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Research Article

Treatment Patterns and Survival in Patients with Intermediate, Advanced, or Terminal Stage of Hepatocellular Carcinoma in France over the Period 2015-2017: A Real-Life Study

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Background. The prognosis of patients with hepatocellular carcinoma (HCC) not eligible to curative treatment is poor. Little information is available on treatment modalities and outcomes of these patients in everyday practice. The aim of this analysis was to describe the characteristics of patients with a newly diagnosed intermediate, advanced, or terminal (IAT) stage of HCC (ICD-10: C220) between 2015 and 2017, either present at diagnosis of HCC or having occurred after disease progression; treatment patterns, HCC aetiologies, and the associated survival were determined using the nationwide claims database. *Methods*. Patients with HCC were identified using the ICD-10 code C220. IAT stages, defined according to the terminology used in the Barcelona Clinic Liver Cancer classification, were indirectly identified by the presence of at least one of the following treatments: transarterial chemoembolization (TACE), transarterial radioembolization (TARE), HCC systemic therapy, best supportive care (BSC), or an ICD-10 code of metastatic HCC. Treatment patterns were described with an algorithm based on a ranking of palliative treatments identified. Survival was analysed by using Kaplan-Meier curves. *Results*. 19,649 eligible patients were identified. Their mean age was 70.5 years (SD: 11.0), and 82.5% were males. For 68.8% of patients, the IAT stage was present at HCC diagnosis. On the whole population, 5,114 patients (26.0%) were treated initially with a TACE or TARE, and 4,681 (23.8%) received a targeted systemic therapy at any moment during follow-up with sorafenib in 99.5% of cases. About 7,628 patients (45.6%) received only BSC. Survival since the diagnosis of the AIT stage of HCC differed according to the type of the first received palliative treatment. Median overall survival was 23.8, 9.6, 7.4, and 1.0 months in patients initially receiving TACE, TARE, systemic therapy, and BSC only, respectively. *Conclusion*. Over the period 2015-2017, hepatocellular carcinoma was still often diagnosed in France at late-stage disease with a very poor prognosis.

1. Introduction

Hepatocellular carcinoma (HCC), which represents the great majority of primary liver cancers [1, 2], develops in almost all cases in the presence of chronic liver disease that has led to liver cirrhosis [2, 3]. In 50% to 60% of cases, HCC is no longer in an early stage at diagnosis [3, 4], especially in patients with alcohol-related liver disease. In this patient population, studies showed that diagnosis is usually made with delay [5, 6]. According to data provided by 17 registries of the US Surveillance, Epidemiology, and End Results (SEER) program, the 5-year relative survival decreased from

36.1% in localized disease to, respectively, 12.8% and 3.1% in regional or distant extension of the disease at diagnosis over 2012-2018 [7].

The Barcelona Clinic Liver Cancer (BCLC) system is the most used staging system for HCC [8]. It determines cancer stage and patient prognosis based on tumour burden, severity of liver disease, and performance status [8]. It also provides recommendations of treatment and/or management for each stage of disease. The BCLC system identifies five stages: two early stages—very early stage (BCLC 0) and early stage (BCLC A)—and three later stages—intermediate stage (BCLC B), advanced stage (BCLC C), and terminal stage (BCLC D)— of the disease. Patients classified in the early stages can benefit from HCC curative treatments (resection, transplantation, or ablation) [8]. Patients in the BCLC D stage have poor liver disease function and/or marked cancer-related symptoms and cannot benefit from transplantation. They could only receive best supportive care (BSC) [8]. Intermediate and advanced stages of disease require transarterial chemoembolization (TACE), transarterial radioembolization (TARE), or systemic treatment [3, 8]. In patients with intermediate stage, TACE has been the most widely used treatment and the standard of care over the past decades [2]. Until its updated guidelines in 2022, the BCLC classification did not include TARE in the therapeutic options for HCC [1, 8, 9]. TARE has not been usually considered as a primary standard of care in guidelines even though it has shown efficacy in phase II investigation [2]. In the 2022 update of the BCLC system, TARE was proposed as a treatment option in some BCLC 0 or A patients and in BCLC B patients meeting "extended liver transplant criteria." TARE was not included in the treatment options for other patients mainly due to negative trials. Regarding systemic treatment, until 2007, no effective therapy existed for patients diagnosed with advanced-stage HCC. Since its approval in 2007 and for one decade, sorafenib, an oral multikinase inhibitor, was the sole agent approved in first-line treatment at this stage of disease [3, 10]. Since 2007, several new drugs have been approved in second-line treatment after progression on sorafenib, and other alternative treatments are also now available in the first-line setting. The recent approval of atezolizumab in combination with bevacizumab heralded the arrival of immunotherapy for the first-line treatment of advanced HCC, and the field is growing with other combination immunotherapies under investigation [11].

As a benchmark for future similar studies, it has seemed interesting to describe in a comprehensive manner the real-life management of intermediate, advanced, or terminal (IAT) stage HCC in France over a period immediately preceding this new era where patients will benefit from an extended therapeutic armamentarium [12].

2. Objectives and Methods

The aim of this analysis was to describe characteristics, treatment patterns, HCC risk factors, and associated survival of patients with HCC newly diagnosed at the IAT stage or having progressed to one of these late stages between 2015 and 2017 in France, using a national claims database, the "Système National des Données de Santé" (SNDS).

2.1. Data Source. This retrospective observational study was conducted using the SNDS database [13] that covers around 99% of the French population (over 66 million inhabitants). This database identifies all items of outpatient and inpatient care reimbursement for each beneficiary. It identifies in a comprehensive manner all visits to physicians, reimbursed drugs (CIP "Codes Identifiant Présentation" or ATC "Anatomic Therapeutic Chemical" codes), laboratory test procedures, medical devices, medical procedures (Common Classification for Medical Procedures codes or CCAM codes), and paramedical care. In addition, due to pairing with the hospital database (PMSI), all public and private hospital stays are documented for each patient, with details about diagnoses (International Classification of Diseases, 10th version [ICD-10]), procedures (CCAM codes), diagnosis-related groups, durations of stays, and month of discharge. In France, the patient's general practitioner can request a full coverage for patients presenting with chronic severe diseases (long-term disease [LTD]). Conditions that are eligible to this coverage belong to a preestablished list (3-digit ICD-10 coded) of 30 groups of major chronic diseases. These data are supplemented by sociodemographic information like year of birth, gender, area of residence, and, eventually, date of death.

