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ORIGINAL ARTICLE

Practice Patterns in Hepatitis B Virus Screening Before Cancer Chemotherapy in a Major US Hospital Network

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Abstract

Background Cancer patients receiving chemotherapy face an increased risk of reactivation of chronic hepatitis B virus infection.

Aim To determine the HBV screening rate in patients receiving cancer chemotherapy in various clinical settings.

Method We identified 11,959 adult cancer patients (age $\geq$ 18 years) receiving parenteral chemotherapy between 2012 and 2015 within a major US hospital network, including a large university hospital, community teaching hospitals, and community oncology clinics.

Result Two thousand and forty-five patients (17.1%) were screened for either HBV surface antigen (HBsAg) or HBV core antibody (HBcAb) before chemotherapy, and 1850 patients (15.5%) had both HBsAg and HBcAb tested before chemotherapy. 8.4% were exposed to HBV, and 0.9% had chronic HBV infection (both HBsAg/HBcAb positive). Patients with hematologic tumor were more often screened than with solid tumor (55.6 vs. 8.3%, $p < 0.001$). Patients receiving chemotherapy with higher HBV reactivation risk had higher yet suboptimal HBV screening rate (41.1% B-depleting agents, 21.5% anthracycline, 14.9% steroid, 64.7% anti-TNF alpha and 18.6% other chemotherapy, $p < 0.001$). Patients with age $\geq$ 50 years (old 16.2% vs. young 23.9%, $p < 0.001$) and Asian ethnicity (Asian 13.6 vs. Caucasian 16.6%, $p < 0.001$) were screened less for HBV despite higher prevalence of HBV exposure (old 9.3% vs. young 4.3%, $p < 0.001$ and Asian 27.8% vs. Caucasian 6.4%, $p < 0.001$). Patients receiving chemotherapy in community oncology clinics were less screened versus community teaching hospitals or university hospital (12.7 vs. 19.1 vs. 19.7%, $p < 0.001$), despite similar prevalence of HBV infection. On multivariate analysis, receiving chemotherapy at a community oncology clinic [odds ratio (OR) 0.57, 95% confidence interval (CI) 0.45–0.72, $p < 0.001$] was independently associated with less HBV screening compared to receiving chemotherapy at a university or community teaching hospital.

Conclusion HBV screening among patients undergoing cancer chemotherapy was suboptimal and less commonly performed in community oncology clinics compared to teaching hospitals.

Keywords Hepatitis B · HBV reactivation · Cancer chemotherapy · HBV prophylaxis · Rituximab

Introduction

Patients receiving cancer chemotherapy face an increased risk of reactivation of chronic hepatitis B virus (HBV) infection, which may be associated with significant morbidity and mortality. Approximately 10.8 million (3.9%) of the US population has prior exposure to HBV with positive HBcAb and 0.3% has chronic HBV infection with positive HBsAg [1]. HBV reactivation rate depends on HBV infection status, host factors [2] as well as chemotherapy regimen [3]. Although HBV reactivation more commonly occurs in patients with positive HBsAg, HBcAb positive/HBsAg negative patients may also experience HBV

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reactivation [4, 5]. The rate of HBV reactivation varies between 3 and 88%, and the mortality rate also ranges from 23 to 71% [2, 6]. However, a systemic review on HBV reactivation revealed that 32% of patients with positive HBsAg receiving chemotherapy had an increase in HBV DNA level by more than tenfold with a corresponding elevation in serum aminotransferase levels, 13% of patients developed hepatic failure and 7% died [7]. Patients receiving B cell-depleting agents such as rituximab, anthracycline or corticosteroid therapy face more than 10% risk of HBV reactivation [3]. Although patients with hematologic malignancy who are undergoing chemotherapy are known to be associated with high risk of HBV reactivation [3, 8, 9], patients with solid malignancy may also experience HBV reactivation [10, 11].

The issue of HBV reactivation in context of cancer chemotherapy has been recognized by federal agencies and medical specialty societies, including the US Food and Drug Administration (FDA), which has placed boxed warnings regarding the risk of HBV reactivation with immune-suppressing and anticancer drugs such as ofatumumab and rituximab [12], and the Centers for Disease Control and Prevention (CDC), which has proposed recommendations for HBV screening in patients with a high risk of HBV reactivation [13]. Major medical societies such as the American Society of Clinical Oncology (ASCO) [14, 15], American Gastroenterological Association (AGA) [16] and American Association for the Study of Liver Diseases (AASLD) [17] have published guidelines addressing prevention and treatment of HBV reactivation before and during chemotherapy.

Despite these guideline recommendations, HBV screening rates have been suboptimal based on studies evaluating screening practices within major cancer centers or large university hospitals. Hwang et al. [18] reported that the HBV screening rate prior to chemotherapy for cancer patients at one major cancer center was 16.2% overall, with improvement observed over 7 years from 2004 to 2011 (14.8–19.9%). Paul et al. [19] reported that among 4008 patients undergoing cancer chemotherapy from 1999 to 2013 at one major university center, HBV screening was performed in 45.5% prior to immunosuppressive therapy in liquid tumor patients, and 73.9% in solid tumor patients. Furthermore, a small study of 244 consecutive patients who underwent rituximab therapy at a community-based safety net hospital from 2006 to 2015 revealed that 60.5% underwent HBV screening prior to chemotherapy [20]. However, there is no study comparing HBV screening pattern in different clinical settings, reflecting real-world data. Herein, we describe the results of a retrospective observational study to investigate the real-world HBV screening rate in cancer patients receiving chemotherapy in a major US health care network involving three clinical settings, including a large university hospital, community teaching hospitals, and affiliated community outpatient oncology clinics.

