Cost evaluation of PAGE-B risk score guided HCC surveillance in patients with treated chronic hepatitis B

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Abstract

Background: The PAGE-B score (Platelet Age GEnder–HBV) selects chronic hepatitis B (cHB) patients showing no relevant 5-year risk for hepatocellular carcinoma (HCC). We, therefore, explored potential cost reduction following the introduction of a PAGE-B tailored ultrasound screening in a cohort of cHB patients receiving stable antiviral therapy.

Methods: cHB patients attending throughout the year 2018 were documented. Patients eligible for PAGE-B score were classified into high (≥18 points), intermediate (10-17 points) and low (≤9 points) HCC risk groups. Patients of the low HCC risk group could postpone HCC screening to reduce HCC screening expenses. Full costs for hepatic ultrasound were assessed.

Results: Throughout the year cHB patients (n=607) attended our clinic, which included PAGE-B eligible patients (n=227, 37.4%) of whom n=94 (15.8%) were allocated to the low HCC risk group. Sonographic HCC screening during a median exam time of 12.4 minutes (IQR 9.2-17.2) resulted in total costs of 22.82 Euro/exam. Additional opportunistic expenses caused by patient´s lost earnings or productivity were 15.6-17.5 €/exam and 26.7 €/exam, respectively. Following a PAGE-B tailored HCC screening at our institution annual costs for cHB patients could be reduced by 15.51%, which equals a cost reduction by 1.91% for our total sonography unit. In comparison, 1.59% up to 3.85% of HBV-infected patients could postpone HCC screening according to population-based estimates from Germany.

Conclusions: PAGE-B risk score adapted screening for HCC is an efficient and cost neutral tool to reduce costs for sonography in patients with chronic hepatitis B receiving antiviral treatment.

Background

Patients suffering from chronic Hepatitis B (cHB) develop a relevant morbidity and mortality caused by hepatocellular carcinoma (HCC) [1]. Surveillance by ultrasonography has therefore been established in cHB patients and improves overall survival of cHB patients [2]. Therefore, cHB treatment guidelines recommend HCC surveillance in all patients with liver cirrhosis every three to six months. In cHB patients without liver cirrhosis a diagnostic screening is generally recommended annually [3, 4].

Additional risk stratification, however, has identified cHB patients with a considerably lower cumulative HCC-incidence, who might not require HCC surveillance. Particularly antiviral therapy with nucleos(t)ide analogues (NA) has reduced the HCC risk of cHB [5, 6], which remains only minimally higher compared to hepatitis B virus carriers without disease activity [7]. This uncertainty of residual HCC development in NA treated patients, was addressed by the PAGE-B risk score (**P**latelet **A**ge **GE**nder–H**B**V) integrating age, gender and thrombocyte count, which selects patients with low HCC risk [8–10]. According to the PAGE-B score patients of the low HCC risk group (≤ 9 points) do not develop HCC under stable NA therapy during a 5-year follow up [8]. The large body of evidence has led to the recommendation of the European Association for the Study of the Liver (EASL), that cHB patients categorized into the low PAGE-B risk group could postpone HCC surveillance [11].

Given this new clinical data, it became possible to optimize allocation of clinical resources for HCC surveillance in cHB patients. However, the cost reduction for HCC surveillance, following a PAGE-B guided screening has not been defined. Hence, we explored the proportion of PAGE-B eligible cHB patients and the corresponding sonography costs to characterize the economic potential of PAGE-B adapted HCC screening.

Methods

Data acquisition and patient selection

For this observational study patient data were retrospectively retrieved from the hospital information system. Chronic cHB patients attending the liver disease out-patient clinic throughout the year 2018 were identified by a positive serum HBs-antigen (HBsAg) and cHB complications such as liver cirrhosis and hepatocellular carcinoma (HCC) were documented. Patients coinfected with hepatitis C, hepatitis D and human immunodeficiency virus were excluded. The PAGE-B score was calculated based on age, gender and thrombocyte count. PAGE-B strata were classified into high (≥ 18 points), intermediate (10–17 points) and low (≤ 9 points) HCC risk groups (**additional** Table 1) [8]. Patients eligible for PAGE-B score assessment had to receive effective antiviral therapy with second generation NA including entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF) for at least one year. The trial was conducted according to the principles of the Declaration of Helsinki. Approval was provided by the local ethic committee and data safety officer.

