STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	Epidemiology, therapy and outcome of hepatocellular carcinoma between 2010 and
		2019 in south-western piedmont
		BACKGROUND: Hepatocellular carcinoma (HCC) is the most common primary liver
		malignancy and the second leading cause of cancer deaths worldwide. It is often
		diagnosed at an advanced stage and therefore its prognosis remains poor, with a low
		5-year survival rate. HCC patients have increasingly complex and constantly changing
		characteristics and therefore updated and comprehensive data are increasingly needed.
		AIM: To analyze the epidemiology and main clinical characteristics of HCC patients
		in a North-West Italy referral center hospital between 2010 and 2019.
		METHOD: In this retrospective study, we analyzed clinical data of all consecutive
		patients with a new diagnosis of HCC evaluated at "Santa Croce e Carle" Hospital in
		Cuneo (North Italy) between 1st January 2010 and 31st December 2019. To highlight
		possible changes in HCC patterns over the ten-year period, we split the population
		into two five-year groups, according to the diagnosis period (2010-2014 and 2015-
		2019)
		RESULTS: 328 HCC natients were included (M/F 255/73; mean age 68.9 +11.3
		vears) 154 in the first period and 174 in the second Henatitis C virus infection was
		the most common HCC risk factor (41%, 135 patients). Alcoholic etiology rate was
		18% hepatitis B virus infection etiology was 5% and non-viral/non-alcoholics
		etiology rate was 22% Child-Pugh score distribution of the patients was: class A
		75% class B 21% and class C 4%. The average MELD score was 10.6 ± 3.7 55
		patients (17%) were affected by portal vein thrombosis and 158 (48%) by portal
		hypertension HCC had average nodule size of 4.6 ± 3.1 cm 204 patients (63%) had a
		number of nodules <3 and 92% (305 patients) had non-metastatic stage. Barcelona
		Clinic Liver Cancer staging distribution of all patients was: 4% very early 32% early
		23% intermediate 34% advanced and 7% terminal Average survival rate was 1.6 +
		0.3 years. Only 20% of the nations underwent curative treatment. Age, presence of
		ascites BCLC stage and therapy were predictors of better prognosis ($n < 0.01$)
		Comparing the two five-year groups we observed a statistically significant difference
		comparing the two rive year groups we observed a statistically significant difference only in global etiology ($n < 0.05$) and AFP levels ($n < 0.01$)
		CONCLUSION: In this study analyzing patients with a new diagnosis of HCC
		between 2010 2019. Hensitis C virus infection was the most common etiology. Most
		of patients presented with an advanced stage disease with poor prognosis. Comparing
		the two five year groups we observed a statistically significant difference only in
		global etiology ($n < 0.05$) and AFP levels ($n < 0.01$)
Later de etter		
Introduction Background/rationala	2	Primary liver concer is a relevant disease with more than 850,000 new cases per year
Dackground/rationale	2	worldwide1 With a 5 year survival of 18%, this peoplasm is currently the second
		leading oncological cause of death globally (after pancreatic cancer) and this figure is
		constantly increasing. Henatocellular carcinoma (HCC) is the most common primary
		liver cancer, accounting for 90% of cases. The World Health Organization (WHO)
		estimates that more than 1 million patients will die of HCC in 2020. In Italy, the
		diagnosis of about 12 800 new cases of HCC was estimated in 2018, about 20% of all
		new cases of cancer with a 5-year survival rate of 200% and a 10 year survival rate of
		10% Various risk factors for the development of HCC are well defined, such as liver
		airchosis (regardless of its atiology), abronic hensititis D views (UDV) and abronic
		entriosis (regardress of its enology), enrolle nepatitis B virus (IDV) and enrolle

		hepatitis C virus (HCV), alcohol abuse and metabolic syndrome. Universal HBV vaccination and the extensive implementation of HCV-action antiviral agents are likely to change the etiological landscape of HCC. However, the increase in non-alcoholic fatty liver disease (NAFLD), along with metabolic syndrome and obesity, will soon become one of the most important HCC causes in Western countries. Significant discoveries have been made in understanding the epidemiology, risk factors and molecular profiles of HCC in recent decades. Furthermore, rational approaches to prevention, diagnosis and treatment have been developed. Where these approaches have been applied to high-incidence populations, they have demonstrated their effectiveness in preventing HCC and reducing its overall mortality. The fact that risk factors can be eliminated, however, does not always translate into global improvements due, for example, to the suboptimal implementation of treatments in underdeveloped areas; Similarly, despite the fact that surveillance is cost-effective in HCC, the global implementation of such programs is still suboptimal and is estimated to involve <50% of the target population in the Western countries. For this reason, the
		in most patients this neoplasm still occurs at an advanced stage. New diagnostic approaches and recent therapeutic advances could achieve a reduction in HCC morbidity and mortality within the next few decades. In the light of all the information set out above, HCC patients have increasingly complex and constantly changing characteristics, which require an individualized and evidence-based approach. This implies the need for recent and exhaustive literature data on this type of patient. The impact of changing risk factors, demographics and new therapies remain unclear to date with few studies in the literature dedicated to these areas.