Methods

Study Populations and Data Source

Data were extracted from our Electronic Health Record (Epic) by Yale Joint Data Analytics Team (JDAT) using search term (keyword, encounter type and code). We identified patients age 18 years or older who completed a parenteral chemotherapy encounter between January 2012 to August 2015 at a large university hospital (1 site), community teaching hospital (2 sites) and/or community oncology clinic (9 sites) within the Yale-New Haven Health System. We excluded patients who received chemotherapy via non-parenteral route or unknown route of administration since it may be difficult to monitor the actual administration and compliance with chemotherapy in those patients based on previously published studies [18]. We also excluded patients without diagnosis of malignancy based on ICD-9 or 10 code who underwent chemotherapy for immunosuppression or anti-inflammatory measures. We collected data on chemotherapy (name of chemotherapy regimen, dose, route of administration and location of administration), cancer diagnosis (ICD-9 or 10 code), and hepatitis B serology test (date of test ordered and result). The study protocol was approved by Yale University Institutional Review Board (protocol ID: 1603017450).

Study Variables

Baseline demographic information on age, gender, and race/ethnicity was collected. Types of tumors were divided into hematologic, solid, and combination of hematologic and solid neoplasm when the patient had diagnosis of both hematologic and solid malignancy. Types of chemotherapy were categorized by American Cancer Society classification. Chemotherapy with known risk of HBV reactivation was separately grouped, including B-depleting agents, anthracycline derivatives, steroid, immunotherapy other than B-depleting agent, anti-tumor necrosis factor (TNF) alpha agents, and cytokine/integrin inhibitors (Supplemental Table 1) [3, 16, 21]. When patients were receiving multiple chemotherapy regimens or if the chemotherapy medications were switched during chemotherapy, the patient was considered to be receiving the chemotherapy with the highest risk of HBV reactivation among multiple chemotherapy in the order of B-depleting agent, anthracycline, steroid, immunotherapy, anti-TNF alpha, cytokine/

integrin inhibitor and other chemotherapy based on previously published risk of HBV reactivation [3, 16], as investigating HBV screening rate in people who are taking chemotherapy with higher risk of HBV reactivation is of greater significance. Location of chemotherapy and HBV screening test were divided into a university medical center, community teaching hospitals, community oncology clinics, and multiple locations if the patient received chemotherapy in two or more various clinical settings including university hospital, community teaching hospitals, or community oncology clinics.

Study Outcomes

HBV screening was defined as HBsAg and/or HBcAb tests ordered prior to the first administration of chemotherapy [16]. Patients who received appropriate HBV screening with both HBsAg and HBcAb were identified. Patients who had HBV serologic tests after the initiation of chemotherapy, which may reflect testing for HBV in response to abnormal liver enzymes or hepatic decompensation, were also identified. HBV infection status was divided into chronic HBV infection (positive HBsAg and HBcAb), occult HBV infection (negative HBsAg, positive HBcAb, negative HBsAb), or resolved HBV infection (negative HBsAg, positive HBcAb, positive HBsAb). Patients with confirmed HBV viremia with positive or detectable HBV DNA without other serologic markers were also included in the HBV infection population.

Statistical Analysis

Statistical analyses were performed using STATA package (STATA/IC version 14.1: STATA Corp LP., College Station, TX). Proportions of HBV screening before and after initiation of chemotherapy as well as HBV infection status were calculated. Appropriate Pearson's Chi-square test or Fisher's exact test was used to analyze differences in patients with or without HBV screening as well as characteristics of patients with or without a history of HBV infection. Multivariate logistic regression analysis was performed to identify factors associated with HBV screening prior to initiation of chemotherapy. Characteristics of patients who had either HBsAb or HBcAg test ordered before initiation of chemotherapy (early screening group) were compared to patients who had both HBsAb and HBcAg test ordered after initiation of chemotherapy (late screening group). Multivariate logistic regression analysis to identify factors associated with early HBV screening as opposed to late HBV screening was also performed.

Results

HBV Screening Before or After Initiation of Chemotherapy

Among 13,058 patients who underwent chemotherapy via parenteral route within the Yale-New Haven Health System January 2012–August 2015, we excluded 1099 patients without diagnosis of cancer and identified 11,959 patients who met inclusion criteria (Fig. 1). A total of 2045 patients (17.1%) had either HBsAg or HBcAb tested before starting chemotherapy, and 1850 patients (15.5%) had appropriate HBV screening testing with both HBsAg and HBcAb before starting chemotherapy. Thousand two hundred and fifty-one (10.5%) patients were tested for either HBsAg or HBcAb after initiation of chemotherapy, and 1000 (8.4%) patients were tested for both HBsAg and HBcAb after initiation of chemotherapy (Table 1).