Table 1
Characteristics of chronic Hepatitis B patients

Population	**Total** (n = 607)	**PAGE-B eligible** (n = 227)	**PAGE-B eligible & low risk** (n = 94)
Variables	**Median (IQR), N (%)**		
Age (years)	46.7 (37.2–57.0)	50.8 (41.8–59.4)	42.9 (33.6–54.0)
Gender (male/female)	359/246 (59.2/40.6)	143/84 (63.0/37.0)	67/27 (71.3/28.7)
HBsAg positive	607 (100)	227 (100)	94 (100)
HBsAg (IU/l)	1665 (358–5222)	1714 (556–4909)	3700 (1199–8527)
Anti HBc-Ab	579 (95.5)	222 (97.8)	91 (96.8)
HBeAg positive	50 (8.3)	29 (12.8)	16 (17.0)
Anti HBe-Ab	517 (85.3)	179 (78.9)	76 (80.9)
HBV DNA < 20 U/l	331 (54.6)	197 (86.8)	74 (78.7)
Laboratory variables			
ALT (U/l)	29 (21–40)	29 (23–34)	28 (20–28)
AST (U/l)	28 (24–35)	29 (21–41)	27(22–33)
Total Bilirubin (mg/dl)	0.45 (0.62–0.85)	0.62 (0.45–0.92)	0.56 (0.40–0.78)
Albumin (g/l)	40 (38–42)	40 (38–42)	30 (38–42)
Quick (%)	96 (87–104)	96 (88–105)	96 (90–108)
Thrombocytes ($x10^9$/l)	219 (175–262)	229 (186–265)	247 (227–286)
Clinical variables			
Deceased	3 (0.5)	1 (0.4)	0 (0.0)
HCC	7 (1.2)	1 (0.4)	0 (0.0)
Liver stiffness (kPa)	4.8 (4.0-6.5)	4.9 (4.1–6.7)	4.5 (3.8–6.2)
Liver stiffness (> 10 kPa)	17 (2.8)	12 (5.3)	2 (2.1)
Risk Scores			
PAGE-B Score	10 (6–14)	10 (6–10)	6 (4–8)
≤ 9 Points	252 (41.6)	94 (41.4)	94 (100)
10–17 Points	273 (45.0)	100 (44.1)	—
≥ 18 Points	81 (13.4)	33 (14.5)	—

Population	Total (n = 607)	PAGE-B eligible (n = 227)	PAGE-B eligible & low risk (n = 94)
Antiviral Therapy			
Entecavir	110 (18.2)	105 (46.3)	41 (43.6)
TDF	118 (19.5)	118 (52.0)	49 (52.1)
TAF	4 (0.7)	4 (1.8)	4 (4.3)
Lamivudine	14 (2.3)	—	—
Adefovir	11 (1.8)	—	—
Telbivudine	1 (0.2)	—	—
Interferon-alpha	3 (0.5)	—	—
no antiviral treatment	345 (56.9)	—	—

Patient characteristics with confirmed chronic hepatitis B (n = 607). The subgroups of PAGE-B eligible patients (n = 227) as well as PAGE-B eligible patients with low HCC risk (n = 94) are shown. All patients attended the infectious and liver disease out-patient clinic during the year 2018. IQR, interquartile range; TDF, Tenofovir disoproxil fumarate; TAF, Tenofovir alafenamide fumarate.

Diagnostic ultrasonography and time acquisition

HCC screening included an ultrasonography of the liver, spleen and adjacent lymph nodes. Each ultrasonography throughout April and May 2019 was monitored with an on-site time tracking device (Timeular® cube) by the examiner himself. The time span for each ultrasound (total exam time) was analyzed. In parallel, the total turnaround time spent at the ultrasound unit was documented for each patient at the out-patient clinic front desk. A patient flow chart of the HCC screening is provided (**additional Fig. 1)**.

A total of n = 268 sonographies were assessed. Eventually, n = 147 (54.9%) exams allowed detailed time assessments, which included selective liver ultrasound in n = 118 patients (44.0%). The exams were frequently performed by a specialist of internal medicine, who provided eleven years of work experience. A smaller proportion of exams (24.5%, n = 36/147) were provided by an assistant doctor with three years of work experience.

Diagnostic ultrasonography expenses

The instrument expenses were 88.000 Euro (€) based on an updated sonography unit (Hitachi Arietta V70) meeting modern standards for HCC screening. The yearly costs were calculated by linear depreciation over a period of 5 years as defined by the German tax legislation (http://geman-taxes.de/pdf/AfA.pdf). Expenses for instrument services were derived from the service contract

(3,500 €/a). Facility expenses, including room rent, energy supply, water supply and cleaning services, were covered by the institutional allowance over 140.91 € per squaremeter per year. Consumable costs were based on listed prices as provided by the institutional purchase department. Work place software licenses for administration (i.s.h.med®, SAP), picture archiving and communication (ViewPoint®, GE healthcare IT) were included.

Average personnel costs were derived from the staff roster of the past two years. The team involved in HCC screening included one medical doctor performing the exam, one nurse providing medical assistance and two healthcare assistants providing administration. Labour costs were based on the collective bargaining agreement for public service employees (38.5 working hours/ week) amended at the 11.02.2015 (E&E-TV UM). Wage labour costs for medical staff (42 working hours/ week) were based on the collective bargaining agreement amended at the 01.01.2015 (TV-Ärzte/Universitätsmedizin).

Biostatistics

Descriptive data are given in median and interquartile range (IQR) throughout the manuscript if not specified accordingly.