The database does not provide any clinical information about HCC prognostic factors and/or stages of the disease as the Barcelona Clinic Liver Cancer (BCLC) stages of patients as well as details about liver function assessment (Child-Pugh score), tumour extension (number, size, vascular invasion, and extrahepatic localization), and performance status.

2.2. Population Selection and Study Period. In a first step, all patients, with an International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code of primary HCC (C22.0) either as the justification for an LTD status or as the reason for hospitalization over the five calendar years 2013-2017, were identified in the SNDS database.

In a second step, to minimize false-positive primary HCC diagnoses, patients with another primitive cancer diagnosed after HCC and without further hospital stay with HCC diagnosis and those with an ICD-10 diagnosis code of "malignant tumour of the liver and biliary tract" other than "hepatocellular carcinoma" (C22.0) —"malignant tumour of the liver without precision" (C22.9), "carcinoma of the intrahepatic bile duct" (C22.1), hepatoblastoma (C22.2), angiosarcoma of the liver (C22.3), other sarcomas of the liver (C22.4), and "other specified carcinomas of the liver" (C22.7)— were excluded. The following patients were also excluded: patients with another associated primitive cancer and markers of management for advanced or metastatic cancer prior to the first identification of HCC, which may be related to the primitive cancer having progressed, and patients with a unique hospital stay mentioning the HCC code and no other HCC-related claims during the follow-up period. Another possible bias may result from

the absence of death notification in the database especially in the elderly, so we also excluded patients with no reimbursement claims recorded over the period 2015-2017 and likely to be deceased.

In a third step, patients with IAT stage HCC or an ICD-10 code of metastatic disease newly identified over the study period (2015-2017) were researched and considered eligible, the remaining patients being excluded at this step. In the absence of clinical data in the SNDS database, the IAT stage HCC was defined by the identification of one of the following palliative HCC treatments in the database: a TACE, a TARE, or a systemic therapy (sorafenib, lenvatinib, regorafenib, or cabozantinib), or other chemotherapy received within a hospital stay for HCC or BSC. Metastatic disease was identified using the ICD-10 diagnosis codes: C77–C79—secondary malignant neoplasms.

Eligible patients had to meet the selection criteria over the analysis period from 1st January 2015 to 31st December 2017. However, the data collection period was extended over the period 2013-2015 to identify the newly diagnosed HCC and the newly diagnosed IAT stage defined by the absence of, respectively, the HCC diagnosis code and IAT stage HCC treatment within at least the two previous years.

The index date was defined as the first date of IAT stage HCC identification in the database over the period 2015-2017 (3 calendar years) (see Supplementary Figure S1).

2.3. HCC Treatment Patterns. Description of patient medical management since the first identification of the IAT stage of HCC was the main objective of the study, but the history of curative HCC treatment was also documented. However, in patients with HCC diagnosed before 2013, history of curative treatment could only be documented for treatments performed since 2013 because of our data extraction period. HCC treatments were identified in the SNDS database by using their specific procedure codes (CCAM codes used in the French Hospital database) for curative treatments, TACE and TARE. HCC systemic treatments were identified by their ATC codes (Supplementary Table S1, Table S2, and Table S3).

In the absence of BCLC stages documented in the SNDS, patients were classified according to the major palliative HCC treatment received considered as a proxy of the likely patient BCLC stage [14]. In this perspective, the following algorithm was used: "TACE," if the patient had a TACE as the first treatment during the follow-up period; if the patient had no TACE but was treated with a TARE, he was categorized in this category. Patients with neither a TACE nor a TARE that benefitted from a systemic treatment as first treatment were categorized as such. Patients were lastly classified in best supportive care (BSC) in all cases where no active HCC palliative treatment was reported during the follow-up, even if they had no specific record of admission in institutions for BSC.

2.4. HCC Aetiology Identification. To identify HCC aetiologies, for each patient, a cause of chronic liver disease and/or the existence of diabetes mellitus (DM) was investigated. Relevant diseases were identified from ICD-10 codes of hospital stay diagnoses (primary or associated) or causes of LTD status over the whole period 2013-2017. Alcohol-related liver diseases were identified by using ICD-10 codes K70 and K71. Viral hepatitis was identified by using the following codes: B182 (hepatitis C); B180 and B181 (hepatitis B); and B188, B189, B190, B199, and Z225 (unspecified chronic viral hepatitis). For metabolic factors, NASH (nonalcoholic steatohepatitis) and NAFLD (nonalcoholic fatty liver disease) were identified by the codes K758 and K760, respectively. Other chronic liver diseases were also searched and considered apart in the category "other chronic hepatopathies" (K72, K73, K74, K752, K753, K754, and K759 and E311). DM was identified by ICD-10 codes E10, E11, E12, E13, and E14 and/or the dispensing of at least one drug from the ATC categories "blood glucose-lowering drugs, excluding insulin" and "insulin and analog" (Supplementary Table S4).

Due to the important overlap of these aetiologies, relevant categories of interest have been established and ranked by using an algorithm that focused in a first step on the two main HCC risk factors: alcohol and/or viral infection. They were each considered alone (alcohol without viral infection or viral infection without alcohol) or associated (alcohol and viral infection). A category of metabolic aetiologies was then constituted grouping DM, NASH, or NAFLD in the absence of any alcohol-related liver disease or viral hepatitis. Another category of "other liver aetiologies" was defined in the absence of alcohol, viral, or metabolic aetiology as previously identified. The last category was defined as "no recorded liver disease or diabetes," meaning the absence in the database of any diagnosis of liver disease or diabetes (Supplementary Figure S2).