HBV Screening Pattern Before Initiation of Chemotherapy

Older patients over age 50 years were less commonly screened for HBV prior to chemotherapy compared to patients less than age 50 years (16.2 vs. 23.9%, $p < 0.001$). Patients with Asian ethnicity (13.6%) and Hispanic ethnicity (14.8%) were less screened for HBV compared to Caucasian (16.6%) or African-American patients (18.6%, $p < 0.001$). Female patients were less commonly screened for HBV than male patients (14.9 vs. 19.6%, $p < 0.001$). Patients receiving chemotherapy at local oncology clinics (12.7%) were less likely to be screened for HBV compared to those at a university medical center (19.7%) or community teaching hospitals (19.1%, $p < 0.001$). A total of 55.6% of patients with hematologic neoplasms were screened for HBV prior to chemotherapy, 22.6% patients with either hematologic or solid neoplasms, and 8.3% patients with solid neoplasms alone ($p < 0.001$). A total of 41.1% of patients receiving B-depleting agents and 64.7% patients receiving anti-TNF alpha therapy were screened for HBV before chemotherapy, while 21.5% of patients receiving anthracycline agents, 14.9% of patients receiving corticosteroid therapy, 16.5% receiving immunotherapy other than B-depleting agents, and 18.6% of patients receiving other chemotherapy agents were screened for HBV ($p < 0.001$, Table 2).

HBV Infection Pattern in Patients Undergoing Cancer Chemotherapy

A total of 8.4% of patients (215/2554) who had available HBsAg, HBcAb or HBV DNA testing had positive results

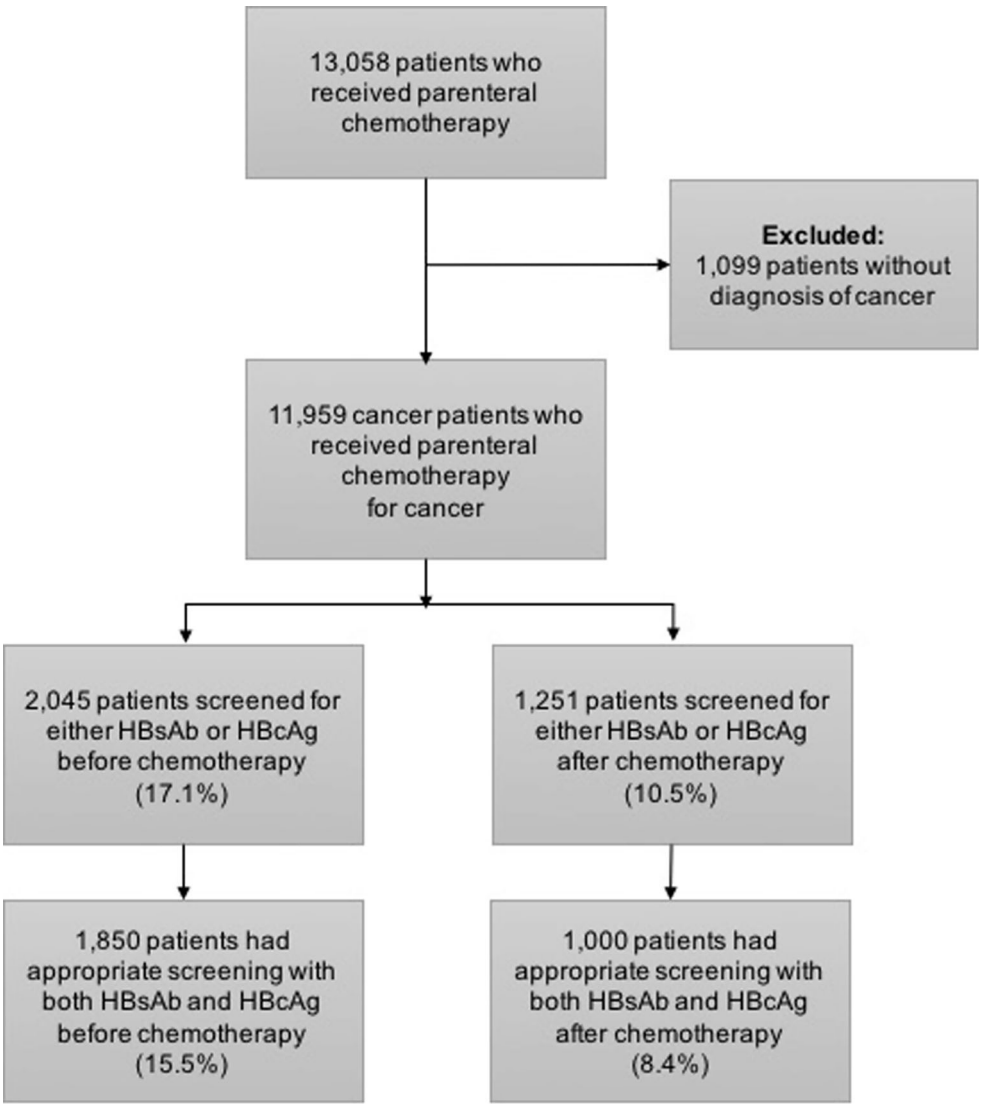

Fig. 1 Study population flowchart

Table 1 Proportion of HBV screening before or after initiation of chemotherapy ($N = 11{,}959$)

	n (%)
Proportions of HBV testing performed	
Either HBsAg or HBcAb before starting chemotherapy	2045/11,959 (17.1)
Both HBsAg and HBcAb before starting chemotherapy	1850/11,959 (15.5)
Either HBsAg or HBcAb after starting chemotherapy	1251/11,959 (10.5)
Both HBsAg and HBcAb after starting chemotherapy	1000/11,959 (8.4)
HBV infection status in cancer patients undergoing chemotherapy	
Prior exposure to HBV (positive HBsAg, HBcAb or HBV DNA)	215/2554 (8.4)
Chronic HBV infection (both HBsAg and HBcAb positive)	22/2508 (0.9)
Occult HBV infection (negative HBsAg/positive HBcAb/negative HBsAb)	30/1375 (2.2)
Resolved HBV infection (negative HBsAg/positive HBcAg/positive HBsAb)	88/1375 (6.4)

in one of these tests indicating prior exposure to HBV. Chronic HBV infection (HBsAg and HBcAb positive) was confirmed in 0.9% of patients (22/2508), occult HBV infection (negative HBsAg/positive HBcAb/negative HBsAb) in 2.2% of patients (30/1375), and resolved HBV infection (negative HBsAg/positive HBcAg/positive HBsAb) in 6.4% (88,1375) of patients (Table 1). Patients older than age 50 years had a higher prevalence of HBV