Objectives	3	This study therefore aims to analyze the epidemiology, presentation and main clinical characteristics and therapeutic management of HCC patients in the geographical area of north-western Italy in the decade 2010-2019.
Methods		
Study design	4	Retrospective cohort study.
Setting	5	In this retrospective analysis, the clinical data of 328 newly diagnosed HCC patients evaluated at the "Santa Croce e Carle" General Hospital of Cuneo (Piedmont, Italy) between 1st January 2010 and December 31st 2019 were analyzed. To highlight possible changes in HCC patterns compared to the decade-period, we divided the population into two five-year groups, according to the diagnosis period (2010-2014 and 2015-2019).
Participants	6	We selected patients by searching the clinical information system and medical records database of the hospital with the codes for HCC (according to the ICD-9M classification system).
Variables	7	 HCC patients were etiologically classified according to the most likely anamnestic cause as follows: 1. HBV: if patients had a history of hepatitis B virus infection with a positive test for the hepatitis B surface antigen (HbSAg). Patients with negative HbSAg but with positive anti-HBc antibodies and a history of antiviral drug therapy were also considered in this group; 2. HCV: if patients had a history of hepatitis C virus infection with positive anti-HCV serum antibodies and HCV-RNA titers. Patients with positive serum anti-HCV antibodies but negative HCV-RNA and history of eradicating drug therapy were also considered in this group; 3. alcoholic: in case of anamnestic history of daily intake of ethanol> 60 g for women

		and> 80 g for men for more than 10 years:
		4 multi-etiology: if there was a combination of causal factors (viral + alcoholic):
		5 NAFI D: in case of demonstration of steatosis on ultrasound and / or bionsy and
		shares of configurate alaskal consumption.
		absence of significant alcohol consumption;
		6. hereditary hemochromatosis: in case of alterations in transferrin saturation (>45%)
		and positivity to the genetic test for one of the HFE / HJV and HAMP / TFR2 /
		SLC40A1 genes;
		7. not known / idiopathic: in case of absence of known recognized causes and / or
		unspecified etiology.
Data sources/		Laboratory findings were documented at the time of initial HCC diagnosis. If they
measurement		were not available on the exact date, results closest to the date of diagnosis within 90
		days were considered. The severity of liver dysfunction was assessed according to the
		Child-Pugh classification. The MELD score, chronic liver disease severity score
		system was calculated to predict survival at three months. It was specified where the
		diagnosis of HCC was confirmed by bionsy and histological examination. HCC was
		diagnosis of free was contributed by biopsy and instological examination. Free was
		classified as unifocal, paucifocal (≤ 3 nodules), multifocal (≥ 3 nodules), infittrative
		and / or massive (infiltrating growth pattern and / or a mass of> 10 cm diameter and
		an indefinite limit). The tumor size of the expanding nodules was also measured (in
		cases of multinodular tumors, the largest was measured). The HCC stage was assessed
		according to the BCLC (Barcelona Clinic Liver Cancer) staging system, updated to
		202212. Performance status was assessed using the Eastern Cooperative Oncology
		Group (ECOG) score.
		Regarding treatment, patients were divided into patients who received curative
		therapy for HCC after diagnosis (liver transplant, surgical resection or percutaneous
		ablation) and patients who received non-curative therapy (TACE - Trans-Arterial
		Chemo Embolization, SIRT - Selective Internal Radiation Therapy, Sorafenib
		chemotherapy or palliation).
Bias	9	The retrospective observational nature of the study did not allow the evaluation of
2100	-	some very interesting variables (such as body mass index for example). Furthermore
		the exclusion of nations for whom it was not possible to derive the variables useful
		for the study exposed to potential selection bios. Finally, the uniqueness of the study
		for the study exposed to potential selection bias. Finally, the uniqueless of the study,
		relating to a population belonging to a center with a specific geographical origin,
		exposed our data to possible reference bias.
Study size	10	the clinical data of 328 newly diagnosed HCC patients evaluated at the "Santa Croce e
		Carle" General Hospital of Cuneo (Piedmont, Italy) between 1st January 2010 and
		December 31st 2019 were analyzed. To highlight possible changes in HCC patterns
		compared to the decade-period, we divided the population into two five-year groups,
		according to the diagnosis period (2010-2014 and 2015-2019).
		We selected patients by searching the clinical information system and medical records
		database of the hospital with the codes for HCC (according to the ICD-9M
		classification system).