2.5. Statistical Method. Kaplan-Meier curves were used to analyse overall survival, from the IAT stage HCC index date, i.e., from the date of the first identification of major palliative treatment or BSC in the SNDS. In the subanalysis of patients treated with sorafenib in the first line of systemic treatment, overall survival was assessed from the date of the first sorafenib dispensing. For these purposes, each patient was traced using their anonymous alphanumeric number to the date of death or of end of the follow-up period (31/10/2017), whichever occurred first. The log rank test was used to evaluate differences between overall survival curves. A Cox proportional hazards model was used to determine independent potential confounders of mortality that were entered into the multivariable model. Statistical analysis was performed with software SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

2.6. Ethics. The study was conducted in accordance with relevant international and French regulatory requirements. Patient data in the database is anonymised using an irreversible double encryption. Since this was a retrospective study of an anonymised database and had no influence on patient care, ethics committee approval was not required. Use of the SNDS database for this type of study got an approval from the French national data protection agency (Commission

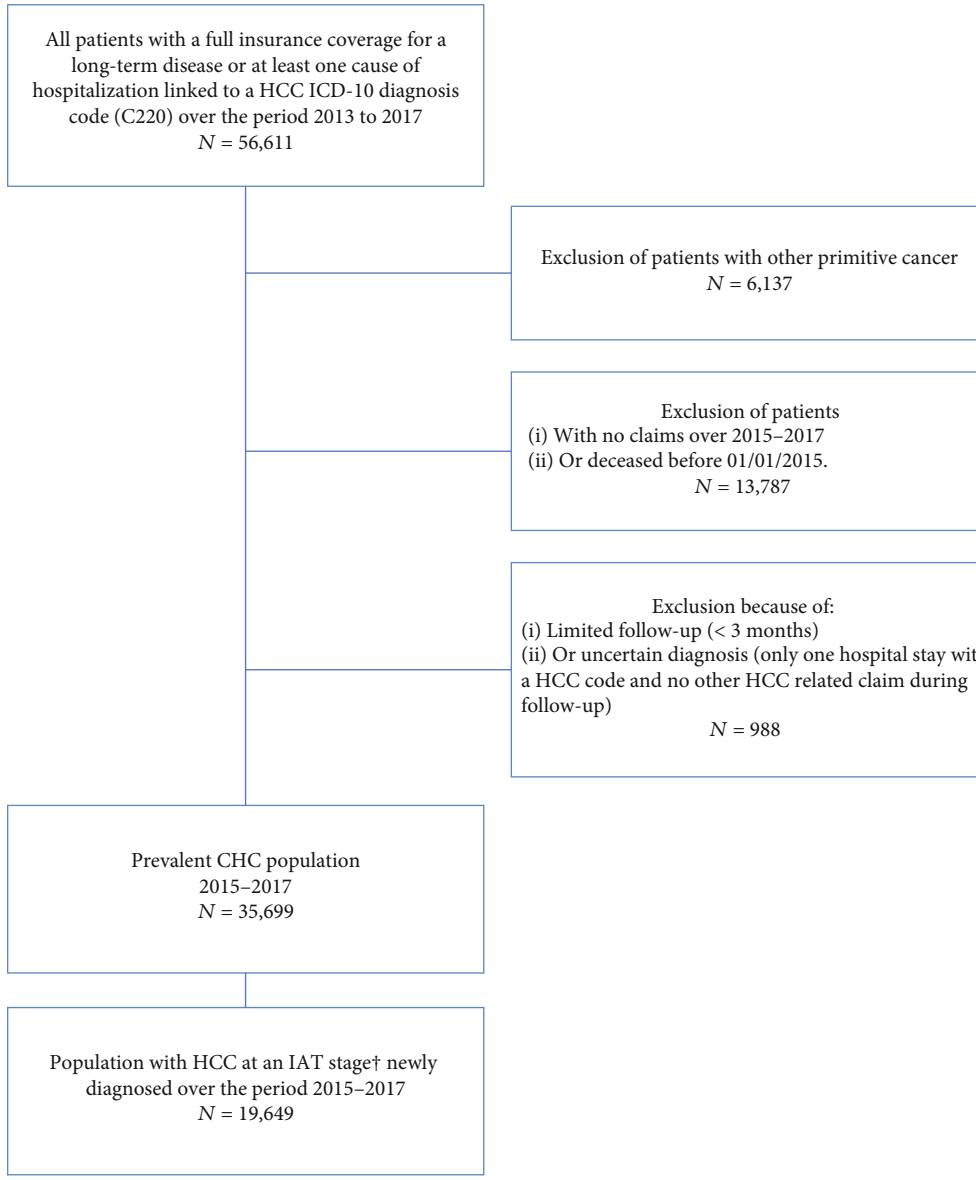


Figure 1: Identification of patients with newly diagnosed IAT stage† HCC between 2015 and 2017 in the SNDS database.

Nationale de l'Informatique et des Libertés: CNIL, decision DR-2019-055, dated February 28, 2019).

3. Results

3.1. Characteristics of the Study Population. Between 2015 and 2017, 19,649 newly diagnosed patients with an IAT HCC were identified in the SNDS database (Figure 1). The characteristics of the patient population and HCC are presented in Table 1. The mean age of these patients was 70.5 (±11.0) years, and 82.5% were male. Among them, 16.3% progressed to the IAT stage after a curative therapy. In 14.9% of cases, HCC was diagnosed before 2015 and then progressed to the IAT stage between 2015 and 2017. In these patients, no curative treatment was identified over the study period, but the absence of curative treatment could not be documented in those patients before 2013 as previously notified. In most cases (69% of patients), the IAT stage was present at HCC diagnosis, and none of these patients received curative treatment.

3.2. HCC Aetiologies. Regardless of combinations of HCC aetiologies, an alcohol-related liver disease was identified in more than half of the patients (52.6%). A metabolic disease (NAFLD, NASH, or DM) was identified in 44.4% and viral infection in only 18.5% of patients (Table 1). In 13.2% of patients, no liver disease or diabetes could be found in the SNDS database (Table 1 and Table S5).

3.3. Treatment Pathways. The treatment pathways of the study population are presented in Table 2. They could be assessed from the index date (diagnosis of IAT stage of HCC) and during a mean follow-up period of 7.9 months (median 5.6 months). This analysis showed that the three

Table 1: Characteristics of patients with newly identified IAT stage† HCC over the period 2015–2017 in the SNDS database.