Table 2 Characteristics of HBV screening pattern in cancer patients prior to chemotherapy

	Total ($N = 11,959$, %)	HBV Screening		
		Yes ($n = 2045$, %)	No ($n = 9914$, %)	p value
Age				
Young (< 50 years)	1396 (11.7)	334 (23.9)	1062 (76.1)	< 0.001
Old (≥ 50 years)	10,563 (88.3)	1711 (16.2)	8852 (83.8)	
Ethnicity				
Caucasian	9331 (78.0)	1548 (16.6)	7783 (83.4)	< 0.001
African-American	1277 (10.7)	238 (18.6)	1039 (81.4)	
Hispanic	506 (4.2)	75 (14.8)	431 (85.2)	
Asian	155 (1.3)	21 (13.6)	134 (86.5)	
Others/Unknown	690 (5.8)	163 (23.6)	527 (76.4)	
Sex				
Male	5649 (47.2)	1107 (19.6)	4542 (80.4)	< 0.001
Female	6310 (52.8)	938 (14.9)	5372 (85.1)	
Location of chemotherapy				
University hospital	7077 (63.1)	1392 (19.7)	5685 (80.3)	< 0.001
Community teaching hospital	472 (4.0)	90 (19.1)	382 (80.9)	
Community oncology clinic	3530 (29.5)	448 (12.7)	3082 (87.3)	
Multiple location	880 (7.4)	115 (13.1)	765 (86.9)	
Tumor type				
Hematologic	2151 (18.0)	1195 (55.6)	956 (44.4)	< 0.001
Solid	9547 (79.8)	791 (8.3)	8756 (91.7)	
Both hematologic and solid	261 (2.2)	59 (22.6)	202 (77.4)	
Chemotherapy type				
B-depleting agent	124 (1.0)	51 (41.1)	73 (58.9)	< 0.001
Anthracycline	1193 (10.0)	257 (21.5)	936 (78.5)	
Steroid therapy	7098 (59.4)	1055 (14.9)	6043 (85.1)	
Immunotherapy, excluding B-depleting agent	158 (1.3)	26 (16.5)	132 (83.5)	
Anti-TNF alpha	17 (0.1)	11 (64.7)	6 (35.3)	
Cytokine/integrin inhibitor	27 (0.2)	22 (81.5)	5 (18.5)	
Other chemotherapy	3342 (28.0)	623 (18.6)	2719 (81.4)	

exposure (9.3 vs. 4.3%, $p < 0.001$). Asian (27.8%) patients followed by African-American (18.5%), Hispanic (10.9%) and Caucasian (6.4%) patients had evidence of prior exposure to HBV ($p < 0.001$). Male patients more commonly had evidence of prior exposure to HBV than female patients (10.2 vs. 6.5%, $p = 0.001$). There was no difference in HBV exposure status among patients receiving chemotherapy across clinical settings or chemotherapy type ($p > 0.05$, Table 3).

Multivariate Analysis on Factors Associated with HBV Screening Prior to Chemotherapy

On multivariate analysis, receiving chemotherapy at a community oncology clinic [odds ratio (OR) 0.57, 95% confidence interval (CI) 0.45–0.72, $p < 0.001$] or multiple locations (OR 0.60, 95% CI 0.52–0.68, $p < 0.001$) was independently associated with less HBV screening compared to a university hospital. Receiving chemotherapy at a community teaching hospital was not associated with lower rates of HBV screening compared to a university hospital (OR 1.02, 95% CI 0.77–1.34, $p = 0.906$). Patients aged more than 50 years old (OR 0.59, 95% CI 0.50–0.69, $p < 0.001$) and female gender (OR 0.85, 95% CI 0.76–0.95, $p = 0.005$) were associated with less HBV screening before cancer chemotherapy. African-American ethnicity (OR 1.33, 95% CI 1.11–1.58, $p = 0.002$) was associated with higher HBV screening compared to Caucasian ethnicity (OR 1.33, 95% CI 1.11–1.58, $p = 0.002$). Hispanic or Asian ethnicity was not associated with lower rates of HBV screening compared to Caucasian ethnicity ($p > 0.05$). Hematologic malignancy (OR 15.17, 95% CI 13.43–17.13, $p < 0.001$) or a combination of hematologic and solid malignancy (OR 3.45, 95% CI 2.54–4.67,

Table 3 Characteristics of patients with history of HBV infection (HBsAg, HBcAb or HBV DNA positive) in cancer patients undergoing chemotherapy

