Survival of patients with advanced hepatocellular carcinoma treated with sorafenib in France during 2009-2018: potentialities and limitations of model adjustment on potential confounding factors in the SNDS French hospital and claim database

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INTRODUCTION

The incidence of primary liver cancer increased significantly in France over the recent years. A national estimate of 10,580 new cases of primary liver cancer was given in 2018 for metropolitan France (1). Hepatocellular carcinoma (HCC) represented approximately 90% of cases (2). HCC often diagnosed at an advanced stage had a very poor prognosis. HCC is currently the fourth leading cause of cancer-related death globally (3). Between 2009 and 2018, sorafenib was the only first-line systemic therapy indicated in this indication. Claim databases cover large populations but have little clinical information: this limits the possibility to adjust analyses on potential confounders.

AIM

To explore solutions to overcome the lack of clinical information in claim databases by modelling survival of patients with advanced hepatocellular carcinoma treated with sorafenib (HCC-s) in France between 2009/2018.

In these analyses on the mortality of patients treated with sorafenib, we explored the possibilities to identify and adjust on proxies in the database for several categories of confounding factors such as the characteristics of the patients, the severity of the disease, the complications and the therapeutic management.

METHOD

STUDY DESIGN

This real world study was conducted using the French nation-wide healthcare claims database (SNDS) which includes all items of reimbursed ambulatory and hospital care in more than 99% of the French population (nearly 66 million persons).

POPULATION

Patients treated with sorafenib for HCC were identified by the ICD-10 code C220 as a cause for Long-Term Disease (LTD) or as a diagnosis of hospitalization between 2009 and 2018.

ETIOLOGIES OF LIVER DISEASE

The etiologies of the underlying chronic liver disease (CLD) were identified from ICD-10 codes and ATC codes of specific treatments.

STATISTICAL ANALYSIS

OS was defined from sorafenib initiation (index date) until death or last follow-up visit for those still alive at the end of study period. The Kaplan-Meier method was used to estimate survival rates. A cox modelling multivariate analysis has been performed to adjust the results on confounding factors.

IDENTIFICATION OF POTENTIAL CONFOUNDING FACTORS

Characteristics of the patients

Age and gender were directly available in the database.

Socioeconomic status was estimated with a proxy based on the coverage for low income (called CMUc).

Underlying cause of the disease

The underlying disease that caused the liver cirrhosis were identified through ICD10 codes that were reported for long term disease and/or during hospital stays before sorafenib initiation.

Proxies of disease severity

- **Complications of the underlying disease**

  The complications of liver cirrhosis were identified through ICD10 codes that were reported during hospital stays before the initiation of sorafenib: bacterial infection, rupture of esophageal varices, upper GI bleeding, ascites, hepatic encephalopathy and jaundice.

- **Therapeutic management**

  We identified and used as proxy of the severity of the HCC, drugs and procedures that were used before the initiation of sorafenib: chemoembolization, radioembolization, duration between HCC identification and sorafenib initiation and local or general surgeries as well as transplantation.

RESULTS

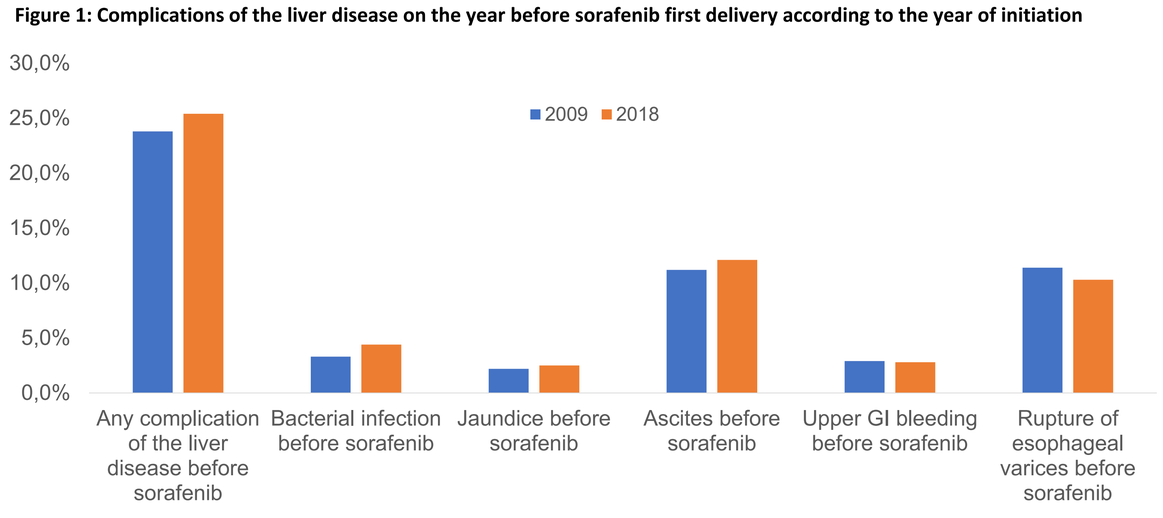
17,680 newly treated with sorafenib HCC patients were identified. Their mean age was 66.9 years (SD:10.3) and 87.6% were male. The mean age increased in most recent years as well as the proportions of patients who already were treated with other procedures before the initiation of sorafenib (table 1).