Newly diagnosed IAT stage† HCC population	Total 19,649 (100%)
Gender male (%)	16,210 (82.5%)
Age (years) at the identification of IAT stage† HCC: mean (SD)	70.5 (11.0)
Duration of follow-up (month): mean (SD)	7.9 (7.3)
History of HCC curative treatment or type of disease progression	
Previous curative treatment	3,205 (16.3%)
No curative treatment (de novo IAT stage† at HCC diagnosis)	13,512 (68.8%)
Undetermined (lack of retrospective data in some patients with HCC diagnosed before 2013)	2,932 (14.9%)
HCC aetiology (several responses possible‡)	
Alcohol intake	10,328 (52.6%)
Viral hepatitis	3,635 (18.5%)
Metabolic risk factors§	8,729 (44.4%)
Other liver diseases	11,218 (57.1%)
None identified liver disease in the database	2,596 (13.2%)

†IAT stage: intermediate, advanced, or terminal stage; ‡a single patient can have several HCC risk factors explaining the sum of percentages greater than 100; §Metabolic risk factors are NAFLD (nonalcoholic fatty liver disease), NASH (nonalcoholic steatohepatitis), or diabetes mellitus.

Table 2: Treatment pathway of patients with newly identified IAT stage† HCC over the period 2015-2017.

Newly identified IAT stage† HCC population	Total 19,649 (100%)
Treatment pathway since the IAT stage† diagnosis	
Best supportive care only	10,584 (53.9%)
Systemic treatment only	3,951 (20.1%)
TACE only	3,382 (17.2%)
TACE and systemic treatment	1,241 (6.3%)
TARE only	176 (0.9%)
TARE and systemic treatment	130 (0.7%)
TACE and TARE	97 (0.5%)
TACE and TARE and systemic treatment	88 (0.4%)
Systemic treatment received	
Targeted systemic treatment	4,681
Sorafenib	4,658
Lenvatinib	5
Regorafenib	334
Cabozantinib	4
Other chemotherapies	1,267
Other chemotherapies without targeted systemic treatment	729

†IAT stage: intermediate, advanced, or terminal stage. TACE: transarterial chemoembolization; TARE: transarterial radioembolization.

main treatments received in descending order were BSC alone, followed by a systemic therapy alone, and then by a TACE alone. Since the diagnosis of the IAT stage, more than one in two patients (54%; $n = 10{,}584$) received only BSC, 20% ($n = 3{,}951$) a systemic therapy only, and 17% ($n = 3{,}382$) a TACE without other HCC palliative treatments during the follow-up. After taking into account patients who previously received a curative treatment, the proportion of patients who received only BSC during their entire treatment pathway could be estimated at 49.4% and at 45.6% after excluding patients without documented history of curative treatments (Table 3).

All treatment pathways considered, at any moment during the follow-up, 28% of all patients received a systemic treatment, 24% a TACE, and 2% a TARE. In 87% of cases, the systemic treatment was a targeted therapy (24% of patients), and in almost all cases (99.5%), the received targeted therapy was sorafenib. The systemic therapy was administered after a TACE or a TARE in, respectively, 6.3% and 0.7% of patients.

3.4. Survival according to the Major HCC Palliative Treatment Received. Overall survival (OS) according to the major palliative HCC treatment received showed contrasted

Table 3: History of curative treatment according to the major palliative treatment or BSC‡ received.

History of curative treatment	Previous curative treatment	No curative treatment (de novo IAT stage† at HCC diagnosis)	Undetermined	Total
	3,205 (16.3%)	1,3512 (68.8%)	2,932 (14.9%)	19,649 (100%)
Major palliative treatment or BSC only received since the IAT stage diagnosis				
TACE	1,398 (43.6%)	3,151 (23.3%)	259 (8.8%)	4,808 (24.5%)
TARE	55 (1.7%)	240 (1.8%)	11 (0.4%)	306 (1.6%)
Systemic treatment	867 (27.1%)	2,493 (18.5%)	591 (20.2%)	3,951 (20.1%)
BSC‡	885 (27.6%)	7,628 (56.5%)	2,071 (70.6%)	10,584 (53.9%)

†IAT stage: intermediate, advanced, or terminal stage; ‡best supportive care.

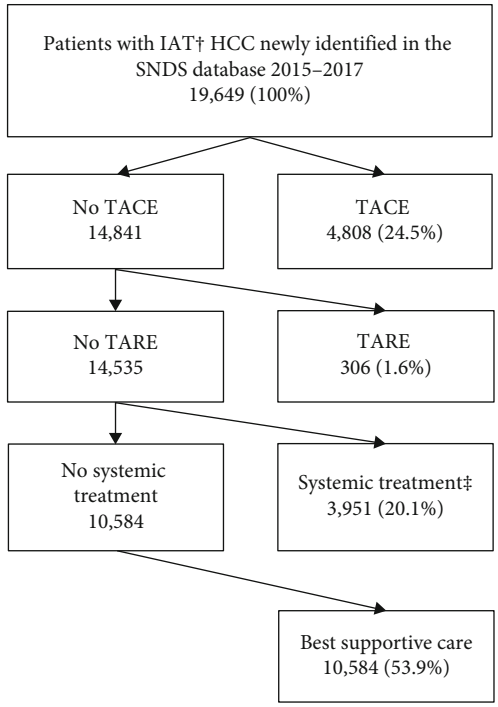
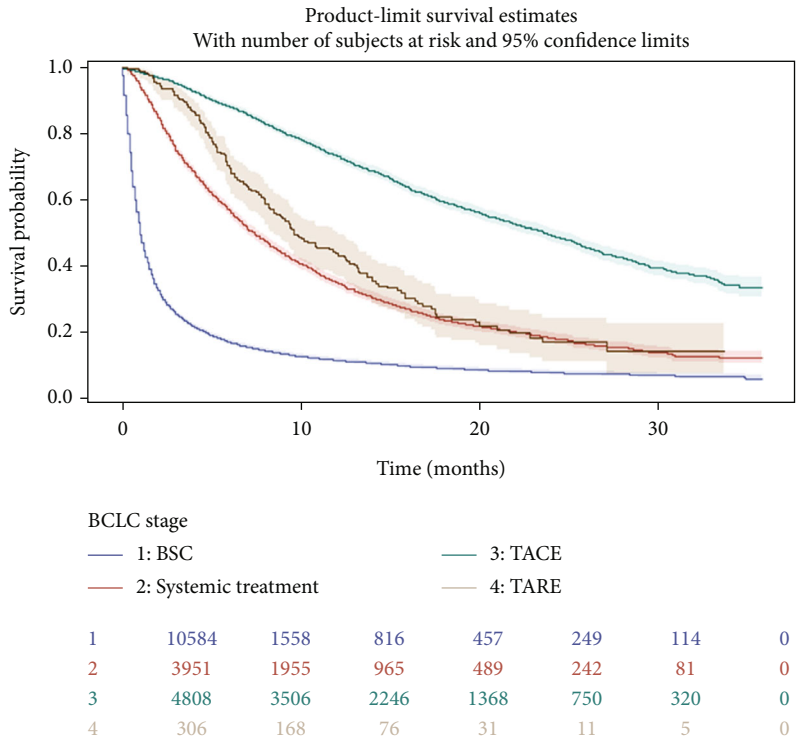


