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Impact of multiple primary cancers on overall survival of patients with hepatocellular carcinoma

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The increasing occurrence of multiple primary cancers (MPC) is a long-term trend, but the prevalence of MPC in patients with hepatocellular carcinoma (HCC) and its impact on overall survival (OS) remains unknown. We retrospectively analyzed 497 patients with HCC treated at two tertiary centers. The cohort was divided into two subgroups – liver transplant (LT, 324 patients) and non-liver transplant (non-LT, 173 patients). We analyzed MPC occurrence, its impact on survival, and identified variables predicting unfavorable outcomes. The MPC were detected in 88 patients (18%). The most common MPC were prostate (17%), skin (15.9%), kidney (12.5%), and lung (10.2%). The median OS of the whole cohort and the LT and non-LT subgroups were 70, 116, and 17 months, respectively (p<0.0001). The median OS in patients with HCC only and HCC with another cancer was 77 (95% CI, 67–96) and 50 months (95% CI, 37–62), respectively (p=0.25). The OS of LT patients was significantly better than that of those in whom LT had been contraindicated owing to concomitant MPC (116 vs. 35 months, p<0.0009). Autoimmune etiology, non-alcoholic steatohepatitis (NASH), HCC as the first diagnosed malignancy, and male sex were identified as factors significantly influencing the patients' outcomes (HR 0.43, 3.2326, 0.70, and 1.43, respectively). The MPC frequency was 18%. The impact of MPC on OS was not significant, except for individuals contraindicated for LT because of MPC. A better prognosis is associated with the autoimmune etiology of cirrhosis, and when HCC is diagnosed as the first malignancy. Male sex and NASH worsened the outcomes.

Key words: type 2 diabetes; liver cirrhosis; liver transplantation; non-alcoholic steatohepatitis; retrospective study

Malignant tumors are increasingly responsible for global population mortality. Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor. According to the latest data, HCC is globally the third most common cause of cancer-related death and the sixth most common newly diagnosed malignant tumor [1]. It typically develops in preexisting liver cirrhosis of diverse etiologies. Chronic hepatitis B virus (HBV) or non-alcoholic steatohepatitis (NASH) are among the risk factors for its development in patients without liver cirrhosis. The staging of HCC in cirrhotic patients follows the established and generally accepted Barcelona Clinic Liver Cancer (BCLC) classification [2]. HCC is a malignancy with an unfavorable prognosis. Its late diagnosis and underlying, often advanced, liver disease contributes to it to a large extent. Even patients diagnosed in the early stages have short overall survival (OS), with a median of 13.4 months, if not diagnosed and treated promptly [3]. In contrast, patients who undergo liver transplantation (LT) for HCC within the Milan criteria have, according to a meta-analysis, an excellent 5-year OS (65–78%) [4]. Median OS for the advanced and terminal stages is 3.4 and 1.6 months, respectively [3]. In patients with HCC without liver cirrhosis, the technical resectability of the tumor is primarily assessed, but BCLC cannot be used. It results from the above that patients' prognosis is determined by early diagnosis, as expected. Patients with HCC usually die from gradual depletion of liver function and fatal bleeding episodes due to portal hypertension are also frequent.

However, HCC is not always the only type of cancer in a particular patient. A long-term trend related to an increase in life expectancy also leads to an increase in the number of diagnosed malignancies of various origins. For these condi-

tions, the term multiple primary cancers (MPC) has been adopted. Defining this condition is important for epidemiological studies of this topic. In contemporary literature, two definitions are most often used, based on the Surveillance Epidemiology and End Results (SEER) and the International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC) projects [5, 6]. Considering the fundamental differences between these definitions, it is understandable that the frequency of MPC has been reported very widely in the literature, with a frequency of 5–18% [7–9]. By definition, synchronous MPC is diagnosed within six months of the diagnosis of the first tumor. This topic assumes critical importance when we realize that MPC not in definite remission may represent a contraindication to LT for HCC. Furthermore, there are studies indicating a close association between concurrent type 2 diabetes mellitus (T2DM) and/or obesity and elevated risk of HCC as well as other malignancies [10–16]. There is a gap in the literature concerning this topic from the HCC point of view. In particular, there is no recently published study dedicated to the influence of MPC on the OS of patients with HCC which would systematically assess the differences between transplanted and non-transplanted HCC patients and their outcomes. Table 1 presents the results.

