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ORIGINAL ARTICLE

Incidence and predictors of hepatocellular carcinoma in NAFLD without diagnosed cirrhosis: a nationwide real-world U.S. study

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Abstract

Background A substantial proportion of patients with nonalcoholic fatty liver disease (NAFLD)-related hepatocellular carcinoma (HCC) do not have cirrhosis. Data regarding the incidence and predictors of HCC development in NAFLD without cirrhosis are limited. We conducted a large, national study of NAFLD patients without documented cirrhosis to examine the incidence and predictors for HCC development.

Methods This retrospective study included 751,603 NAFLD patients (54% female) without documented cirrhosis derived from the deidentified Optum Clinformatics® Data Mart Database. Patients with cirrhosis, platelets < 120,000/μL or FIB-4 values > 2.67 were excluded.

Results The mean age was 53.7 ± 15.0 years, 45.9% were male, 39.5% had diabetes, 57.6% were White, 18.4% Hispanic, 8.2% Black and 4.9% were Asian. The mean platelet count was 264,000 ± 72,000/μL, and 96.3% of patients had a FIB-4 < 1.30. Over 1,686,607 person-years of follow-up, there were 76 incident cases of HCC, resulting in an HCC incidence rate of 0.05 per 1000 person-years. There was a higher HCC incidence rate among patients with platelets ≤ 150,000/μL, versus those with platelets > 150,000/μL (0.23 per 1000 person-years, vs. 0.04 per 1000 person-years, $p = 0.02$) but not in subgroup analyses for age, sex, race/ethnicity or diabetes. Using multivariable Cox proportional hazards model adjusted multiple confounders, platelet count ≤ 150,000/μL remained an independent predictor of HCC development (adjusted HR 5.80, 95% CI 1.67–20.1, $p = 0.006$).

Conclusion HCC incidence in NAFLD without documented cirrhosis was below the threshold for cost-effective HCC surveillance in overall and multiple subgroup analyses. Platelet count < 150,000/μL may be a useful predictor of HCC development in this population.

Keywords HCC surveillance · Diabetes mellitus · Platelet count · Thrombocytopenia · Non-cirrhotic · Natural history · Liver cancer · Hepatoma · Screening · Steatosis

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Abbreviations

NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
HCC	Hepatocellular carcinoma

Introduction

Non-alcoholic fatty liver disease (NAFLD) is present in a third of the world's population [1–3] and is projected to rise exponentially in line with the global obesity epidemic [4]. NAFLD comprises non-alcoholic fatty liver, the benign form of NAFLD, and non-alcoholic steatohepatitis (NASH), the inflammatory form of NAFLD that may progress to fibrosis, hepatocellular carcinoma (HCC) and cirrhosis [5–10].

NAFLD-related HCC is the fastest-growing cause of HCC worldwide, and mortality rates are projected to increase dramatically within the next decade [4, 11–14].

More than 30% of NAFLD-related HCC occurs in patients without cirrhosis [15, 16]. However, major society guidelines do not recommend routine HCC surveillance in the absence of known cirrhosis or advanced fibrosis [17–20]. This contributes to a substantially lower proportion of patients with NAFLD-related HCC receiving HCC surveillance before HCC diagnosis, compared to patients with HCC from other etiologies [16]. There are limited data for the characteristics, incidence, and predictors of HCC development in NAFLD patients without cirrhosis to guide surveillance strategies. Therefore, we utilized a large national U.S. database that includes laboratory data to determine the incidence and predictors of HCC development among NAFLD patients without documented cirrhosis.

Methods

Study design and data source

This is a retrospective study of a national sample of NAFLD patients without a documented diagnosis of cirrhosis from Optum's Clinformatics® Data Mart (CDM) Database through the Population Health Science Center at Stanford University, Stanford, California, US. CDM is a de-identified administrative health claims database for beneficiaries of commercial and Medicare Advantage health plans. This claims database provides both medical and prescription drug coverage for approximately 61 million patients, as well as the results of outpatient laboratory tests from contracted national reference laboratory vendors for approximately 31 million patients. The study was approved by the Institutional Review Board at Stanford University, Stanford, California, USA.

