may continue to promote the development of liver disease and counteract the positive effects of HCV treatment on end-stage liver disease and HCC. As a result, a recent appeal for the MAFLD to be taken into account as part of the worldwide drive to eradicate HCV has been made by an international group of specialists on viral hepatitis.^{17–21} Third, despite the fact that HBV-HCC accounts for a lesser percentage of cases of diagnosed HCC, which is likely primarily due to the implementation of a universal program for pediatric hepatitis B vaccination, the sharp rise in these instances over the research period is concerning. This pattern indicates the need for a free catch-up HBV vaccination program, more active case detection of HBV patients, and viral load management.

Changes in HCC features over the course of the study are another important finding of this experiment. The age of

patients with HCC considerably increased from 2010 to 2015 to 2016 to 2020, which is commensurate with the ageing of the population. Notably, the proportion of women also greatly grew during that time. According to a recent study, among all primary malignancies between 2008 and 2017,¹ liver cancer had the biggest annual percentage increase in incidence among women worldwide. We also noticed an increase in metabolic comorbidities including diabetes and obesity during the course of the trial. This increase is probably compensating for the rise in MAFLD-HCC that we saw.

Nearly 13% of HCC cases identified by the veterans administration between 20025 and 2010 do not appear to have cirrhosis, and individuals with MAFLD had a fivefold higher chance of developing HCC without cirrhosis than patients with HCV-related HCC.⁹ These data indicate an alarming potential increase in HCC in the absence of cirrhosis, which is consistent with the observed increase in MAFLD-HCC. Despite the fact that we were unable to detect a significant difference in cirrhosis between different HCC-related etiologies, this was likely due to the small sample size and available FIB-4 score.

There were some limitations on this study. When diagnosing MAFLD, we relied on the absence of other liver disorders or the existence of metabolic dysfunction in the absence of other risk factors after considering all consecutive

patients who presented during the study period to identify risk variables. The MAFLD cohort may be underestimated because other individuals may not have all the necessary diagnostic criteria for MAFLD. The burden of MAFLD-related HCC is, thus, conservatively estimated by our findings. We were unable to check for fibrosis and the existence of cirrhosis in all individuals since the study was retrospective. Last but not the least, despite being based on a sizable cohort drawn from one of the largest centers in Egypt, additional studies conducted at the national level would be necessary to provide a more precise national estimation for the trends of HCC in Egypt.

Limitation of our study is that there are no much data about other metabolic risk factors such as lipid profile that may increase the percentage of MAFLD related HCC, as 13% of HCC was due to unknown cause that may be attributed to MAFLD; also, since our data only come from one center in Egypt, multicentric research is preferable.

In summary, we discovered for the first time that MAFLD is the fastest-growing cause of HCC in the Egyptian population, indicating that the influence of the MAFLD burden on HCC has not yet been acknowledged. Over the course of the trial, the percentage of HCC linked to HCV rapidly decreased, signaling the beginning of the antiviral treatments' effects. In order to overcome practice hurdles and address the growing burden of this group of patients, additional research is required to pinpoint effective strategies and serve as a roadmap for action plans.

Conclusion

MAFLD-related HCC increased significantly during the last 10 years. Despite HCV is the main cause of HCC, it is declining over the past years. In order to address this mounting burden, integrated action plans are required.

Patients' Consent

A general authorization was included to collect nominative data and analyze anonymized data with a waiver of informed consent due to the low risk to participants and the disproportionate difficulty in obtaining informed consent due to HCC's high mortality.

Note

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Ethical Approval

The ethics committee in Minia University, Egypt, approved this study.

Data Availability Statement

The authors' institution does not allow public data access.

Conflict of Interest

None declared.

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