Our primary hypothesis was that the association of HCC with another primary cancer leads to significantly decreased OS in patients with HCC, especially in the patients potentially intended to be transplanted for HCC; secondly, we hypothesized that concurrent T2DM and/or obesity would be associated with worse outcomes.

Patients and methods

We retrospectively analyzed two cohorts of patients treated at two tertiary centers in the Czech Republic. The Institute for Clinical and Experimental Medicine Prague (IKEM) is a transplantation center, and the Department of Medicine 1st Faculty of Medicine Charles University, and Military University Hospital Prague (MUH) represents a tertiary full-scale treatment center for patients with HCC, except LT.

The cohort included all patients diagnosed with HCC with underlying liver cirrhosis between 2002 and 2022 who were followed up and treated at IKEM or MUH. The patients' data were extracted from the electronic patients' database (by P.H. in MUH and S.F. in IKEM) and fully anonymized for further statistical analysis. The IKEM cohort included all the patients who had undergone LT for HCC. The MUH cohort included HCC patients treated with all therapeutic modalities (i.e., resection, locoregional methods, and systemic therapy) except for LT. The diagnosis of liver cirrhosis was established by non-invasive liver stiffness measurement (shear wave or vibration-controlled transient elastography) and/or histology and/or history of decompensation. The diagnosis of HCC was based on the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines and was determined in patients with liver cirrhosis according to non-invasive diagnostic criteria using imaging techniques (multiphase computed tomography, dynamic contrast magnetic resonance) and/or histology [17, 18]. In the IKEM cohort, HCC diagnosis was also confirmed by liver explant histology in all the cases. Patients with HCC in non-cirrhotic livers were not included in the study.

The study was approved by the Ethics Committee of Central Military Hospital in Prague, Czech Republic (ERB approval number MUH: 108/18-87/2023), and was carried out in compliance with the Helsinki Declaration. The patients' informed consent was not required by local law because of the retrospective design of the study and the use of data from which the patient's identification information had been removed.

Statistical analysis. In addition to the basic demographic data of the cohort, the presence of obesity and T2DM,

Table 1. Studies dealing with HCC and MPC.

Author (year, reference)	MPC/HCC patients	MPC share (%)	The most commonly reported MPC
Riesz (1979) [31]	17/66	25.7	genitourinary, gastric, colorectal
Lin (1987) [25]	12/562	2.1	gastric
Lai (1990) [35]	13/440	2.9	colorectal, thyroid, retroperitoneal
Kanematsu (1992) [26]	7/93	7.5	gastric, colorectal
Takayasu (1992) [27]	33/393	8.4	gastric, colorectal, pharyngeal
Nzeako (1994) [36]	74/1349	5.5	prostate, colorectal, lung
Di Stasi (1994) [32]	32/317	10.1	lymphoproliferative, colorectal, gastric
Onitsuka (1995) [28]	10/146	6.8	gastric, colorectal
De Pangher (1996) [22]	29/143	20.3	prostate, colorectal, bladder
Shimada (1996) [29]	41/463	8.8	gastric, colorectal, genitourinary
Koide (1999) [30]	10/340	2.9	exclusively synchronous gastric
Bruno (1999) [37]	5/37	13.5	genitourinary
Wong (2007) [38]	23/306	7.5	genitourinary, colorectal, breast
Fernández-Ruiz (2009) [39]	18/245	7.3	colorectal, head and neck, genitourinary

smoking status, number and types of MPC, and their associations were also assessed. Clinical characteristics were descriptively analyzed and reported as medians and ranges. The Chi-square test or Fisher's exact test were used for frequency analysis, according to the sample size. For continuous variables, the Mann-Whitney test was used because of the non-parametric distribution of data.