Ouantitative variables	11	age, date of diagnosis of HCC, laboratory data (bilirubin, AFP, creatinine, INR,
		albumin), scores (Child-Pugh, MELD, BCLC, ECOG), surveillance and survival.
Statistical methods	12	Continuous variables were presented as mean and deviation standard and categorical
Saustear methods	14	variables as absolute and relative frequencies. Group comparisons were performed
		using the ANOVA test for continuous variables and the Deerson of test for acted and
		using the First valuest for continuous variables and the reason χ^2 test for categorical
		variables. Survival was calculated from the time from was diagnosed to death; the
		data was censored atter 5 years of follow-up. The Kaplan-Meier method was used for
		the survival analysis and the difference between the survival curves was assessed

assumed by accepting an alpha:0.05 error. All statistical analysis was performed using Retudio 2022.02.0 software based on R version 4.1.2. Results Participants 13* The study included 328 patients with HCC, 154 in the first period (2010-2014) and 174 in the second period (2015-2019). Descriptive data 14* The mean age at death was 69.7 years in the first period and 72.4 years in the second period (pc:0.05). The male/femule ratio was 25573. Outcome data 15* cause of liver disease, Child-Pugh's classification, MELD score, BCLC system, therapeutic procedures, overall aurivial. Main results 16 The most common cause of liver disease was HCV infection (135 cases, 41%), followed by alcoholic citology (58 cases, 18%). HBV infection (135 case, 44%), followed by alcoholic citology (58 cases, 18%). HBV infection was identified in only 15 cases (5%), while multiple eitology (viri 1 alcoholic) was found in 36 patients (11%). 7 patients (2%) had NAFLD and 4 patients (1%) had harPolicy (16%). 7 patients (2%), hud NAFLD and 4 patients (1%), had hereditary hemochromatosis. In 73 patients (22%), the eitology was unknown/diopathic. The likelihood of portal thrombosis was statistically higher in patients with more advanced BCIC stage (100% of cases) (p<0.01), with a non-unifocal HCC (78%) of cases) (p<0.01), and with portal hyperiension (85% of cases) (p<0.01), and hard Freat sugges according to the BCLC system: 12 patients (4%) belonged to BCL stage 0, 105 (32%) to BCLC stage 0, 100, (case), in Patients (24%) to BCLC stage 0, 105 (32%) to BCLC stage 0, 120 yointents (36%), for patients (24%) and percutaneous radiofrequency alhalion in 56 cases (17%), 12 cases (38%). SIRT in 46 cases (14%) and sys			prognostic factors associated with the probability of death. Statistical significance was
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Outcome data 15* cause of liver disease, Child-Pugh's classification , MELD score, BCLC system, therapeutic procedures, overall survival. Main results 16 The most common cause of liver disease was HCV infection (135 cases, 41%), followed by alcoholic etiology (St cases, 18%). IHSV infection was identified in only 15 cases (5%), while multiple etiology (viral + alcoholic) was found in 36 patients (11%). 7 patients (2%) had NAFLD and 4 patients (1%) had hereditary hemochromatosis. In 73 patients (22%), the etiology was unknown/adiopathic. The likelihood of portal thrombosis was statistically higher in patients with more advanced BCLC stage (100% of cases in BCLC C-D stage) (p-0.01), with AFP>200 ng/dL (83% of cases) (p-0.01), with a non-unifocal HCC (78% of cases) (p-0.01) and with portal hypertension (85% of cases) (p-0.01). According to Child-Pugh's classification, 247 patients (75%) were class A, 68 patients (21%) class B and 13 patients (4%) class C. The mean MELD score was 10.6 (+3.7). Patients were grouped into five different stages according to the BCLC stage A, 74 (23%) to BCLC stage B, 113 (34%) to BCLC C stage 0, 105 (32%) to BCLC stage A, 74 (23%) to BCLC stage B, 113 (34%) to BCLC C stage (C-D) 137 patients (42%) were at the early stage (0-A). 64 patients (20%) undervent curative therapeutic procedures: surgical resection in 8 cases (2%) and precutaneous radiofrequeuexy ablation in 56 cases (17%); 264 patients (80%) undervent non- curative therapeutic procedures: TACE in 124 cases (5%). 77 patients (23%) and systemic chemotherapy with Sorafenib in 17 cases (5%). 77 patients (23%) received palliation or no therapy at all. No patients undervent invit-ration. The likelihood of curative therapy was statistically higher in patients with unifocal HCC (73% of cases) (p<0.01), early BCLC stage (62% of cases in BCLC stage 0-A) (p<0.01), aFP199 ng/dL (77% of cases) (p<0.05), without asc			second period (p<0.05). The male/female ratio was 255/73.