Figure 2: Distribution of patients with newly identified IAT stage† HCC between 2015 and 2017 according to the major palliative treatment received ($N = 19,649$).

results. In patients that benefitted from a TACE (4,808 patients representing 24% of all patients), the median survival was 23.8 months (95% CI 22.4–24.9). It dropped to 9.6 months (95% CI 8.5–12.1) when treatment started with TARE (306 patients representing 1.6% of all patients) and to 7.4 months (95% CI 7.0–7.8) only when the major palliative treatment was a systemic treatment (3,951 patients representing 20.1% of all patients). In the group of patients having received only BSC, the median OS was only 1.0 month (95% CI 1.0–1.1) (Figures 2 and 3).

3.4.1. Factors Associated with Survival. Unadjusted and adjusted hazard ratios (HR) of mortality risk according to history of HCC curative treatment, major palliative treatments received, HCC aetiologies, gender, and age are presented in Table 4. In the univariate analysis, the type of major palliative treatment received was by far the main factor associated to mortality risk which increased from 1.97 to 6.67 times (unadjusted HR) in patients who did not receive TACE compared to those who did, the highest mortality risk being found in patients having received BSC only. Similar results (adjusted HR: 1.90 to 6.16) were obtained after adjustment. The absence of HCC curative treatment and type of disease progression were also important mortality risk factors as patients with a de novo IAT stage at HCC diagnosis had mortality increased by a factor 2.34 (unadjusted HR) and a factor 1.74 after adjustment for the other risk factors as compared to patients with HCC which progressed after a previous curative therapy. It might be noticed that mortality in men was lower than that in women before adjustment (0.89 unadjusted HR), but this difference disappeared after adjustment. Regarding mortality risk according to HCC aetiologies, the relative negative effects of aetiology remained significant after adjustment for history of HCC curative treatment and/or type of disease progression, palliative treatment subgroups, gender, and age. Thus, compared to patients with HCC associated to viral hepatitis only, the adjusted mortality risk was significantly increased by 16-27% for the other aetiologies except for patients with "other liver disease" for whom this risk was increased by 40%. Alcohol-related liver diseases and metabolic diseases had a similar adjusted excess mortality. In the Cox model performed, age group did not significantly influence survival when taking patients under 60 years of age as reference.

3.5. Population Treated with Sorafenib in First Line. The population treated with sorafenib in the first line (of systemic treatment) is described in Table 5. It consisted of 4,658 patients of whom 3,466 (74.4%) were not previously treated with TACE or TARE at the IAT stage identification, while 1,079 (23.2%) and 113 (2.4%) received a TACE and a TARE, respectively, before sorafenib. The mean age of these patients was slightly inferior to that of the whole study



Major palliative treatment‡	TACE	TARE	Systemic treatment	BSC
3 months	95.1% [94.4-95.7]	91.7% [87.8-94.4]	75.0% [73.6-76.3]	25.6% [24.8-26.5]
6 months	88.1% [87.1-89.0]	69.6% [63.6-74.8]	56.8% [55.2-58.4]	17.2% [16.5-17.9]
12 months	73.3% [71.8-74.7]	43.9% [37.3-50.3]	35.1% [33.3-36.6]	11.7% [11.1-12.4]
24 months	49.2% [47.2-51.1]	17.3% [11.3-24.5]	18.5% [16.9-20.1]	8.0% [7.4-8.7]
Median survival	23.8 months IC 95%: [22.4-24.9]	9.6 months IC 95%: [8.5-12.1]	7.4 months IC 95%: [7.0-7.8]	1.0 months IC 95%: [1.0-1.1]

Figure 3: Overall survival of patients with newly diagnosed IAT† HCC according to the major HCC palliative treatment or BSC received.

population (67.2 ± 9.9 vs. 70.5 ± 11.0), and conversely, those included a proportion of men slightly higher (87.2% vs. 82.5%).

As in the whole study population, most patients in this population had a de novo IAT stage at HCC diagnosis although this proportion was slightly lower in the sorafenib subgroup (63.5% vs. 68.8%). Conversely, the proportion of patients who received a curative treatment was slightly higher in the sorafenib subgroup (23%) than in the whole study population (16%).

Regarding HCC aetiologies, in the whole sorafenib subgroup as well as in its treatment pathway subgroups, alcohol was the most frequent identified risk factor, followed by metabolic risk factors and/or viral hepatitis (without alcohol), except in the "sorafenib after TARE" subgroup in which metabolic risk factors were only the fifth more frequent identified risk factor.

In the 4,658 patients treated with sorafenib, 1,495 (32.1%) had one delivery of this treatment only and 2,249 (48.3%) had three deliveries or more. In the subgroup of 3,163 (67.9%) patients who received at least two deliveries of sorafenib, the mean and median durations of treatment were, respectively, 5.0 (±5.2) and 3 months. In 35.7% of these patients, the sorafenib dosage was adjusted at least once during follow-up. The mean and median daily doses of sorafenib were, respectively, 762 (±612) and 700 mg. In 62.5% of cases (60.1-64.8), this treatment was discontinued at 12 months, but this proportion dropped to 40.3% (38.6-41.8) when using mortality as a competitive risk.