In addition, we performed the Kaplan-Meier analysis of OS according to different factors to compare the cohorts. Survival curves were compared using the log-rank test. Testing the empirical distribution was used to determine the statistical significance between the groups. Hazard ratios (HR) were computed using Cox proportional-hazards regression. The median follow-up was determined based on the Kaplan-Meier reverse analysis. Statistical assessment was performed using the MedCalc® software, version 20.106 (MedCalc Software Ltd., Ostend, Belgium). Statistical significance was set at p-value <0.05.

Results

Study population. At our two facilities, we included 497 patients with HCC whose complete demographic and treatment data were available. The data are summarized in Table 2. The median follow-up of the entire cohort was 71 months (95% CI, 59–79).

Frequency of MPC. In the entire cohort, an MPC was diagnosed in 88 patients (18%). In the LT subgroup, MPC was diagnosed in 58 cases (18%) and in the non-LT subgroup in 30 cases (17%). In the LT subgroup, HCC was the first diagnosed tumor in 34 cases (59%), contrarily, in the non-LT subgroup, HCC was the first malignancy only in 4 cases (13%). Seventy-nine patients had another primary cancer in addition to HCC. Eight patients had three MPC, and in one case, we identified four MPC.

Types of MPC. In addition to HCC, the next primary neoplasia was prostatic cancer in 15 cases, skin cancer

Table 2. Demographic and clinical characteristics of patients.

Characteristics	Total	LT patients	Non-LT patients	p-value
n (%)	497 (100)	324 (65)	173 (35)	< 0.0001
Age at the time of diagnosis (median, years)	65 (26-85)	64 (26-76)	71 (37-85)	< 0.0001
Sex				0.4420
Males, n (%)	388 (78)	250 (77)	138 (80)	0.4948
Females, n (%)	109 (22)	74 (23)	35 (20)	0.7254
Initial BCLC stage, n (%)				
0+A	251 (51)	203 (63)	48 (28)	< 0.0001
B	134 (27)	78 (24)	56 (32)	0.3073
C	84 (17)	39 (12)	45 (26)	0.1084
D	28 (6)	4 (1)	24 (14)	0.4693
Primary treatment modality, n (%)				
LT	324 (65)	324 (100)	0 (0)	
Resection	38 (8)	0 (0)	38 (22)	
Radiofrequency ablation	4 (1)	0 (0)	4 (2)	
Transarterial chemoembolization	60 (12)	0 (0)	60 (35)	
Systemic therapy	44 (9)	0 (0)	44 (25)	
Best supportive care	27 (5)	0 (0)	27 (16)	
Etiology, n (%)				
Alcoholic liver disease	191 (38)	126 (39)	65 (38)	0.8933
Autoimmune*	48 (10)	48 (15)	0 (0)	
NASH	95 (19)	28 (9)	67 (39)	< 0.05
Other	3 (1)	3 (1)	0 (0)	
Viral	160 (32)	120 (37)	40 (23)	0.1053
T2DM, n (%)	217 (44)	134 (41)	83 (48)	0.3134
BMI >30, n (%)	171 (34)	95 (29)	76 (44)	< 0.05
Smoking, n (%)	291 (59)	186 (57)	105 (61)	0.5068
AFP cut-off				
>200 µg/l	106 (21)	42 (13)	64 (37)	< 0.05
>400 µg/l	83 (17)	28 (9)	55 (32)	< 0.05

Note: *the autoimmune etiology includes patients with autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis
Abbreviations: AFP-alpha fetoprotein; BCLC-Barcelona Clinic Liver Cancer staging system [2]; BMI-body mass index; NASH-non-alcoholic steatohepatitis; LT-liver transplantation; T2DM-type 2 diabetes mellitus

(excluding basalioma) in 14 cases, kidney cancer in 11 cases, lung cancer in nine cases, colorectal cancer in eight cases, six breast cancers, five non-Hodgkin's B-cell lymphomas (B-NHL), five cases of head and neck cancer, four cases of esophageal and urinary bladder cancer, leukemia in three cases, soft tissue malignancy and uterine cancer, and cancer of unknown primary origin in two cases, and one case of each of the following: gastrinoma, gastric cancer, neuroendocrine tumor, pancreatic cancer, brain cancer, oropharyngeal cancer, teratoma, and thyroid cancer. The data are summarized in Figure 1.