Study population, inclusion, and exclusion criteria

To identify patients with NAFLD without documented cirrhosis, we searched the CDM database from January 1, 2003, to March 31, 2021 for adult (aged ≥ 18 years) patients with NAFLD using ICD 9 codes (571.8, 571.9) and ICD 10 codes (K760, K7581). To reduce bias introduced by discontinuity in enrollment and large gaps between each enrollment, we excluded people who had gaps between two enrollments that were more than six months apart. We excluded patients with a diagnosis of hepatitis B virus (HBV), hepatitis C virus (HCV), significant alcohol use, alcohol-associated liver disease, other liver diseases, HIV infection, cirrhosis, and any cancer other than HCC, at any point of time (at baseline and through follow-up). Additionally, to avoid inclusion of patients with advanced fibrosis or undiagnosed cirrhosis, we also excluded those with platelet count < 120,000/μL or FIB-4 values > 2.67 for the cohort who had laboratory data [21–23] (Fig. 1). FIB-4 was calculated using the formula: (Age* × AST)/(Platelets x $\sqrt{}$[ALT]). Patients with baseline HCC (index diagnosis within 6 months from NAFLD index diagnosis date) were included in the analysis for patient characteristics but excluded from analyses for HCC incidence.

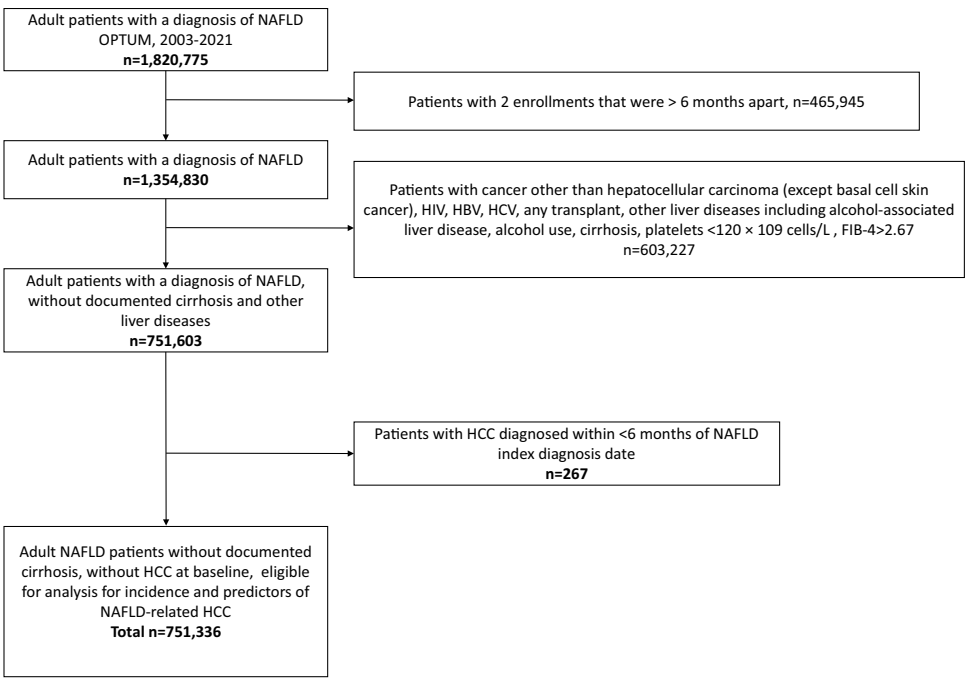

Fig. 1 Study flow diagram

Study objectives

The primary objective was to determine the incidence of HCC development in NAFLD patients without documented cirrhosis. The secondary objectives were to identify predictors for HCC development and to characterize patients with NAFLD-related HCC that occurred in the absence of documented cirrhosis.

Study variables

Baseline demographic, clinical, and laboratory characteristics were obtained within six months of the index NAFLD date. For the analysis of incidence and predictors for NAFLD-related HCC development, we excluded patients with HCC diagnosed within six months of the index NAFLD diagnosis date and those who died or were followed up for less than 6 months after the index NAFLD date. The baseline date was defined as the index NAFLD date and within 6 months from this date. The patients were censored at the time of HCC development, death, or last follow-up, whichever came first.

