Characteristics of Chronic Hepatitis B Patients in a 20-Year, Real-World Study of Treatment Patterns in a US Health Care Delivery System

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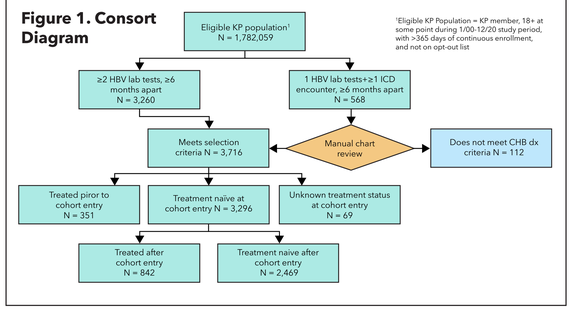
PREMISE

- Chronic hepatitis B (CHB) infection is an important public health concern due to its worldwide prevalence and potential for severe complications, including cirrhosis, hepatocellular carcinoma, and death.
- CHB treatment is recommended for those at highest risk of severe complications, noted by elevated Hepatitis B Virus (HBV) DNA and markers of liver inflammation.
- The objectives of this analysis were to compare 1) baseline cohort characteristics for treated and untreated CHB patients in routine clinical practice and 2) characteristics of newly treated CHB patients by treatment type.

METHODS

- ***Study Design***
  - Retrospective, observational cohort analysis
- ***Data Source***
  - Automated abstraction of Kaiser Permanente Northwest (KPNW) and Kaiser Permanente Hawaii (KPHI) electronic health records
- ***Study time period***
  - January 1, 2000 – December 31, 2020
- ***Patient Selection Criteria* (Figure 1)**
  - ≥18 years of age AND
  - Meeting CHB diagnosis:
    - ≥2 positive HBV laboratory results (HBsAg, HBeAg, or HBV DNA), ≥6 months apart OR
    - 1 positive laboratory test and 1 ICD-coded encounter (ICD9: 070.32 and 070.33, ICD10: B18.1 and B18.0) ≥6 months apart, with chart reviews completed for cases that needed further clarification; AND
  - 1-year of continuous enrollment prior to cohort entry.
  - Cohort entry date: earliest date at which all selection criteria were met, with the 1st HBV-defining lab or ICD code date considered HBV diagnosis date once an individual meets the 2nd HBV lab or ICD criteria.
  - Exclusion criteria: opting out of Kaiser Permanente research activities
- ***Study Variables***
  - Medication dispensing date and days' supply for CHB treatment (nucleos[t]ide analogs [NA] and/or peginterferon [Peg-IFN]) were abstracted 1 year prior to cohort entry (as early as 1/1/1999) through end of study follow-up.
  - Overall *"Treated"* status was defined as receipt of a minimum of 30-day continuous NA or IFN supply during the 1 year prior to cohort entry through the end of study follow-up.
  - *"Treated prior to cohort entry"* was defined as initiation of treatment prior to cohort entry date.
  - *"Treated after cohort entry"* was defined as initiation of treatment on or after cohort entry date.
  - *"Treatment naïve"* was defined as no treatment initiation prior to or after cohort entry.
  - Demographic and clinical characteristics were abstracted from 12 months prior to 2 weeks post cohort entry date for all participants and for a similar period around date of first dispensing for those treated after cohort entry.
- ***Statistical Analysis***
  - Differences in patient characteristics by treatment status were assessed with the Chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables.
- ***Human subjects***
  - KPNW Institutional Review Board reviewed and approved the study protocol for both study sites.

Figure 1. Consort Diagram



[1]Eligible KP Population = KP member, 18+ at some point during 1/00-12/20 study period, with >365 days of continuous enrollment, and not on opt-out list

RESULTS

- We found 3,716 CHB-infected individuals from an eligible population of 1,782,059 across both study sites (0.21%). Of these, 351 (9%) were treated prior to cohort entry and 3,296 (90%) were treatment naïve for a total study population of 3,647; 69 (2%) had uncertain treatment status at cohort entry and were excluded from further analysis.
  - CHB cohort members were followed for an average of 7.9 years from cohort entry (median 6 years).
- Patient characteristics of those with known treatment status at cohort entry are shown in **Table 1.**
  - *Treated* patients were more likely than *treatment naïve* patients to be male, older, White, and enrolled in Medicare or Medicaid. *Treated* patients had shorter follow-up time (mean 5.6 years; median 4) than *treatment naïve* patients (8.1 and 6 years, respectively; p<0.0001).
  - *Treated* patients were more likely to have a higher FIB-4 score, to be HBeAg-positive, and have lower HBV DNA levels.
  - *Treated* patients were more likely to have comorbid diagnoses and a higher Charlson Comorbidity Index (CCI) Score.