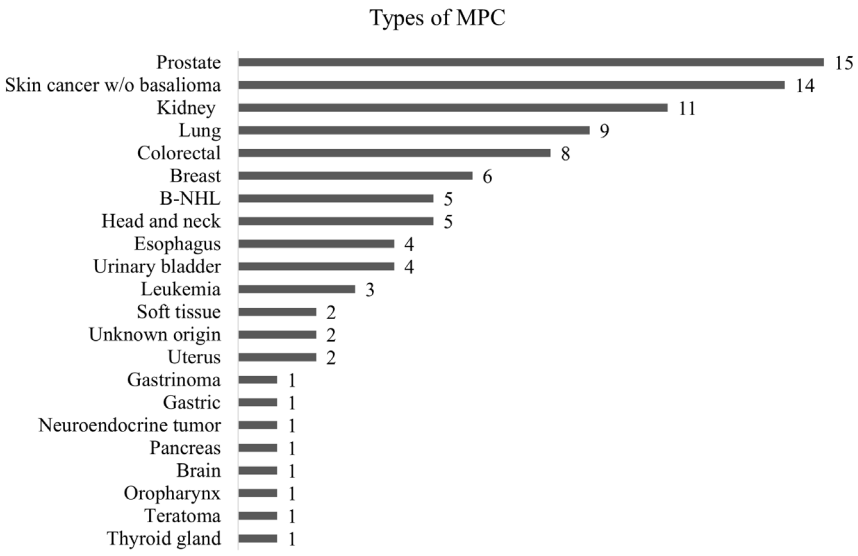

Figure 1. Types of MPC and their frequencies.

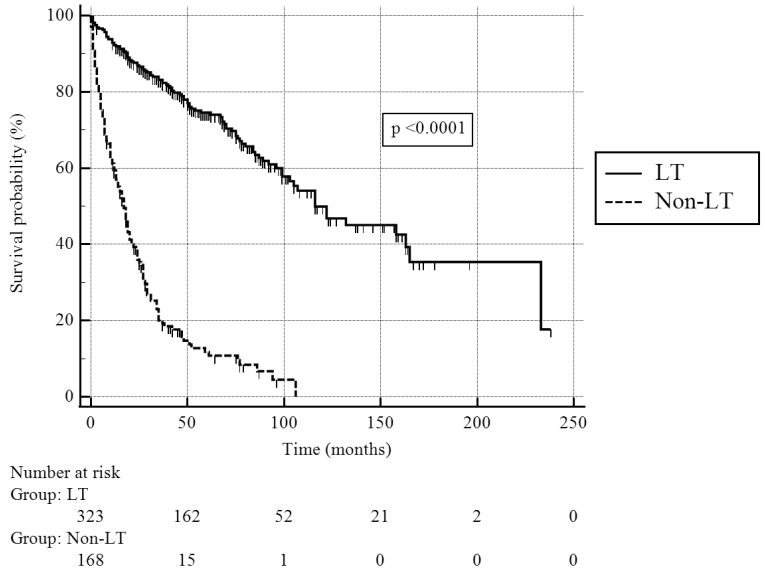

Figure 2. Comparison of Kaplan-Meier curves for OS in LT and Non-LT subgroups.