	HBV infection ($n = 215$, %)	Without HBV infection ($n = 1339$, %)	p value
Age (Mean, SD)			
Young (< 50 years)	20 (4.3)	442 (95.7)	< 0.001
Old (≥ 50 years)	195 (9.3)	1897 (90.7)	
Ethnicity			
Caucasian	122 (6.4)	1789 (93.6)	< 0.001
African-American	58 (18.5)	256 (81.5)	
Hispanic	15 (10.9)	123 (89.1)	
Asian	10 (27.8)	26 (72.2)	
Others/Unknown	10 (6.5)	145 (93.6)	
Sex			
Male	135 (10.2)	1187 (89.8)	0.001
Female	80 (6.5)	1152 (93.5)	
Location of chemotherapy			
University hospital	165 (8.8)	1712 (91.2)	0.587
Community teaching hospital	8 (9.6)	75 (90.4)	
Community oncology clinic	29 (6.9)	389 (93.1)	
Multiple location	13 (7.4)	163 (92.6)	
Chemotherapy type			
B-depleting agent	8 (11.8)	60 (88.2)	0.120
Anthracycline	30 (6.7)	420 (93.3)	
Steroid therapy	135 (9.6)	1269 (90.4)	
Immunotherapy, excluding B-depleting agent	1 (2.9)	34 (97.1)	
Anti-TNF alpha	0 (0.0)	14 (100.0)	
Cytokine/integrin inhibitor	0 (0.0)	9 (100.0)	
Other chemotherapy	41 (7.1)	533 (92.9)	

$p < 0.001$) was associated with higher HBV screening rate compared to solid malignancy. Receiving high-risk chemotherapy such as B-depleting agents (OR 0.70, 95% CI 0.47–1.04, $p = 0.079$) was not associated with higher HBV screening rate compared to other chemotherapy regimens. Receipt of anthracycline agents (OR 0.52, 95% CI 0.43–0.64, $p < 0.001$) or corticosteroids (OR 0.81, 95% CI 0.71–0.92, $p = 0.001$) was associated with lower HBV screening rates compared to other chemotherapy regimens (Table 4).

Comparison of Patients Who Had HBV Screening Before and After Chemotherapy

When compared to patients who had either HBsAg or HBcAb screening performed before initiation of the chemotherapy (early screening group), patients who had both HBsAb and HBsAg test performed after initiation of the chemotherapy (late screening group), no difference in age or ethnicity was identified. While Caucasian (16.6%) and African-American (18.6%) ethnicity was associated with higher early screening compared to Hispanic (14.8%) and Asian (13.6%) ethnicity, higher late screening was observed in the Hispanic (10.5%) and Asian (11.0%) ethnicity groups compared to Caucasian (8.3%) and African-American ethnicity groups (8.1%, $p = 0.011$). While more male patients were screened early than female patients (19.6 vs. 14.9%), only a small difference was observed between male and female patients undergoing late screening (8.5 vs. 8.2%, $p = 0.002$). Patients receiving care at multiple locations had similar HBV testing rate after initiation of chemotherapy compared to patients at a university hospital (10.2 vs. 10.3%), while patients at a university hospital had more HBV screening before chemotherapy compared to patients receiving care at multiple locations (19.7 vs. 13.1%, $p < 0.001$). Hematologic malignancy and receipt of B-depleting agents were associated with higher early screening than late screening (55.6 vs. 23.4%, $p < 0.001$ and 41.1 vs. 35.5%, $p < 0.001$, respectively) (Table 5).

On multivariate analysis, receipt of chemotherapy at multiple locations (OR 1.48, 95% CI 1.10–1.99,

Table 4 Multivariate logistic analysis on factors associated with HBV screening

	Adjusted OR (95% CI)	*p* value
Location (reference = university hospital)		
Community hospital	1.02 (0.77–1.34)	0.906
Local oncology clinics	0.57 (0.45–0.72)	< 0.001
Multiple locations	0.60 (0.52–0.68)	< 0.001
Age[3] 50 years (reference = age < 50)	0.59 (0.50–0.69)	< 0.001
Female (reference = male)	0.85 (0.76–0.95)	0.005
Race (reference = Caucasian)		
African-American	1.33 (1.11–1.58)	0.002
Hispanic	1.09 (0.82–1.45)	0.560
Asian	0.97 (0.58–1.63)	0.913
Other	1.28 (1.02–1.60)	0.032
Cancer type (reference = solid)		
Hematologic	15.17 (13.43–17.13)	< 0.001
Both solid/hematologic	3.45 (2.54–4.67)	< 0.001
Chemotherapy type (reference = other chemotherapy)		
B-depleting agents (rituximab)	0.70 (0.47–1.04)	0.079
Anthracycline	0.52 (0.43–0.64)	< 0.001
Steroid	0.81 (0.71–0.92)	0.001
Immunotherapy, excluding B-depleting agent	1.77 (1.14–2.76)	0.012
Anti-TNF alpha	8.93 (3.00–26.55)	< 0.001
Cytokine/integrin inhibitor	8.51 (2.81–25.77)	< 0.001

$p = 0.010$) and female gender (OR 1.21, 95% CI 1.03–1.42, $p = 0.017$) were associated with late screening. Hematologic malignancy was associated with early screening (OR 0.68, 95% CI 0.57–0.81, $p < 0.001$) compared to solid malignancy (Table 6).