Statistical analysis

Categorical variables were reported as counts and percentages while continuous variables were reported either as mean with standard deviation (SD) or median with interquartile range (IQR). Comparisons between subgroups were performed using the Pearson chi-squared test for categorical variables and the Student's *t* test of variance or Wilcoxon rank-sum test for continuous variables. The Kaplan–Meier method was used to evaluate HCC incidence with a comparison between subgroups performed using the log-rank test. We performed a sensitivity analysis to evaluate HCC incidence in patients who had available FIB-4 data, this analysis only included patients with FIB-4 ≤ 2.67 (patients with FIB-4 > 2.67 were excluded from the study), the established FIB-4 threshold for advanced fibrosis in NAFLD [23]. Univariable and multivariable logistic regression were performed to identify factors associated with HCC development. Variables with potential association with HCC development based on previous literature or with univariable hazard ratios (HRs) < 0.10 were included in the multivariable models to estimate adjusted HRs (aHRs). HRs were reported with 95% CIs. All analyses were conducted using STATA 17.0, and *p* values < 0.05 were considered statistically significant.

Results

Study population

A total of 1,820,775 adult patients with a diagnosis of NAFLD were identified from the database. After excluding patients with other etiologies of liver disease, those with cirrhosis, platelets of < 120,000/μL or FIB-4 values > 2.67, 751,603 NAFLD patients without documented cirrhosis were included in the study, of which 751,336 were eligible for the analyses for incidence and predictors of HCC (among whom 76 developed HCC beyond 6 months of follow-up), and 267 had baseline HCC (within 6 months from index NAFLD date) and were included only in the analysis for characteristics of NAFLD-related HCC without cirrhosis (Fig. 1). The mean age was 53.7 ± 15.0 years, 45.9% were male, 57.6% were White, 18.4% were Hispanic, 8.2% were Black, 4.9% were Asian and 39.5% had diabetes (Table 1). Overall, the mean platelet count was 264,000(± 72,000)/μL, 96.3% of patients had a FIB-4 < 1.30, and 3.7% had a FIB-4 from 1.30 to 2.67. There was a total of 1,686,607 person-years of follow-up.

NAFLD patients without documented cirrhosis who subsequently developed HCC were older (57.6 versus 56.3 years, $p = 0.03$) and were more likely to have diabetes (52.6% versus 39.5%, $p = 0.02$) compared to patients who did not develop HCC (Table 1). Among the subgroup with FIB-4 data (222,563, 29.6%), the percentage with FIB-4 ≤ 1.30 was 96.3% in patients who did not develop HCC compared to 100% in patients who developed HCC ($p = 0.038$). The mean platelet count was 264,000 (± 72,000)/μL in patients who developed HCC compared to 240,000 (± 6000)/μL in patients who developed HCC ($p = 0.11$). Additionally, there were no significant differences in ALT levels between the two groups.

Incidence of HCC development in NAFLD patients without documented cirrhosis

Among patients without HCC at baseline, a total of 76 patients developed HCC over a total follow-up of 1,686,607 person-years, yielding an overall HCC incidence rate of 0.05 per 1000 person-years (95% CI 0.04–0.06). A sensitivity analysis for patients with available FIB-4 data revealed a similar incidence rate of HCC (0.04 per 1,000 person-years [95% CI 0.03–0.06]). The cumulative incidence of HCC at 1-, 3- and 5-years were 0.005% (95% CI 0.004–0.007), 0.01% (95% CI 0.01–0.02), and 0.02% (95% CI 0.02–0.03), respectively (Supplemental Fig. 1). The incidence rate of HCC stratified by age,

Table 1 Baseline characteristics of NAFLD patients without documented cirrhosis or baseline* hepatocellular carcinoma