Overall survival. Up to 1st July 2022, 250 (50.3%) of included patients had died. The median OS of the entire cohort was 70 months (95% CI, 51–85). The median OS was 116 months (95% CI, 99–165) in the LT subgroup and 17 months (95% CI, 13–20) in the non-LT subgroup; this difference was statistically significant (p<0.0001), as shown in Figure 2. The median OS in patients with HCC only and HCC with another primary malignancy was 77 months (95% CI, 67–96) and 50 months (95% CI, 37–62), respectively; however, the difference between groups did not reach statistical significance (p=0.2545), as shown in Figure 3.

Comparing the subgroup of patients who underwent LT for HCC and patients with HCC who had undergone a pre-transplant workup and had been rejected owing to a concomitant MPC, we found a significant difference in OS (p<0.0009). In the first-mentioned group, the median OS was 116 months (95% CI, 99–165); the patients initially suitable but finally rejected from the LT program achieved a median OS of 35 months (95% CI, 19–94), as illustrated in Figure 4.

Risk factors of death in the whole cohort. We performed a Cox regression analysis of the selected risk factors of death. The analysis included obesity, defined as a Body Mass Index (BMI) ≥ 30, smoking status, sex, underlying etiology of liver cirrhosis, sequence of HCC diagnosis, and presence of T2DM. None of the above-mentioned parameters reached a level of statistical significance, except for autoimmune (Hazard Ratio (HR) 0.4332; 95% CI, 0.2285–0.8212; p=0.0104) and NASH (HR 3.2326; 95% CI, 2.4123–4.3320; p<0.0001) etiologies of cirrhosis, HCC as the first diagnosed malignancy (HR 0.6880; 95% CI, 0.4784–0.9894; p=0.0436), and male sex (HR 1.4318; 95% CI, 1.0493–1.9535; p=0.0236). Statistically significant results are summarized in Table 3.

Discussion

Our study represents, to the best of our knowledge, the second-largest cohort published in this field to date, with an interesting focus on differences between patients who underwent LT for HCC and the others. In our pilot study published in 2023

Table 3. Cox regression of the statistically significant risk factors of death in the whole cohort.

Characteristics	Hazard ratio	p-value	95% CI
Autoimmune* etiology	0.4332	0.0104	0.2285–0.8212
NASH etiology	3.2326	<0.0001	2.4123–4.3320
HCC as the first-diagnosed tumor	0.6880	0.0436	0.4784–0.9894
Male sex	1.4318	0.0236	1.0493–1.9535

Note: *the autoimmune etiology includes patients with autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis
Abbreviations: HCC-hepatocellular carcinoma; NASH-non-alcoholic steatohepatitis

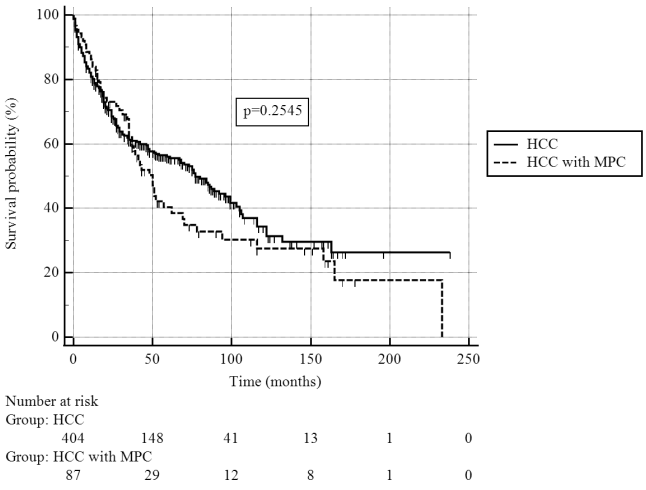

Figure 3. Comparison of Kaplan-Meier curves for OS in HCC only and HCC+MPC subgroups.