Among the 1,495 patients who received only one delivery of sorafenib, 1,117 (74.7%) died within an average of 3.3 (3.9) months after the first treatment delivery. A switch to a second systemic treatment line was performed in only 34 (2.3%) patients. In the whole population, the median overall survival from the start of sorafenib treatment was 7.3 (95% CI 7.0–7.7) months. This one differed markedly according to the treatment pathway from 10.4 (95% CI 9.7-11.2) months in patients that benefitted from a previous TACE to 6.5 (95% CI 6.2–6.9) months in those who received sorafenib only. A Cox model of survival according to age, gender, history of HCC curative treatment and/or type of disease progression, HCC aetiologies, and initial palliative treatment by TACE was performed (Table 6). After adjustment to the other risk factors, it appeared that patients that benefitted from an initial TACE had a significant 33%

Table 4: Mortality risk (hazard ratio) in patients with IAT† HCC according to patient characteristics, HCC aetiology, and treatment patterns ($N = 19{,}649$).

Variables	Number of patients	Unadjusted HR	95% CI	Adjusted HR	95% CI
Gender					
Female	3,439	Reference		Reference	
Male	16,210	0.89	0.85-0.93	1.03	0.98-1.08
Age at the IAT stage† diagnosis (years)					
<60	3,095	Reference		Reference	
60–79	12,080	1.08	1.02-1.13	1.03	0.98-1.09
≥80	4,474	1.55	1.47-1.64	1.06	1.00-1.12
History of HCC curative treatment or type of disease progression					
Previous curative treatment: HCC secondary progression to IAT† stage	3,205	Reference		Reference	
No curative treatment: patients with de novo IAT† stage at HCC diagnosis	13,512	2.34	2.21-2.47	1.74	1.64-1.84
Undetermined (lack of retrospective data) in some patients with HCC diagnosed before 2013	2,932	2.95	2.76-3.14	1.77	1.66-1.89
HCC aetiology					
Viral hepatitis without alcohol‡	2,204	Reference	—	Reference	—
Alcohol-related liver disease without viral hepatitis‡	8,897	1.40	1.32-1.48	1.27	1.20-1.35
Alcohol-related liver disease and viral hepatitis‡	1,431	1.15	1.06-1.25	1.18	1.09-1.29
Metabolic risk factors alone	3,331	1.51	1.41-1.61	1.18	1.11-1.27
Other liver diseases	1,190	1.58	1.45-1.72	1.39	1.28-1.52
No identified liver disease or diabetes mellitus	2,596	1.64	1.53-1.76	1.16	1.08-1.25
Major HCC palliative treatment subgroups (see Figure 2)					
TACE	4,808	Reference		Reference	
TARE	306	1.97	1.68-2.31	1.90	1.62-2.23
Systemic treatment	3,951	2.50	2.35-2.66	2.48	2.33-2.64
BSC	10,584	6.67	6.33-7.03	6.16	5.84-6.50

†IAT: intermediate, advanced, or terminal stage; HR: hazard ratio; 95% CI: 95% confidence interval; ‡with or without metabolic risk factors: NASH (nonalcoholic steatohepatitis); NAFLD (nonalcoholic fatty liver disease), or diabetes mellitus; TACE: transarterial chemoembolization; TARE: transarterial radioembolization; BSC: best supportive care.

reduction of mortality (HR: 0.669) while patients without history of curative HCC treatment and those for whom this medical history was undetermined had a mortality, respectively, of 34.9% to 68.0% higher as compared to those who received curative treatment. The effect of age, gender, and HCC aetiologies except for metabolic risk factors was not statistically significant.

4. Discussion

This retrospective real-word study described the characteristics of patients with a newly diagnosed IAT HCC over a 3-year period, their treatment patterns, the identified HCC aetiologies, and associated overall survival. The SNDS database does not include clinical data such as the BCLC stage. We then classified patients according to the major palliative treatment received as a proxy of the BCLC stage. This study showed that, over the 2015-2017 period, more than two-thirds of patients (68.8%) were in the IAT stage at HCC diagnosis, only 16% of patients had a history of curative treatment, and more than half of patients received only BSC in the IAT stage. Among the latter, 8.4% previously received curative treatment, and for 19.6% of them, the existence of such a treatment could not be documented. The

Table 5: Characteristics of patients with IAT stage† HCC treated with sorafenib (first line of systemic treatment) according to HCC aetiology and treatment patterns.

Population with IAT stage† HCC treated with sorafenib	Total 4,658 (100%)	Sorafenib after TACE only 1,079 (23.2%)	Sorafenib after TARE only 113 (2.4%)	Sorafenib only 3,466 (74.4%)
Gender male (%)	4,063 (87.2%)	950 (88.0%)	97 (85.8%)	3,016 (87.0%)
Age (years) at identification of IAT stage† HCC: mean (SD)	67.2 (9.9)	67.0 (9.3)	64.8 (11.0)	67.4 (10.0)
Duration of follow up: mean (SD) (month)	7.9 (7.3)	8.9 (7.5)	7.6 (6.2)	7.6 (7.2)
HCC aetiology (one answer only)				
Alcohol *without* viral hepatitis‡	1,949 (41.8%)	507 (47.0%)	41 (36.3%)	1,401 (40.4%)
Alcohol- *and* viral hepatitis-related liver disease‡	404 (8.7%)	112 (10.4%)	18 (15.9%)	274 (7.9%)
Viral hepatitis-related liver disease *without* alcohol‡	682 (14.6%)	189 (17.5%)	22 (19.5%)	471 (13.6%)
Metabolic risk factors	833 (17.9%)	162 (15.0%)	11 (9.7%)	660 (19.0%)
Other liver diseases	268 (5.8%))	53 (4.9%)	8 (7.1%)	207 (6.0%)
No identified liver disease or diabetes mellitus	522 (11.2%)	56 (5.2%)	13 (11.5%)	453 (13.1%)
History of HCC curative treatment or type of disease progression				
Previous curative treatment	1,061 (22.8%)	325 (30.1%)	26 (23.0%)	710 (20.5%)
No curative treatment (de novo IAT stage† at HCC diagnosis)	2,959 (63.5%)	686 (63.6%)	86 (76.1%)	2,187 (63.1%)
Undetermined (lack of retrospective data)	638 (13.7%)	68 (6.3%)	1 (0.9%)	569 (16.4%)
Sorafenib treatment modalities				
Number of deliveries				
Mean (SD) number of sorafenib deliveries during the study period	3.7 (3.8)	3.9 (3.9)	3.4 (3.0)	3.7 (3.9)
Only one delivery of sorafenib	1,495 (32.1%)	309 (28.6%)	39 (34.5%)	1,147 (33.1%)
2 sorafenib deliveries	914 (19.6%)	201 (18.6%)	22 (19.5%)	691 (19.9%)
≥3 sorafenib deliveries	2,249 (48.3%)	569 (52.7%)	52 (46.0%)	1,628 (47.0%)
Analysis in patient subgroup who received ≥2 sorafenib deliveries				
Number of patients (%)	3,163 (67.9%)	770 (71.4%)	74 (65.5%)	2,319 (66.9%)
Sorafenib dose				
Daily dose (mg): mean (SD)	762 (612)	717 (321)	804 (553)	775 (683)
≥1 dose adaptation (patients)	1,128 (35.7%)	293 (38.0%)	23 (31.1%)	812 (35.0%)
In patients alive at treatment discontinuation	1,067 (33.7%)	286 (38.1%)	26 (35.1%)	755 (32.6%)
No deaths observed during the study period	407 (12.9%)	115 (14.9%)	12 (16.2%)	280 (12.1%)
Delayed death after the treatment discontinuation	660 (20.9%)	171 (22.2%)	14 (18.9)	475 (20.5%)
Median survival: month (95% CI)	7.3 (7.0 -7.7)	10.4 (9.7-11.2)	8.2 (6.0 -8.8)	6.5 (6.2 -6.9)