Discussion

Patients with positive HBsAg and/or HBcAb are at risk for HBV reactivation in context of cancer chemotherapy, which may be associated with substantial morbidity and mortality. Screening for HBV with HBsAg and/or HBcAb in patients undergoing immunosuppressive drug therapy is recommended by major gastroenterology and oncology specialty societies including ASCO [14, 15], AGA [16], and AASLD [17]. However, HBV screening in patients undergoing cancer chemotherapy has been reported to be low in multiple university or cancer center settings [18–20]. The overall HBV screening rate (defined as testing for HBsAg and/or HBcAb) in our cohort was low (17.1%, $n = 11{,}959$), and strikingly similar to data reported in other cohorts of patients undergoing cancer chemotherapy, including a major US cancer center (17% screening, $n = 10{,}729$) [18, 27], a US university hospital (16% screening, $n = 8005$) [22], a Chinese university hospital (17.1% screening, $n = 6646$) [23], a Canadian university hospital (14% screening, $n = 208$) [24], and a major Japanese cancer center (19.9% screening, $n = 3302$) [25]. HBV screening (defined as testing for HBsAg only) was observed in 53% of a cohort of US veterans undergoing cancer chemotherapy, although was restricted to those prescribed anti-CD20 therapy and did not evaluate testing in context of other chemotherapy regimens [26].

Our study largely confirms prior observations of low HBV screening rates among patients undergoing cancer chemotherapy, but is the first to our knowledge which directly examines differences in screening rate across clinical settings (university hospital, community teaching hospital, community oncology clinic). Our report confirmed that pre-cancer chemotherapy HBV screening was more commonly performed in a university hospital (19.7%) or community teaching hospital setting (19.1%) than in community oncology clinics (12.7%), despite the absence of a difference in HBV infection across settings, and on multivariate analysis, receiving chemotherapy in a community oncology clinic was associated with a lower rate of HBV screening (OR 0.57, 95% CI 0.45–0.72, $p < 0.001$). Our study was not designed to examine determinants for this disparity in screening practices, although possible reasons may include variable awareness of and adherence to society guideline recommendations addressing HBV screening, stronger multi-specialty collaboration between oncology and GI/hepatology within teaching hospitals, and differences in standardized chemotherapy order protocols. Although screening was more common in the teaching

Table 5 Comparison of HBV screening pattern before and after initiation of chemotherapy

	Either HBsAb or HBsAg test before chemotherapy ($n = 2045$, (%))	Both HBsAb and HBsAg test after chemotherapy ($n = 1000$, (%))	p value
Age			
Young (< 50 years)	334 (23.9)	176 (12.6)	0.379
Old (≥ 50 years)	1711 (16.2)	824 (7.8)	
Ethnicity			
Caucasian	1548 (16.6)	770 (8.3)	0.011
African-American	238 (18.6)	104 (8.1)	
Hispanic	75 (14.8)	53 (10.5)	
Asian	21 (13.6)	17 (11.0)	
Others/Unknown	163 (23.6)	56 (8.1)	
Sex			
Male	1107 (19.6)	481 (8.5)	0.002
Female	938 (14.9)	519 (8.2)	
Location of chemotherapy			
University hospital	1392 (19.7)	718 (10.2)	< 0.001
Community teaching hospital	90 (19.1)	31 (6.6)	
Community oncology clinic	448 (12.7)	160 (4.5)	
Multiple location	115 (13.1)	91 (10.3)	
Tumor type			
Hematologic	1195 (55.6)	503 (23.4)	< 0.001
Solid	791 (8.3)	439 (4.6)	
Both hematologic and solid	59 (22.6)	58 (22.2)	
Chemotherapy type			
B-depleting agent	51 (41.1)	44 (35.5)	< 0.001
Anthracycline	257 (21.5)	228 (19.1)	
Steroid therapy	1055 (14.9)	542 (7.6)	
Immunotherapy, excluding B-depleting agent	26 (16.5)	7 (4.4)	
Anti-TNF alpha	11 (64.7)	2 (11.8)	
Cytokine/integrin inhibitor	22 (81.5)	1 (3.7)	
Other chemotherapy	623 (18.6)	176 (5.3)	

hospital settings, the overall rate remained very low, and signals an ongoing deficit for which future research is needed to identify effective systems-based solutions.

Our study additionally examined differences in HBV screening based on type of malignancy, type of chemotherapy regimen, as well as timing of HBV screening before or after initiation of chemotherapy. First, we reported that patients with a hematologic malignancy were more likely to undergo screening than patients with either a mixed hematologic and solid (22.6%) or solid malignancy (55.6 vs. 22.6 vs. 8.3%, $p < 0.001$). On multivariate analysis, hematologic malignancy (OR 15.2, 95% CI 13.43–17.13) and mixed hematologic/solid malignancy (OR 3.5, 95% CI 2.54–4.67) were associated with a higher likelihood of screening than solid malignancy, which likely stems from a stronger association between hematologic malignancies and HBV reactivation.

Second, we reported that patients undergoing chemotherapy regimens associated with moderate to high risk of HBV reactivation [3] had higher rates of HBV screening, including B cell-depleting agents (41.1%), anthracycline (21.5%) and corticosteroid therapy (14.9%) compared to the other chemotherapy group ($p < 0.001$). However, this was not determined to be statistically significant after adjusting for confounding variables on multivariate analysis. Although these findings are expected, the overall low screening rate of 41.1% underscores that even in context of regimens with the very highest risk for reactivation, HBV testing was still performed in fewer than half of patients. Specifically, among patients undergoing rituximab therapy, for whom the anticipated risk for

Table 6 Multivariate analysis on factors associated with screening after initiation of chemotherapy compared to screening before chemotherapy