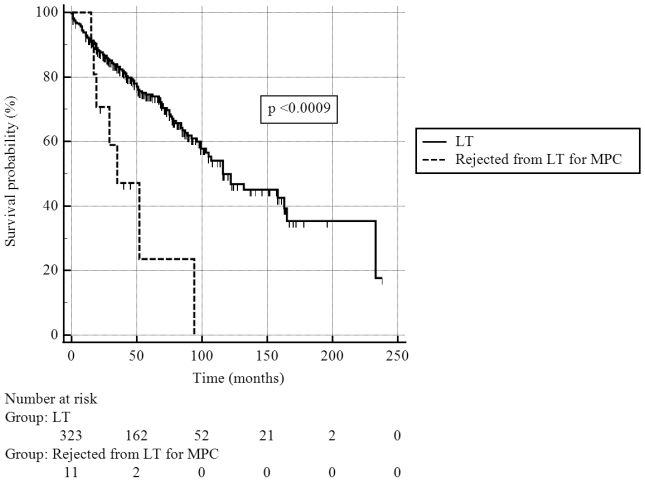

Figure 4. Comparison of Kaplan-Meier curves for OS in LT patients with HCC and patients in whom LT was denied owing to the concurrent MPC.

[19], researchers from MUH investigated the presence and impact of T2DM on the occurrence of MPC in patients with HCC. It turned out that 50% of patients with both HCC and MPC had concurrent T2DM, 31% of them receiving insulin therapy. Nevertheless, no statistically significant influence of T2DM on OS had been observed. These initial results laid the groundwork for a subsequent study incorporating a cohort from IKEM, providing a more comprehensive analysis owing to the inclusion of a substantial number of HCC patients who underwent LT and enabling a detailed analysis of other potential risk factors for the development of MPC and their impact on OS.

MPC are well-known clinical entities with identified factors of their occurrence (e.g., improving OS, cancer screening programs, wide use of imaging methods, close follow-up after the first cancer diagnosis) [20, 21], but there is a wide variety in their estimated frequency. From the perspective of HCC, MPC epidemiology is largely influenced by regional differences. In a large retrospective study by Scottish authors that included data from 57,393 patients with malignancy, the incidence of primary liver cancer was not assessed [7]. Conversely, in a Japanese study, HCC was the first diagnosed malignancy from MPC in more than 4% of cases, and a synchronous or metachronous tumor in almost 7% of MPC cases [9]. In our cohort, MPC was observed in 18% of patients with HCC, and its occurrence did not differ significantly between transplanted (18%) and non-transplanted patients (17%). This frequency seems to be higher than in previously reported studies (Table 1); only de Pangher Manzini et al. referred to a higher frequency (20.3%) [22]. In the Czech Republic, newly diagnosed cancers are reported in the national cancer registry according to the International Classification of Diseases 10 (ICD-10). There is an increasing trend in the incidence of HCC (C220) in the Czech population. In 2001, the incidence of C220 was 9.6/100,000 and the last published incidence data from 2018 increased to 12 per 100,000 [23]. Therefore, the authors can explain this more frequent association of HCC and MPC by improved diagnostics and expansion of therapeutic modalities for cancers in the past two decades, as well as by the simple increase in HCC occurrence. From the European perspective, the Czech Republic takes 29th–31st place in the HCC incidence scale [24].

Interestingly, the association between tumor sequence and LT status has not been studied so far. In our LT subgroup, HCC was identified as the first malignancy in 59%, in contrast to 13% of non-transplanted patients. HCC diagnosed as the first malignancy led, of course, to a higher chance of LT with a better OS (HR 0.6880; 95% CI, 0.4784–0.9894; p=0.0436), as concurrent tumors represent traditionally, in many cases, contraindications to LT. This fact was even more expressed when comparing patients who had undergone LT and those whose HCC staging had been favorable but LT had been denied owing to a newly diagnosed MPC (median OS 116 vs. 35 months). This subgroup of patients suffered significantly in terms of OS compared to the other subgroups.