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C. The mean MELD score was 10.6 (±3.7). Patients were grouped into five different stages according to the BCLC system: 12 patients (4%) belonged to BCLC stage 0, 105 (32%) to BCLC stage A, 74 (23%) to BCLC stage B, 113 (34%) to BCLC C stage and 24 (7%) to BCLC stage D; 117 patients (36%), 74 patients (23%) and late stage (C-D) 137 patients (42%) were at the early stage (0-A). 64 patients (20%) underwent curative therapeutic procedures: surgical resection in 8 cases (2%) and percutaneous radiofrequency ablation in 56 cases (17%); 264 patients (80%) underwent non- curative therapeutic procedures: TACE in 124 cases (38%), SIRT in 46 cases (14%) and systemic chemotherapy with Sorafenib in 17 cases (5%). 77 patients (23%) received palliation or no therapy at all. No patients underwent liver transplantation. The likelihood of curative therapy was statistically higher in patients with unifocal HCC (73% of cases) (p<0.01), early BCLC stage (62% of cases in BCLC stage 0-A) (p<0.01), good performance status (81% of cases with ECOG score 0) (p<0.01), AFP<199 ng/dL (77% of cases) (p<0.05), without ascites (91% of cases) (p<0.05). A statistically significant difference in the likelihood of curative or non-curative therapy between the etiological groups was not evaluated. Among patients with viral etiology, 21 out of 91 (23%) patients in the first period and 20 out of 95 patients (21%) in the second period underwent antiviral therapy. Overall, among patients with viral etiology, 41 patients (22%) underwent antiviral therapy. Overall 1-year survival was 60.4% [95% CI 55.3-65.9], while 5-year overall survival was 17.1% [95% CI 13.5-21.7]. The median overall survival was 576 days [95% CI 476-695]. In the first period, 1-year survival was 56.5% [95% CI 49.1-64.9%], while in the second period 63.8% [95% CI 57.0-71.3%]. The median survival of the first period was 517 days [95% CI 361-757], while in the second period it was 603 days [95% CI 476-757] (p<0.08)			247 patients (75%) were class A, 68 patients (21%) class B and 13 patients (4%) class
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[95% CI 476-757] (p<0.08)			period was 517 days [95% CI 361-757], while in the second period it was 603 days
Discussion			[95% CI 476-757] (p<0.08)
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using the Log-Rank test. A Cox proportional risk model was adopted to test the role of

Key results

17 The aim of this study was therefore to analyze the clinical characteristics of a large

	newly diagnosed HCC cases in more recent years (174 in the 2015-2019 period vs 154 in the 2010-2014 period). We found that the mean age of newly diagnosed HCC patients increased from 67.6 to 70.0 years (p<0.1). In our study there was also a significant proportion (22%) of HCC apparently of idiopathic etiology. We also found a low rate of etiology related to a clear diagnosis of NAFLD (2%). Regarding tumor stage, during the entire study period, the most common HCC presentation pattern was a single nodule with a diameter between 3 and 5 cm. Regarding liver function, the majority of our population was in Child A class, in line with other national studies. In the second period (2015-2019) we found a trend (to the limits of significance) regarding the decrease in the multifocal pattern at diagnosis and a frank significance about lower AFP values at diagnosis. Regarding the staging of HCC, we highlighted two incidence peaks in BCLC stage A (early) and stage C (advanced) at the time of diagnosis. As many as 42% of the total sample was either in the advanced or terminal stage (BCLC stage C-D). By dividing this data into two five-year-olds, this percentage
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	dropped from 47% of the first to 37% of the second (this trend also bordering on
	significance). From a therapeutic point of view, we found an adoption of curative
	therapies (surgical resection / ablation with RF) in 20% of cases, however
	underutilized compared to the fact that 36% of cases had 0-A (early) BCLC staging.
	Among the curative therapies, the most frequently used was percutaneous ablation
	with radiofrequency was the most frequently used. Our patients' prognosis was
	characterized by modest overall survival values at one year (60%) and yery low at 5
	years (17%).
18	The retrospective observational nature of the study did not allow the evaluation of
	some very interesting variables (such as body mass index, for example). Furthermore,
	the exclusion of patients for whom it was not possible to derive the variables useful
	for the study exposed to potential selection bias. Finally, the uniqueness of the study,
	relating to a population belonging to a center with a specific geographical origin,
	exposed our data to possible reference bias.
19	this study presents detailed information on periodic changes in risk factors and liver
	function characteristics, tumor stage and treatment modalities performed at diagnosis
	in a large cohort of patients with HCC in a referral center in the area of the Northern
	Italy. The approach to HCC is far from adequate and HCC remains undertreated or
	inappropriately treated despite the positive changes that have occurred in recent years.
	This should therefore be a stimulus for a better implementation of the surveillance of
	patients at risk according to the guidelines of the main national and international
	scientific societies, with subsequent better use of the various therapeutic opportunities
	available.
20	No funding received.
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