	Total cohort $n=751,336$	Did not develop HCC ($n=751,260$)	Developed HCC ($n=76$)	p value
Age (year)	53.7 ± 15.0	53.7 ± 15.0	57.6 ± 16.1	0.03
Ethnicity, *n* (%)				0.07
White	433,048 (57.6)	433,006 (57.6)	42 (55.3)	
Hispanic	137,927 (18.4)	137,915 (18.4)	12 (15.8)	
Black	61,205 (8.2)	61,198 (8.2)	7 (9.2)	
Asian	36,830 (4.9)	36,821 (4.9)	9 (11.8)	
Other	82,326 (11.0)	82,320 (11.0)	6 (7.9)	
Male, *n* (%) ($n=751,236$)	344,503 (45.9)	344,473 (45.9)	30 (39.5)	0.26
Diabetes, n (%) ($n=751,336$)	296,975 (39.5)	296,935 (39.5)	40 (52.6)	0.02
Cardiovascular disease, *n* (%) ($n=751,336$)	74,870 (10.0)	74,857 (10.0)	13 (17.1)	0.04
Hyperlipidemia, *n* (%) ($n=751,336$)	517,397 (68.9)	517,340 (68.9)	57 (75.0)	0.24
Smoker, *n* (%) ($n=751,336$)	125,922 (16.8)	125,906 (16.8)	16 (21.1)	0.32
ALT (median [IQR]) [U/L] ($n=277,230$)	30 (19–51)	30 (19–51)	29 (15–46)	0.26
AST (median [IQR]) [U/L] ($n=286,107$)	24 (19–36)	24 (19–36)	27 (20–36)	0.86
GGT (median [IQR])[U/L](n = 24,909)	39 (23–76)	39 (23–76)	48 (18–116)	0.78
Platelet (mean, SD)[U/L]($n=246,158$)	264 ± 72	264 ± 72	240 ± 67	0.11
Total bilirubin (mg/dL) ($n=276,099$)	0.5 ± 0.3	0.5 ± 0.3	0.5 ± 0.3	0.79
INR ($n=24,253$)	1.2 ± 0.6	1.2 ± 0.6	1.0 ± 0.1	0.40
Creatinine (mg/dL) ($n=292,569$)	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.78
HbA1c ($n=175,780$)	6.7 ± 1.5	6.7 ± 1.5	6.6 ± 1.1	0.98
FIB-4 ($n=222,563$)				0.38
≤ 1.30	214,427 (96.3)	214,407 (96.3)	20 (100)	
1.30–2.67	8136 (3.7)	8136 (3.7)	0	
Medication use, *n* (%) ($n=751,336$)				
Aspirin	10,794 (1.4)	10,793 (1.4)	1 (1.3)	0.93
Statin	316,368 (42.1)	316,337 (42.1)	31 (40.8)	0.82
Metformin	147,479 (19.6)	147,464 (19.6)	15 (19.7)	0.98
Insulin	58,813 (7.8)	58,803 (7.8)	10 (13.2)	0.08

Values expressed as mean ± standard deviation, number (percentage) or median (interquartile range)

HCC hepatocellular carcinoma, *NAFLD* non-alcoholic fatty liver disease, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyl transferase

*Prior to or within 6 months following NAFLD index date

sex, race/ethnicity, presence of diabetes, and platelet count are summarized in Fig. 2. There was a higher incidence (per 1000 person-years) of HCC among patients with platelet count ≤ 150,000/μL, compared to patients with platelet count > 150,000/μL (0.23 per 1000 person-years, 95% CI 0.08–0.73 vs. 0.04 per 1000 person-years, 95% CI 0.03–0.06, $p=0.02$). Patients with diabetes did not have a significantly higher HCC incidence compared to those without diabetes (0.05 per 1,000 person-years, 95% CI 0.04–0.07 versus 0.04 per 1,000 person-years, 95% CI 0.03–0.05, $p=0.22$). Similarly, there were no significant differences in the HCC incidence rate among the subgroups by age, sex, or race/ethnicity (Fig. 2).