†IAT: intermediate, advanced, or terminal stage; ‡with or without metabolic risk factors: NASH (nonalcoholic steatohepatitis), NAFLD (nonalcoholic fatty liver disease) or diabetes mellitus; 95% CI: 95% confidence interval.

proportion of patients who did not receive any anti-HCC treatment, whether curative or palliative, could be estimated at about 46%. Another study found a similar result. In Sweden, Henriksson et al. analysed data collected in the national registry of liver and bile duct tumours, related to 3,308 patients with newly diagnosed HCC over the period 2009-2016. In this population, the rate of patients who received only BSC was about 40% [15]. This large proportion of patients was, however, slightly higher in our study (46%) probably because the current analysis was limited to the sole advanced stages of the disease while the Swedish study included incident HCC cases regardless of their BCLC stage. This high proportion of patients offered BSC was not explained by Henrikson et al., but they noted a surprisingly large proportion of patients with an ECOG score of 0-1 and a low Child-Pugh grade in patients who received only BSC suggesting the possibility of further improvement in the treatment of HCC in their country. In our study, the absence of clinical information in the SNDS database did not allow to provide any specific reason for this result except the fact that these patients were older at the IAT stage diagnosis than the others (median age 73 years vs. 67 to 69 years, $p < 0.0001$). However, the high proportion of HCC diagnosed at a late stage most likely reflects an insufficient

Table 6: Mortality risk (hazard ratio) in patients with IAT† HCC treated with sorafenib (in first line of systemic treatment) according to patient characteristics, HCC aetiology, and previous HCC treatments (median overall survival: 7.3 months; 95% CI: 7-7.7).

Variables		Number of patients	Adjusted hazard ratio	95% hazard ratio confidence limits		p value
Age (years)	<40	52	REF			
	40-49	118	1.126	0.728	1.743	0.5930
	50-59	807	1.243	0.847	1.822	0.2659
	60-69	1,704	1.120	0.767	1.636	0.5572
	70-79	1,515	1.143	0.782	1.67	0.4897
	≥80	462	1.110	0.752	1.639	0.5990
Gender	Female	595	REF			
	Male	4,063	0.982	0.88	1.095	0.7400
History of HCC curative treatment or type of disease progression	Previous curative treatment	1,061	REF			
	No curative treatment (de novo IAT stage† at HCC diagnosis)	2,959	1.680	1.529	1.845	<.0001
	Undetermined (lack of retrospective data)	638	1.349	1.189	1.531	<.0001
HCC aetiology (one answer only)	Viral hepatitis without alcohol‡		REF			
	Alcohol-related liver disease without viral hepatitis‡	1,949	1.027	0.916	1.151	0.6477
	Alcohol-related liver disease and viral hepatitis‡	404	1.051	0.901	1.227	0.5258
	Other liver diseases	268	1.122	0.943	1.335	0.1932
	Metabolic risk factors only	833	1.145	1.004	1.307	0.0439
	No identified liver disease or diabetes mellitus	522	0.947	0.817	1.099	0.4748
Previous TACE	No	3,579	REF			
	Yes	1,079	0.669	0.611	0.733	<.0001

†IAT: intermediate, advanced, or terminal stage; ‡with or without metabolic risk factors: NAFLD (nonalcoholic fatty liver disease), NASH (nonalcoholic steatohepatitis), or diabetes mellitus; TACE: transarterial chemoembolization.

follow-up and screening for HCC in known cirrhotic patients as well as an insufficient screening for cirrhosis. This may be partly explained by the high proportion of patients with alcoholic aetiology who are difficult to follow in clinical practice and of patients with NASH in whom fibrosis/cirrhosis is poorly identified. Improving these screenings would allow to increase the proportion of patients who could benefit from HCC treatment.

About 24% of patients received systemic therapy. A TACE followed by a systemic treatment (with or without TARE) was prescribed to 6.7% of them. This rate appeared lower than that observed in the INSIGHT study (27.2%). This prospective real-life study included 782 patients with HCC treated with sorafenib for the first time between 2008 and 2014 in Austria and Germany. In these patients, 27.2% were previously treated with TACE [16]. This difference could be explained by either an impaired general condition of patients that did not allow subsequent systemic treatment or a follow-up duration insufficient to observe all recurrences after TACE in the present study.

In our study, an alcohol-related liver disease, found in more than half of patients (53%), was the main identified HCC risk factor. In alcoholic patients, several factors are likely to limit their access to all HCC treatments, mainly the curative options. In a prospective, observational, and multicentre study, Costentin et al. showed that in alcoholic patients, cirrhosis was unrecognized before the HCC diagnosis more frequently than in other HCC patients. This fact might explain the delay or the absence of screening programs allowing an earlier diagnosis in these patients. In addition, the same study showed that even in patients included in a cirrhosis follow-up program, the alcoholic patients had higher rates of œsophageal varices and higher Child-Pugh scores which also could explain a reduced access to curative treatments in this population [5].