	Adjusted OR (95% CI)	*p* value
Location (reference = university hospital)		
Community hospital	0.69 (0.45–1.05)	0.084
Community oncology clinics	0.72 (0.58–0.89)	0.002
Multiple locations	1.48 (1.10–1.99)	0.010
Age[3] 50 years (reference = age < 50)	1.15 (0.93–1.43)	0.197
Female (reference = male)	1.21 (1.03–1.42)	0.017
Race (reference = Caucasian)		
African-American	0.82 (0.64–1.06)	0.136
Hispanic	1.21 (0.83–1.77)	0.310
Asian	1.36 (0.70–2.65)	0.361
Other	0.78 (0.56–1.07)	0.127
Cancer type (reference = solid)		
Hematologic	0.68 (0.57–0.81)	< 0.001
Both solid/hematologic	1.42 (0.96–2.11)	0.080
Chemotherapy type (reference = other chemotherapy)		
B-depleting agents (rituximab)	3.44 (2.20–5.38)	< 0.001
Anthracycline	3.40 (2.64–4.39)	< 0.001
Steroid	1.67 (1.36–2.04)	< 0.001
Immunotherapy, excluding B-depleting agent	0.72 (0.31–1.71)	0.459
Anti-TNF alpha	0.57 (0.12–2.61)	0.468
Cytokine/integrin inhibitor	0.18 (0.02–1.32)	0.092

reactivation is estimated at > 10% among HBcAb positive and/or HBsAg positive patients [3], detailed language requiring pre-treatment HBV screening is present both in FDA product label [12], and society guidelines by ASCO [14, 15], AGA [16], and AASLD [17]. Our report supports previous findings in a national US veteran cohort undergoing anti-CD20 chemotherapy [26] and contributes additional evidence of a wide gap between FDA and guideline recommendations versus clinical practice.

Third, we reported that in addition to the 2045 of 11,959 patients (17.1%) in our cohort who underwent HBV screening prior to chemotherapy, an additional 1251 (10.5%) completed screening following initiation of chemotherapy (defined as either HBsAg and/or HBcAb). This appeared to be observed most commonly among patients receiving chemotherapy at either the university hospital (10.2%) or multiple locations (10.3%) as opposed to either a community teaching hospital (6.6%) or community oncology clinic (4.5%), $p < 0.001$. HBV testing after chemotherapy initiation was also more common with hematologic rather than solid tumor (23.4 vs. 4.6%, $p < 0.001$), and with higher-risk chemotherapy regimens such as B-depleting agents and anthracyclines versus other chemotherapy regimens (35.5 vs. 19.1 vs. 5.3%, $p < 0.001$); these observations remained significant after controlling for other variables on multivariate analysis. Although our analysis was not designed to identify determinants for variable timing of HBV screening in patients initiating chemotherapy, we suspect this may represent a referral effect in which patients initiating chemotherapy at community oncology clinics were referred to the university center where screening was more likely to be completed post-initiation, particularly among patients with hematologic malignancy or undergoing chemotherapy identified as higher risk for reactivation.

This study has several strengths. The analysis was performed in a large university hospital network with large sample size ($n = 11,959$ patients) and adequate power to identify key predictors of HBV screening across subgroups. Due to the incorporation of community outpatient and inpatient practices within this network, this study was well-positioned to examine the potential impact of clinical setting on HBV screening practices with diminished referral bias, a common limitation of prior studies performed exclusively in major cancer centers or university hospitals. Analysis of this population was conducted through data analytic strategies within a common electronic health record (EHR) for the hospital network, which permitted access to comprehensive clinical and laboratory data from inpatient and outpatient settings, thereby limiting potential risk of underestimating HBV screening from missing laboratory data performed outside the university hospital.

Multivariate analysis was conducted to adequately control for confounding variables which may have influenced interpretation of causal association as identified on univariate analysis. Finally, this study included a sizeable proportion of patients who are typically under-represented in clinical trials, including patients who self-identify as African-American or Hispanic.

This study was conducted at a single hospital network with a university-based National Cancer Institute-designated cancer center, and therefore these findings may not apply to clinical settings outside an academic hospital network. The study design was a retrospective cohort analysis of patients receiving cancer chemotherapy during a 3-year time period, and therefore a number of variables of potential relevance to HBV screening could not be examined, and the impact of emerging society guideline recommendations on screening practices could not be assessed. However, multivariate analysis was performed to control for key confounding variables related to the primary HBV screening endpoint. Furthermore, the study population had a low proportion of Asian patients and other populations who would have independently met CDC criteria for HBV screening outside the context of cancer chemotherapy, although prior studies in cohorts with higher prevalence of HBV in the study population revealed similar screening rates. Finally, HBV screening performed either prior to launch of the hospital network EHR or obtained by clinical practices outside the hospital network could not be excluded.

In summary, in a large cohort of 11,959 patients undergoing cancer chemotherapy at a major US university hospital network, HBV screening was suboptimal despite established FDA and medical society guideline recommendations for patients undergoing immunosuppressive drug therapy. Patients with hematologic malignancies, undergoing B cell-depleting therapies, and receiving cancer chemotherapy in university and/or community teaching hospitals were more likely to undergo HBV screening, although overall screening even in context of higher baseline risk for HBV reactivation remained poor. This study provides robust contemporary evidence for an ongoing gap between guideline recommendations and clinical practice previously described in oncology, dermatology, and rheumatology settings [24, 28, 29] which requires further examination for patient, provider, and systems determinants for non-screening, and may help inform educational interventions [30] and future research aimed at evaluating novel strategies for standardizing HBV screening in at-risk patients.