Predictors of HCC development in NAFLD patients without documented cirrhosis

In unadjusted analysis, a platelet count ≤ 150,000/μL was a predictor of HCC development (HR 5.83, 95% CI 1.74–19.6, $p=0.004$) but not age, sex, race/ethnicity, cigarette use, diabetes, ALT, or AST levels (Table 2). In multivariable Cox regression, adjusting for potential associated factors by prior reports (age, sex, race/ethnicity, diabetes) and factors with univariable HR with $p \le 0.10$ (platelet count), older age (aHR 1.03, 95% CI 1.01–1.07, $p=0.04$) and platelet count ≤ 150,000/μL (aHR 5.80, 95% CI 1.67–20.1, $p=0.006$) were significant independent predictors of HCC development in NAFLD

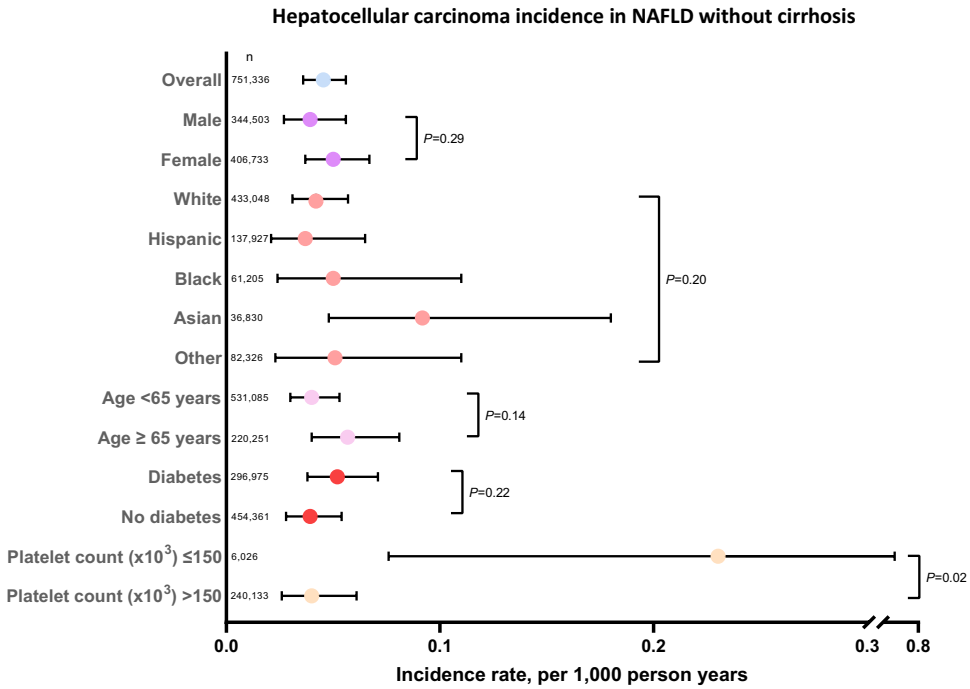

Fig. 2 The incidence rate of hepatocellular carcinoma in nonalcoholic fatty liver disease without documented cirrhosis, overall and by subgroups

without cirrhosis (Model 1, Table 2). These findings remained consistent in a separate model (Model 2) that only included variables with $p \leq 1.0$ in Model 1 (age, sex, and platelet count) (Table 2).

Characteristics of NAFLD-related HCC without documented cirrhosis

A total of 343 NAFLD-HCC cases without documented cirrhosis (267 baseline HCC and 76 incident HCC) were included in this analysis. The baseline characteristics of these patients, overall and stratified by race/ethnicity, are summarized in Table 3. Overall, 39.4% had diabetes, 13.4% had cardiovascular disease, and 20.1% were smokers. The median (IQR) AST (26), ALT (28 [18–49]), GGT (46 [18–92]), and mean platelet count (245 [± 95] × 10^3/μL) were all within normal limits. The majority of patients (93.6%) had FIB-4 ≤ 1.30, and the remaining 6.4% had FIB-4 from 1.30–2.67. By race/ethnicity, Hispanics with NAFLD-related HCC had the highest proportion with diabetes (57.4%), followed by Whites (39.5%), Blacks (36.6%), and Asians (32.6%) ($p = 0.004$). Asians were the oldest (mean age 58.7 ± 14.8 years) compared to a mean age of 56–57 years among the White, Black, and Hispanic groups ($p < 0.0001$). There were no significant differences in the distribution of laboratory characteristics among the racial/ethnic groups.