As expected, survival analysis showed that the type of major palliative treatment received, considered as an indirect marker of the BCLC stage at IAT stage diagnosis, was the most influential factor on survival with a 2.5-fold and 6.2-fold higher risk of death in patients treated with systemic therapy and BSC, respectively, compared to those treated with TACE. For TARE, patients who received this treatment had a 2-fold higher risk of death than patients treated with TACE. This result can be explained by the marketing authorization for TARE which restricted this treatment in France to patients with branch portal vein thrombosis during the

study period. Similarly, the mortality risk was increase by 74% in patients who could not benefit from curative treatment compared to those who had benefitted. This mortality risk was even higher in the subgroup of patients with an unknown history of curative treatment (+77%). Unfortunately, study data on these patients did not allow to interpret this HR. More generally, survival data from our study could not be put into perspective with those provided by other comparable observational studies focusing on newly diagnosed IAT HCC patients. Most studies performed over this period were addressing the utilization and outcomes of sorafenib. It is the reason why we performed a subgroup analysis on this specific population.

Sorafenib was approved after the publication of the SHARP trial in 2008 [17]. In this trial, sorafenib at 400 mg twice a day in the first line was compared to a placebo in an HCC population including 82% of patients in the BCLC C stage and 18% in the BCLC B stage. The median OS of 10.7 months in the sorafenib group was higher than that in the present real-life study (7.3 months). As was shown in the exploratory subanalyses of the SHARP trial, this OS result was maintained irrespective of aetiology, performance status, tumour stage, and prior therapy. The overall effect of aetiology on OS was also nonsignificant which is in accordance with our results. The SARAH trial which compared sorafenib to 90Y-resin microsphere radioembolization (TARE) in advanced HCC and enrolled 467 patients (237 receiving TARE and 222 sorafenib) from 25 centres in France was a phase III trial designed for superiority [18]. The median OS was 9.9 months in the sorafenib group which was again superior to our results.

Several studies in Western populations were performed in field practice after the SHARP study. In an Italian study [19], a sample of 296 patients treated by sorafenib in current practice was enrolled by 6 liver centres in an observational retrospective cohort [20]. A percentage of 75% of them was BCLC-C and the rest BCLC-B which was in line with our population that had a previous TACE or TARE in 25.6% and sorafenib only in 74.4% of cases. The median treatment duration was 3.8 months which was close to our results. The median OS was 10.5 months overall, a similar figure to the SHARP trial but higher than our results. Another similar study was conducted in 8 medical centres in South America (South American Liver Research Network) and included 127 patients treated with sorafenib over the period 2010-2017 [21]. The median OS was 8.0 months (interquartile range 2 to 17) in line with our results. Another study of interest was based on an analysis of the SEER-Medicare database performed on 228 Medicare beneficiaries with HCC diagnosis made from 2007 to 2009 and who received sorafenib within 6 months of diagnosis [22]. The median survival of the sorafenib-treated patients was 150.5 days (5 months) which appeared close to the corresponding median OS observed in our subgroup of sorafenib-only treated patients of 6.5 months. Thus, comparisons with literature data showed that OS in patients treated with sorafenib in our study was generally close to OS obtained in observational studies but lower than in trials due to patient and/or centre selections.

Our study has some limitations mainly related to the lack of clinical data in the SNDS database. Given the lack of a BCLC stage in the database, we used the major palliative treatment received as a surrogate marker of this stage. However, this method has some limitations. It does not allow us to identify patients whose management did not comply with the BCLC treatment recommendations for each stage of the disease. Thus, the BCLC stage A patients treated with TACE due to their reluctance to have a liver resection could not be identified as well as the BCLC stage B patients treated with sorafenib. However, the fact that the type of major palliative received was the most influential factor on survival suggests that these situations were not frequent and that the major treatment may be considered as a relatively reliable marker of the BCLC stage. Likewise, the two-year period prior to the study period (2015-2017) used to collect HCC patient history appeared insufficient to confirm the absence of curative treatment in patients diagnosed with HCC prior to 2013.

5. Conclusion

Over the period 2015-2017, in France, HCC was still often diagnosed in a late stage of disease. In 46% of cases, patients were not eligible for a curative or a palliative anti-HCC treatment. There is an urgent need to improve early diagnosis and surveillance. In terms of number of cases, alcohol remained the main risk factor for HCC in France.

Data Availability

Owing to the nature of this analysis on a claims database, the datasets analysed in this study were available through the National System of Health Data, and the authors cannot share the data with any third parties or make the data publicly available owing to protections around the sharing of personal health data (General Data Protection Regulation: GDPR). The formal authorization of access to the database was signed with CNAM (Caisse Nationale d'Assurance Maladie) on July 4, 2019, under the agreement N°TPS 163343.

Conflicts of Interest

JFB is connected to Bayer Healthcare, Eisai, MSD, IPSEN, Roche, Astra-Zeneca, BMS, and AMGEN; CL is an employee of CEMKA; MZ is an employee of CEMKA; FF is an employee of CEMKA; MD is an employee of IPSEN; NK is an employee of IPSEN; PM is connected to MSD, IPSEN, Eisai, Abbvie, Sanofi, Gilead Sciences, Pfizer, Evive Biotech, Novo Nordisk, Bayer Healthcare, Surrozen, and Intercept.

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Supplementary Materials

Supplementary Figure S1: inclusion and follow-up period. Supplementary Table S1: procedure codes used to identify

curative treatments. Supplementary Table S2: procedure codes used to identify chemo- and radioembolization. Supplementary Table S3: codes used to identify HCC systemic treatments. Supplementary Table S4: ICD-10 diagnosis and ATC codes used to identify HCC aetiologies investigated: causes of chronic liver diseases and diabetes mellitus. Supplementary Figure S2: algorithm used to classify and rank HCC aetiologies. Supplementary Table S5: distribution of aetiologies (one aetiology per patient) in the incident intermediate, advanced, or terminal stage HCC population ($N = 19{,}649$). *(Supplementary Materials)*

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