Table 1: characteristics of patients, hepatic etiologies and proxies of the disease severity before the initiation of sorafenib in 2009 and 2018

HCC **Population**	2009	2018
Sex, Male N (%)	1,380 (87.5%)	1,627 (87.8%)
Mean age (years) at sorafenib initiation	66.2	68.1
CMUc coverage	6.1%	7.3%
HCC etiologies (several etiologies possible)		
• Viral Hepatitis B	136 (8.6%)	120 (6.5%)
• Viral Hepatitis C	288 (18.3%)	345 (18.6%)
• Alcohol	867 (55.0%)	925 (49.9%)
• NASH/NAFLD	55 (3.5%)	170 (9.2%)
• Diabetes	621 (39.4%)	826 (44.6%)
Treatment management before sorafenib initiation		
• Ablation, surgery, transplantation	214 (13.6%)	521 (28.1%)
• Chemoembolization	385 (24.4%)	635 (34.3%)
• Radioembolization	34 (2.2%)	76 (4.1%)
Delay between Hepatic cancer diagnosis and sorafenib initiation	4.5 months	13.6 months

An increase of the proportions of patients having complications before sorafenib initiation was observed between 2009 and 2018 which suggest that underlying disease severity increased in more recent years

Figure 1: Complications of the liver disease on the year before sorafenib first delivery according to the year of initiation



The median survival decreased over the period: from 10.0 months in 2009 to 7.3 months in 2018 (figure 2).

However, after adjustment on patient's profile and clinical characteristics this increase in mortality rate still only until 2012 (figure 3). After, OS appears stable over the time.

Figure 2: Median OS according to the calendar year of sorafenib initiation

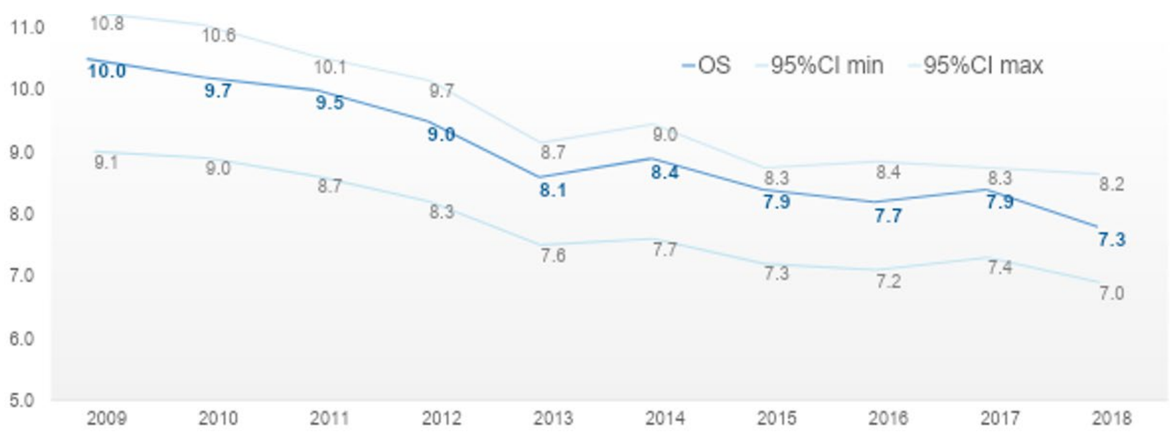


Figure 3: Evolution of death risk on the study period (measured by the HR) before and after adjustment on potential confounding factors (HR taking 2009 as reference)

DISCUSSION

The utilization of National exhaustive databases such as the SNDS allows to explore outcomes that can be directly identified on large scale populations in a real world setting.

These databases have however several strong limitations because they have few clinical information. This limits the possibility to explore potential biases and explanations of paradoxical findings such as an increase in mortality in more recent years.

Our analysis was an attempt to identify proxies for disease severity and complications and adjust the analysis on the overall mortality on some of the confounding factors.

The results are modified after these adjustment and suggest that the proxies we used are confounding factors. However they do not replace the absence of more robust clinical data that could be available in observational studies or registries.

CONCLUSION

Identification of **disease severity proxies** in claim databases are possible by using algorithms to **identify complications** and treatment procedures. Such factors can help to model outcomes. **Absence of clinical information** and many **unmeasured confounding factors** remain a major limit to generalize findings.

CONTACT INFORMATION

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