Discussion

In this large, multi-ethnic, nationwide, real-world study of 751,603 NAFLD patients without documented cirrhosis, platelet count < 120,000/μL or FIB-4 > 2.67, we determined that the incidence of HCC was below the conventional threshold for cost-effective HCC surveillance. The low incidence of HCC remained consistent across multiple subgroup analyses for age, race/ethnicity, platelet count, and the presence of diabetes. HCC incidence was higher among patients with platelet counts ≤ 150,000/μL compared to patients with platelet counts > 150,000/μL, and platelet count ≤ 150,000/μL was independently associated with a sixfold higher risk of HCC development, even after adjusting for multiple confounders. We determined that the average age of NAFLD-related HCC in the absence of cirrhosis was around 57 years and that more than half (55%) were female.

These data have important clinical implications. Performing routine HCC surveillance in patients with NAFLD without cirrhosis is unlikely to be cost-effective, even among subgroups such as patients with diabetes [22, 24]. However, we determined that platelet count < 150,000/μL was a strong and independent predictor of HCC development in NAFLD patients without documented cirrhosis. Despite the statistically higher annual incidence of HCC in patients with platelet count < 150,000/μL, this still did not

Table 2 Predictors of hepatocellular carcinoma development among NAFLD patients without documented cirrhosis and without baseline hepatocellular carcinoma

Variable	Univariable analysis		Multivariable analysis Model 1		Multivariable analysis Model 2 (only significant variables from Model 1)	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value		*p* value
Age	1.01 (0.99–1.03)	0.07	1.03 (1.01–1.07)	0.04	1.04 (1.01–1.07)	0.03
Sex						
Female	Reference		Reference			
Male	0.78 (0.49–1.23)	0.29	0.45 (0.17–1.16)	0.10	0.46 (0.18–1.18)	0.11
Ethnicity						
White	Reference		Reference			
Hispanic	0.88 (0.46–1.67)	0.69	0.79 (0.28–2.23)	0.66		
Black	1.20 (0.54–2.67)	0.65	0.90 (0.20–4.03)	0.89		
Asian	2.24 (1.09–4.61)	0.03	1.72 (0.49–6.07)	0.40		
Other	1.22 (0.52–2.87)	0.66	0.57 (0.07–4.35)	0.59		
Smoker						
No	Reference					
Yes	1.08 (0.62–1.88)	0.78				
Diabetes						
No	Reference		Reference			
Yes	1.36 (0.86–2.13)	0.19	0.98 (0.43–2.23)	0.97		
Dyslipidemia						
No	Reference					
Yes	0.88 (0.52–1.48)	0.63				
Platelet						
> 150	Reference					
≤ 150	5.83 (1.74–19.6)	0.004	5.80 (1.67–20.1)	0.006	5.79 (1.67–20.1)	0.006
ALT						
≤ ULN	Reference					
> ULN	1.08 (0.51–2.31)	0.83				
AST						
≤ 40 U/L	Reference					
> 40 U/L	0.68 (0.24–1.96)	0.47				
GGT						
≤ 40 U/L	Reference					
> 40 U/L	1.55 (0.35–6.93)	0.57				
HbA1c						
≤ 7	Reference					
> 7	1.67 (0.61–4.60)	0.32				
Baseline AFP	0.86 (0.52–1.42)	0.55				
Aspirin						
No	Reference					
Yes	0.70 (0.10–5.04)	0.72				
Metformin						
No	Reference					
Yes	0.77 (0.44–1.36)	0.37				
Statin						
No	Reference					
Yes	0.70 (0.44–1.10)	0.12				
Insulin						
No	Reference					
Yes	1.54 (0.79–3.00)	0.20				

Table 2 (continued) *NAFLD* non-alcoholic fatty liver disease, *HCC* hepatocellular carcinoma, *AST* aspartate transaminase, *ALT* alanine transaminase, *GGT* gamma-glutamyl transferase

Table 3 Baseline characteristics of patients with NAFLD-related HCC (including both baseline* and incident cases) without documented cirrhosis, overall and by race/ethnicity