Table 1. Demographic and Clinical Characteristics of CHB Cohort Participants, by Treatment Status at Cohort Entry

	All n = 3,647 N (%)	Treated Prior to Cohort Entry n = 351 N (%)	Treatment Naïve n = 3,296 N (%)	p-value
Sex				<0.0001
Male	1,862 (51)	244 (70)	1,618 (49)	
Female	1,785 (49)	107 (31)	1,678 (51)	
Age				<0.0001
18-19	77 (2)	0	77 (2)	
20-39	1,343 (37)	84 (24)	1,259 (38)	
40-64	1,913 (53)	230 (66)	1,683 (51)	
65+	314 (9)	37 (11)	277 (8)	
Race				<0.0001
Asian	2,305 (63)	201 (57)	2,104 (64)	
White	542 (15)	89 (25)	453 (14)	
Hawaiian/Pacific Islander	393 (11)	22 (6)	371 (11)	
Other/Unknown	407 (11)	39 (11)	368 (11)	
Ethnicity				0.1741
Non-Hispanic	3,312 (91)	320 (91)	2,992 (91)	
Hispanic	74 (2)	11 (3)	63 (2)	
Unknown	261 (7)	20 (6)	241 (7)	
Insurance status				0.0002
Commercial	2,885 (79)	254 (72)	2,631 (80)	
Medicare	347 (10)	56 (16)	291 (9)	
Medicaid	277 (8)	30 (9)	247 (8)	
Other	138 (4)	11 (3)	127 (4)	
Hepatitis B surface antigen (HBsAg)				0.0017
Positive	2,295 (63)	196 (56)	2,099 (64)	
Negative	272 (8)	39 (11)	233 (7)	
Missing	1,080 (30)	116 (33)	964 (29)	
Hepatitis B e antigen (HBeAg)				<0.0001
Positive	448 (12)	90 (26)	358 (11)	
Negative	1,930 (53)	170 (48)	1,760 (53)	
Missing	1,269 (35)	91 (26)	1,178 (36)	
Hepatitis B virus DNA (HBV DNA)				<0.0001
<2,000	1,648 (45)	227 (65)	964 (29)	
2,000 - <20,000	353 (10)	17 (5)	336 (10)	
≥20,000	476 (13)	42 (12)	434 (13)	
Missing	1,170 (32)	65 (19)	1,105 (34)	
Alanine transaminase blood test (ALT)				0.2853
0 to <1x ULN	1,717 (47)	159 (45)	1,558 (47)	
1x to <2x ULN	1,141 (31)	119 (34)	1,022 (31)	
2x to <5x ULN	401 (11)	42 (12)	359 (11)	
≥5x ULN	111 (3)	16 (5)	95 (3)	
Missing	277 (8)	15 (4)	262 (8)	
Fibrosis-4 Index (FIB-4 Index)				<0.0001
0-3.25	2,713 (74)	276 (79)	2,437 (74)	
≥3.25	255 (7)	47 (13)	208 (6)	
Missing	679 (19)	28 (8)	651 (20)	
Body Mass Index (BMI)				0.3001
<18.5	88 (2)	4 (1)	84 (3)	
18.5-24.99	1,325 (36)	141 (40)	1,184 (36)	
25-29.99	882 (24)	98 (28)	784 (24)	
≥30	536 (15)	58 (17)	478 (15)	
Missing	816 (22)	50 (14)	766 (23)	
Charlson Comorbidity Index (CCI)				<0.0001
0	2,712 (74)	184 (52)	2,528 (77)	
1	383 (11)	40 (11)	343 (10)	
2+	552 (15)	127 (36)	425 (13)	
Underlying Chronic Disease				
NAFLD[1]	81 (2)	19 (5)	62 (2)	<0.0001
Other LD[2]	181 (5)	59 (17)	122 (4)	<0.0001
AUD[3]	326 (9)	46 (13)	280 (9)	0.0.0040
CKD[4]	232 (6)	35 (10)	197 (6)	0.0036
Cancer	228 (6)	39 (11)	189 (6)	<0.0001
CVD[5]	844 (23)	109 (31)	735 (22)	0.0002

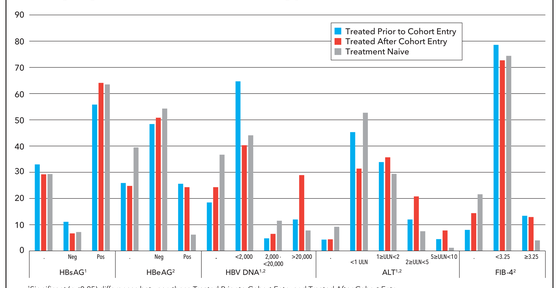
1 Nonalcoholic fatty liver disease; 2 Other Liver disease; 3 Alcohol use disorder; 4 Chronic kidney disease; 5 Cardiovascular diseases

Table 2. Demographic and Clinical Characteristics of CHB Patients Treated After Cohort Entry, by Treatment Type