Author's contribution YEK drafted the manuscript; YEK, SMS, and JKL contributed to the conception and design; and SMS and JKL contributed to critical revisions of the manuscript.

Compliance with ethical standards

Conflict of interest YEK and SMS have no conflict of interest; JKL has received research contracts (to institution) and consulting honoraria from Bristol-Myers Squibb and Gilead.

References

1. Roberts H, Kruszon-Moran D, Ly KN, et al. Prevalence of chronic hepatitis B virus (HBV) infection in U.S. households: National Health and Nutrition Examination Survey (NHANES), 1988–2012. *Hepatology*. 2016;63:388–397.
2. Kawsar HI, Shahnewaz J, Gopalakrishna KV, Spiro TP, Daw HA. Hepatitis B reactivation in cancer patients: role of prechemotherapy screening and antiviral prophylaxis. *Clin Adv Hematol Oncol*. 2012;10:370–378.
3. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148:221–244.
4. Torres HA, Davila M. Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. *Nat Rev Clin Oncol*. 2012;9:156–166.
5. Hoofnagle JH. Reactivation of hepatitis B. *Hepatology*. 2009;49:S156–S165.
6. Shouval D, Shibolet O. Immunosuppression and HBV reactivation. *Semin Liver Dis*. 2013;33:167–177.
7. Loomba R, Rowley A, Wesley R, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med*. 2008;148:519–528.
8. Hsu C, Hsiung CA, Su IJ, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. *Hepatology*. 2008;47:844–853.
9. Lau GK, Yiu HH, Fong DY, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. *Gastroenterology*. 2003;125:1742–1749.
10. Paul S, Saxena A, Terrin N, et al. Hepatitis B virus reactivation and prophylaxis during solid tumor chemotherapy: a systematic review and meta-analysis. *Ann Intern Med*. 2016;164:30–40.
11. Voican CS, Mir O, Loulergue P, et al. Hepatitis B virus reactivation in patients with solid tumors receiving systemic anticancer treatment. *Ann Oncol*. 2016;27:2172–2218.
12. US Food and Drug Administration. Boxed warning and new recommendations to decrease risk of hepatitis B reactivation with the immune-suppressing and anti-cancer drugs Arzerra (ofatumumab) and Rituxan (rituximab). Drug Safety Communications. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM369436.pdf. Published September 25, 2013.
13. Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep*. 2008;57:1–20.
14. Hwang JP, Somerfield MR, Alston-Johnson DE, et al. Hepatitis B virus screening for patients with cancer before therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update. *J Clin Oncol*. 2015;33:2212–2220.

15. Artz A, Somerfield M, Feld J, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. *J Clin Oncol*. 2010;28:3199–3202.
16. Reddy KR, Beavers KL, Hammond SP, et al. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148:215–219.
17. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50:661–662.
18. Hwang JP, Fisch MJ, Lok AS, et al. Trends in hepatitis B virus screening at the onset of chemotherapy in a large US cancer center. *BMC Cancer*. 2013;13:534.
19. Paul S, Shuja A, Tam I, et al. Gastroenterologists have suboptimal hepatitis B virus screening rates in patients receiving immunosuppressive therapy. *Dig Dis Sci*. 2016;61:2236–2241.
20. Junus K, Aguilar M, Patel P, et al. Improvements in hepatitis B virus screening before rituximab therapy: a community-based, safety-net hospital experience. *Cancer*. 2017;123:650–656.
21. Cheung KS, Seto WK, Lai CL, et al. Prevention and management of hepatitis B virus reactivation in cancer patients. *Hepatol Int*. 2016;10:407–414.
22. Wi CI, Loo NM, Larson JJ, et al. Low level of hepatitis B virus screening among patients receiving chemotherapy. *Clin Gastroenterol Hepatol*. 2015;13:970–975.
23. Wang Y, Luo XM, Yang D, et al. Testing for hepatitis B infection in prospective chemotherapy patients: a retrospective study. *World J Gastroenterol*. 2013;19:923–930.
24. Lee R, Vu K, Bell CM, Hicks LK. Screening for hepatitis B surface antigen before chemotherapy: current practice and opportunities for improvement. *Curr Oncol*. 2010;17:32–38.
25. Ikeda M, Yamamoto H, Kaneko M, et al. Screening rate for hepatitis B virus infection in patients undergoing chemotherapy in Japan. *Int J Clin Oncol*. 2016;21:1162–1166.
26. Hunt CM, Beste LA, Lowy E, et al. Veterans health administration hepatitis B testing and treatment with anti-CD20 antibody administration. *World J Gastroenterol*. 2016;22:4732–4740.
27. Hwang JP, Fisch MJ, Zhang H, et al. Low rates of hepatitis B virus screening at the onset of chemotherapy. *J Oncol Pract*. 2012;8:e32–e39.
28. Stine JG, Bass M, Ibrahim D, Khokhar OS, Lewis JH. Dermatologists' awareness of and screening practices for hepatitis B virus infection before initiating tumor necrosis factor-alpha inhibitor therapy. *South Med J*. 2011;104:781–788.
29. Stine JG, Khokhar OS, Charalambopoulos J, Shanmugam VK, Lewis JH. Rheumatologists' awareness of and screening practices for hepatitis B virus infection prior to initiating immunomodulatory therapy. *Arthritis Care Res*. 2010;62:704–711.
30. Dyson JK, Jopson L, Ng S, et al. Improving testing for hepatitis B before treatment with rituximab. *Eur J Gastroenterol Hepatol*. 2016;28:1172–1178.

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