	Total $n=343$	White ($n=162$)	Hispanic ($n=61$)	Black ($n=41$)	Asian ($n=43$)	Other ($n=36$)	p value
Age (year)	56.9 ± 15.4	57.4 ± 15.7	56.2 ± 16.5	56.4 ± 16.0	58.7 ± 14.8	54.0 ± 12.4	< 0.0001
Male, *n* (%)	156 (45.5)	71 (43.8)	29 (47.5)	20 (48.8)	22 (51.2)	14 (38.9)	0.80
Diabetes, *n* (%) ($n=343$)	135 (39.4)	64 (39.5)	35 (57.4)	15 (36.6)	14 (32.6)	7 (19.4)	0.004
Cardiovascular disease, *n* (%) ($n=343$)	46 (13.4)	26 (16.1)	6 (9.8)	7 (17.1)	3 (7.0)	4 (11.1)	0.43
Overweight/obesity, *n* (%) ($n=343$)	151 (44.0)	79 (48.8)	34 (55.7)	23 (56.1)	8 (18.6)	7 (19.4)	< 0.001
Smoker, *n* (%) ($n=343$)	69 (20.1)	38 (23.5)	6 (9.8)	13 (31.7)	6 (14.0)	6 (16.7)	0.04
ALT (mean, SD)[U/L] ($n=140$)	28 (18–49)	27 (19–57)	29 (15–47)	27 (18–67)	29 (16–42)	26 (25–100)	0.73
AST (mean, SD)[U/L] ($n=138$)	26 (19–37)	25 (18–37)	26 (19–38)	30 (20–34)	28 (18–34)	34 (22–63)	0.69
GGT (mean, SD)[U/L] ($n=29$)	46 (18–92)	51 (17–92)	72 (41–157)	34 (23–45)	14 (13–48)	53 (46–216)	0.49
Platelet (mean, SD)[U/L] ($n=122$)	245 ± 95	245 ± 71	225 ± 57	235 ± 51	286 ± 201	236 ± 57	0.35
Total bilirubin (mg/dL) ($n=142$)	0.6 ± 0.3	0.6 ± 0.4	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.6 ± 0.5	0.55
International normalized ratio ($n=41$)	1.0 ± 0.1	1.0 ± 0.2	1.1 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.85
Creatinine (mg/dL) ($n=139$)	0.9 (0.7–1.0)	0.9 (0.7–1.0)	0.8 (0.7–0.9)	1.0 (0.9–1.1)	0.8 (0.7–0.9)	0.9 (0.7–1.0)	0.08
HbA1c ($n=66$)	6.5 ± 1.3	6.3 ± 1.1	7.0 ± 1.9	6.5 ± 0.9	5.9 ± 0.4	5.7 ± 0.4	0.29
FIB-4 ($n=110$)							0.67
≤ 1.30	103 (93.6)	45 (95.7)	21 (87.5)	16 (94.1)	14 (93.3)	7 (100)	
1.30–2.67	7 (6.4)	2 (4.3)	3 (12.5)	1 (5.9)	1 (6.7)	0	

Values expressed as mean ± standard deviation, number (percentage) or median (interquartile range)

NAFLD non-alcoholic fatty liver disease, *HCC* hepatocellular carcinoma, *AST* aspartate transaminase, *ALT* alanine transaminase, *GGT* gamma-glutamyl transferase

*Included 267 patients with HCC at baseline

reach the conventional thresholds considered cost-effective for surveillance [25]. Older age was also an independent predictor for HCC development, but we did not find statistically significant differences in HCC incidence between patients aged ≥ 65 years versus those < 65 years. HCC incidence may be higher among patients with increased age and platelet count ≤ 150,000/μL, but further studies with larger sample sizes to allow for stratification by both age and platelet counts are required to validate this hypothesis. Current cost-effectiveness thresholds for HCC surveillance are based on current surveillance modalities (ultrasound + AFP) and may change if the field moves toward serum biomarker-based surveillance (e.g., GALAD) [26, 27]. This may be a more tenable solution for expanding HCC surveillance to patients with NAFLD without cirrhosis. The incidence of HCC was numerically higher in females compared to males, although this was not statistically significant. This may be related to the older age of onset of NAFLD-related HCC, diminishing the protective influence of estrogen due to the onset of menopause in females, but this hypothesis requires validation [16, 28]. More than half of the patients who developed NAFLD-related HCC were female, highlighting the growing burden of NAFLD-related HCC among females [29].