The three most common types of associated cancers in our cohort, with 78% of males, were prostate, skin, and kidney cancer. The typical characteristic of HCC is male sex predominance, which determines the associated MPC. The incidence ratio between males and females in the Czech Republic reported in 2018 was for the kidney 1.8:1 [23]. Regional conditions may be the hallmark of the MPC association pattern. Studies from Asia have reported an almost uniform association between HCC and gastric cancer [25–30]. Conversely, in Western countries, only Riesz et al. and Di Stasi et al. reported gastric cancer among the three most frequent cancers associated with HCC. Our cohort had only one case of gastric cancer (1.14% of all MPC) [31, 32].

In contrast to our estimation, there was no statistically significant difference in OS between patients with HCC plus MPC and those with HCC alone (77 vs. 50 months, p=0.2545). There are several possible explanations for this phenomenon. First, the diagnostics and overall care for cancer survivors are more systematic, with closer follow-up. In the MUH cohort, HCC was diagnosed simultaneously with the underlying chronic liver disease in 64.7% of cases (unpublished data). The patients had been referred to our institution for newly diagnosed tumors without previous knowledge of the presence of chronic liver disease. This only increases the influence of closer medical surveillance in patients with HCC and MPC, even when liver disease is not detected. The only exception from these results was the significantly different OS between patients who had undergone LT for HCC and patients with HCC complying with LT criteria and denied due to a concomitant MPC (116 vs. 35 months, p<0.0009). These above-mentioned patients, diagnosed with another cancer during the pretransplant workup, had utterly different survival outcomes. Even if it is not a large group of patients, its impact on the individual is unquestionable. The need for oncology consultation in the era of rapidly improving therapeutic modalities should be axiomatic and may enable LT and therefore, increase OS in these selected individuals.

Surprisingly, obesity, T2DM, and smoking were not associated with worse OS as independent factors. By contrast, NASH, an underlying etiology of cirrhosis, was associated with a significantly increased risk of death (HR, 3.2). An interesting finding was the positive influence of the autoimmune etiology of the underlying liver disease on OS, with an HR of 0.4332. This could be explained by the fact that, in this subgroup of patients, the underlying liver disease had been known for a long time before it had been complicated by HCC, and these patients were taking part in ultrasound surveillance. Therefore, the diagnosis of HCC was made in the early stages, and all these forty-eight patients underwent LT. A similar relationship was observed in the sequence of the diagnosis of HCC and MPC. If HCC was the first diagnosed cancer (HR 0.6880), it led to curative treatment in more cases, particularly LT; the consecutive cancer types were then treatable with better outcomes than is usually possible in HCC. The last independent significant risk factor in our study was male sex (HR 1.4318). The male-to-female ratio was similar in both cohorts; therefore, LT did not bias the better outcomes. Furthermore, no statistically significant differences were observed between females and the whole cohort in terms of initial HCC staging, frequency of LT, etiology of liver disease distribution, and frequency of MPC. There are several factors that may contribute to the better OS observed in female cancer patients. The influence of sex hormones on disease progression is notable, and interestingly, the efficacy and toxicity of chemotherapy also differ significantly between males and females [33].

The recently published study by Macq et al. [34], using data from the Belgian Cancer Registry, reported an MPC frequency of 12.2% in the general population. The frequency of MPC varied according to the type of primary malignancy diagnosed first. Although HCC was not specifically studied as the first diagnosed malignancy, the findings were notable: HCC was involved in 13.4% of MPC cases, and MPCs in this cohort were associated with lower relative survival rates. However, an exception was observed with a slight increase (+0.02%) in the relative survival rate in women with HCC. The authors attribute this finding to an earlier stage of HCC, most likely owing to a closer follow-up in patients with a history of other cancers. This observation aligns with our findings.

The limitations of the study were its retrospective design and the predominance of transplanted patients in the entire cohort, which is not in line with the real-life staging distribution of newly diagnosed HCC patients.

In conclusion, the MPC frequency in patients with HCC was 18%. The impact of MPC on OS in patients with HCC was not significant, except for individuals contraindicated for LT because of MPC. Male sex and NASH were factors predicting poor outcomes in MPC patients.

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