	NRTI (n = 802) N (%)	Peg-IFN (n = 40) N (%)	p-value
Sex			0.2224
Male	484 (60)	28 (70)	
Female	318 (40)	12 (30)	
Age			<0.0001
18-19	5 (1)	0	
20-39	169 (21)	22 (55)	
40-64	509 (64)	18 (45)	
65+	119 (15)	0	
Hepatitis B surface antigen (HBsAg)			0.6326
Positive	234 (29)	15 (38)	
Negative	45 (6)	2 (5)	
Missing	523 (65)	23 (58)	
Hepatitis B e antigen (HBeAg)			0.4113
Positive	135 (17)	12 (30)	
Negative	220 (27)	14 (35)	
Missing	447 (56)	14 (35)	
Hepatitis B virus DNA (HBV DNA)			0.1388
<2,000	160 (20)	5 (13)	
2,000 - <20,000	72 (9)	4 (10)	
≥20,000	338 (42)	27 (68)	
Missing	232 (29)	4 (10)	
Alanine transaminase blood test (ALT)			0.0604
0 to <1x ULN	156 (20)	5 (13)	
1x to <2x ULN	189 (24)	6 (15)	
2x to <5x ULN	124 (16)	8 (20)	
≥5x ULN	61 (8)	7 (18)	
Missing	272 (34)	14 (35)	
Fibrosis-4 Index (FIB-4 Index)			0.4923
0-3.25	350 (44)	21 (53)	
≥3.25	118 (15)	5 (13)	
Missing	334 (42)	14 (35)	
Charlson Comorbidity Index (CCI)			0.0020
0	444 (55)	33 (83)	
1	107 (13)	4 (10)	
2+	251 (31)	3 (8)	

- Of the 3,296 *treatment naïve* individuals at cohort entry, 842 (25%) were *treated after cohort entry* and 2,469 (75%) remained untreated for the duration of the study. Clinical characteristics of these two groups are shown in **Figure 2**.
  - Patients who were treated after cohort entry had significantly higher ALT and HBV DNA levels, and were more likely to be HBsAg-positive, when compared with those treated before cohort entry. The two groups were not significantly different, with respect to patients who were HBeAg-positive or who had a FIB-4 score ≥3.25.
  - HBsAg status of patients treated after cohort entry was not significantly different from those remaining treatment naïve; however, the former group had higher HBeAg-positivity, HBV DNA, and ALT levels, and a greater proportion had a FIB-4 score ≥3.25.
- Among those newly initiating treatment after cohort entry, 802 (95%) received NA and 40 (5%) received IFN. **(Table 2)**.
  - Those initiating NA were older than those initiating IFN; we found no difference by sex.
  - We found no significant differences in treatment type initiated, by CHB lab testing, ALT level, or high FIB-4 score.
  - Those initiating NA had a higher proportion of patients with other liver disease and cancer (p<0.05 for both, data not shown) and had a higher underlying comorbidity score than those starting IFN.

Figure 2. CHB and Liver-Related Laboratory Markers at Cohort Entry, by Treatment Sub-cohort Type



[1]Significant (p<0.05) differences between those Treated Prior to Cohort Entry and Treated After Cohort Entry.
[2]Significant (p<0.05) differences observed between those Treated After Cohort Entry and those Treatment Naïve during study period

LIMITATIONS

- Our study may have missed treatments dispensed prior to patients joining KPNW and KPHI health plans, so some treatment naïve individuals may be misclassified. We aimed to minimize this by requiring 1 year of health plan enrollment prior to cohort entry.
- We did not require 1 year of enrollment prior to treatment initiation, so characteristics assessed at that point may be more likely to be missing.
- Missing data on CHB lab testing may not adequately assess patient eligibility for treatment.
- The small sample size across a 20-year period from two study sites may limit the generalizability to other CHB populations.

CONCLUSION

- Although we observed a higher proportion of CHB patients receiving treatment than previously reported, two-thirds remained treatment naïve throughout the study period.
- A quarter of participants who were initially treatment naïve subsequently received treatment.
- Patients who subsequently received treatment were more likely to be HBeAg-positive, have higher HBV DNA and ALT levels, and were more likely to have a FIB-4 score ≥3.25 compared to those who remained treatment naïve.
- Among treated CHB patients at cohort entry, those receiving NA were older and had significantly worse underlying clinical comorbidity than those receiving IFN, although HBV-specific markers did not differ between the two groups.
- These points suggest considerable unmet needs remain in understanding the role of treatment recommendations for CHB patients at risk of disease progression and highlights the importance of targeted treatment recommendations towards those at highest risk of severe sequelae.
- Further work is needed to understand the relative risk of developing long-term CHB outcomes by treatment status, including among those with limited HBV-specific laboratory markers.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the contributions of Terry Kimes, Judy Donald, and Richard Meenan (KPNW) and Sixiang "Shawn" Nie and Carmen Wong (KPHI) to this effort.

DISCLOSURE

This work was supported by an Institutional Research Grant to the Kaiser Permanente Center for Health Research from Vir Biotechnology. SS, AA, VT, and CR are employees and shareholders of Vir Biotechnology. MS, YD, AR and NT have no disclosures.

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