Several studies have evaluated the incidence of HCC in NAFLD patients without a diagnosis of cirrhosis [22, 24, 30–32]. However, it was previously unclear what factors were associated with HCC development in NAFLD patients without cirrhosis, and how the incidence of HCC varied among subgroups such as age, sex, race/ethnicity, diabetes, and other clinical characteristics. The current study builds upon existing literature by identifying predictors of HCC development and evaluating the variation of HCC incidence in clinically relevant subgroups such as by the presence of diabetes or platelet count. The current findings are consistent with a previous study [22] that determined a HCC incidence rate of 0.04/1000 PYs in NAFLD patients without cirrhosis or high FIB-4, and expands on that study by providing incidence rates in various subgroups. To our knowledge, this is the largest study of HCC incidence in NAFLD patients

without cirrhosis that provides detailed clinical and laboratory data. Previous studies did not provide granular laboratory and clinical data for patients without cirrhosis [22, 31], or were limited by modest sample sizes [33].

The strengths of the current study include the large nationwide sample size that was not restricted to referral or tertiary centers, real-world setting, and evaluation of clinically applicable predictors of HCC. However, this study has several limitations. Laboratory data were available in a subgroup of patients, but this subgroup still included over 220,000 patients. It is possible that some of the included patients had undiagnosed cirrhosis, and misclassification might occur with the use of ICD codes. However, sensitivity analysis of patients with data for FIB-4 (patients with FIB-4 > 2.67 were excluded) determined a similar incidence of HCC as the overall analysis. It is possible that some of the patients with platelet counts < 150,000/μL (all patients with platelet counts < 120,000/μL were excluded) may have undiagnosed cirrhosis; however, 90% of patients in the analysis for platelet counts < 150,000/μL had available data for FIB-4 and those with FIB-4 > 2.67 were excluded. Likewise, some patients with FIB-4 values from 1.30 to 2.67 might have undiagnosed cirrhosis. However, only 4% of patients with FIB-4 data had a FIB-4 of 1.30–2.67, and the remaining 96% had FIB-4 below 1.30, making it less likely that patients with cirrhosis were included. We lacked access to M2BPGi and albumin and were not able to determine cut-points for these variables which might be predictive of future HCC development. We did not have data to accurately determine the presence of metabolic syndrome and hypothyroidism, which should be evaluated as predictors for HCC development in future studies. Hypothyroidism is associated with oxidative stress in the liver, increased lipid peroxidation, insulin resistance, increased insulin-like growth factor-1 levels, and systemic chronic inflammation, which may predispose to NAFLD-related HCC [34–37]. Future studies are required to define if there are specific mechanisms linking hypothyroidism with NAFLD-related HCC. Likewise, the metabolic syndrome and its components are strongly associated with the development of NASH, advanced fibrosis, and subsequently HCC development [7, 10, 38]. Further research is required to determine the incidence of NAFLD-related HCC among people with the metabolic syndrome who do not have cirrhosis.

Conclusions

In this large, multiethnic, nationwide, real-world study of NAFLD patients without documented cirrhosis, we determined that the incidence of HCC was below the conventional threshold for cost-effective HCC surveillance, both overall and in multiple subgroup analyses for age, race/ethnicity, platelet count and the presence of diabetes. Platelet count < 150,000/μL and older age were independent predictors of HCC development in NAFLD patients without documented cirrhosis. These readily available clinical parameters may be utilized in combination or with other biomarkers in the future to identify NAFLD patients without cirrhosis who may benefit from HCC surveillance but require further validation. These data highlight the need for improved strategies to identify NAFLD patients without cirrhosis who are at higher risk of HCC.

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Declarations

Conflict of interest MHN: Research funding: Pfizer, Enanta, Gilead, CurveBio, Exact Sciences, Helio Health, Glycotest, National Cancer Institute, B.K. Kee Foundation, Vir Biotech; Consulting: Gilead, Intercept, GSK, Exact Science, Novartis, Janssen, Bayer. RC: Research funding: Gilead, Siemens Healthineers. DQH: Advisory board/consulting: Gilead. Sally Tran, Scott Barnett, Biyao Zou, Yee Hui Yeo, and Ramsey Cheung declare no conflicts of interest.

Ethical approval The study was approved by the Institutional Review Board at Stanford University, Stanford, California, USA. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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