Results

Patient characteristics and PAGE-B score

A cohort of n = 607 patients with positive serum HBsAg were identified during the year 2018, who underwent laboratory work up and regular HCC screening during a total n = 1.210 visits per year. Patients with confirmed cHB receiving second-generation NA for a minimum of one year (n = 227) were eligible for HCC risk assessment by the PAGE-B score. This led to the identification of patients of high (n = 33), intermediate (n = 100) and low (n = 94) HCC risk, respectively (Table 1). Throughout the year, three patients of the total cHB cohort died, whereas no mortality was observed in the low HCC risk subpopulation. Patients with low HCC risk did also not develop any HCC during this time period. The patient numbers with a low risk PAGE-B score (≤ 9 points) were applied to calculate cost reduction by PAGE-B adapted HCC screening.

Time requirements of sonographic HCC screening

The examiner and assistant staff were occupied for a median total exam time of 12.4 min (IQR 9.2–17.2 min) during liver ultrasound. This included a hands-on time of 5.4 min (IQR 4.1–7.8 min) for the examiner. The remaining time span was used for room preparations and documentation of the findings. The total exam time of the liver ultrasound was selected for subsequent work cost calculations during HCC screening. An administrative time of 30 seconds were estimated for the out-patient clinic as well as the endoscopy ward, respectively.

In parallel, patients were involved in HCC screening during a median total turnaround time of 45.0 min (IQR 34.0-59.8 min). The median total turnaround time was applied for calculation of external

opportunistic costs for sonographic HCC screening.

Full cost calculation of sonographic HCC screening

Full cost calculation for sonography included costs for instruments, software, technical services, facilities and consumables (Table 2). Average personnel costs expenses for administration (0.346 €/min), medical assistance (0.418 €/min) and physicians (0.574 €/min) were adjusted to the median total exam time and administration time as outlined above.

Table 2
Expenses for the sonography unit

Facility expenses[#]	**Euro/m^2/year**	**Euro/room[#]/year**
Facility fee	67.8	10,712.4
Facility services	62.76	9,916.08
Energy supply	4.98	786.84
Water supply	3.68	581.44
Consumable expenses	**Amount/exam**	**Euro/exam**
Paper cover (n)	1	0.08
Paper towels (n)	6	0.08
Desinfection towel (n)	1	0.05
Sonography gel (g)	4.9 g	0.01
Disposable gloves (n)	(2)	0.07
Print out (Paper/Toner) (n)	1	0.01
Fixed costs	**Amount**	**Cost (Euro)**
Computer[§]	1	625.94
Printer hardware	1	143.72
Administration workplace license	1/year	1904
Viewpoint workplace license	1/year	500

[#]Facility expenses were calculated on basis of the sonography room (15.8 m^2). Consumable spendings and IT-support costs were derived from the institutional listed prices. [§]Including operating system software license.

Full costs calculation for HCC screening eventually resulted in a total of 22.82 €/exam (Table 3). A capacity utilization of 75% was applied for the diagnostic sonography unit, as our institution runs two

additional work places, used as back up for diagnostic or interventional sonographies. The capacity utilization grade was applied to correct for fixed costs, whereas consumable costs and personnel costs were purely based on exam numbers. A yearly interest rate was applied to account for general price increases as well as personnel expenses. The approximated yearly inflation rates were obtained from the German federal office for statistics survey [12].

Table 3
Full cost calculation for a single liver sonography (75% capacity utilization)

	Costs per exam					
	2018	**2019**	**2020**	**2021**	**2022**	**Factor**
Consumables costs						
Paper cover	0.080	0.081	0.082	0.082	0.083	1.01
Paper towels	0.080	0.081	0.082	0.082	0.083	1.01
Desinfection towel	0.050	0.051	0.051	0.052	0.052	1.01
Sonography gel	0.010	0.010	0.010	0.010	0.010	1.01
Disposable gloves	0.070	0.071	0.071	0.072	0.073	1.01
Print out (Paper/Toner)	0.010	0.010	0.010	0.010	0.010	1.01
Fixed costs						
Sonography instrument	3.755	3.755	3.755	3.755	3.755	1.00
Instrument Service	0.747	0.747	0.747	0.747	0.747	1.00
Computer hardware	0.134	0.000	0.000	0.000	0.000	1.00
Printer hardware	0.031	0.000	0.000	0.000	0.000	1.00
SAP workplace license	0.406	0.406	0.406	0.406	0.406	1.00
Viewpoint workplace license	0.107	0.107	0.107	0.107	0.107	1.00
Facility fee	2.285	2.308	2.331	2.355	2.378	1.01
Facility services	2.115	2.137	2.158	2.180	2.201	1.01
Energy supply	0.168	0.171	0.175	0.178	0.182	1.02
Water supply	0.124	0.125	0.127	0.128	0.129	1.01
Personnel costs						
Administration (out-patient clinic)	0.209	0.213	0.218	0.222	0.226	1.02
Administration (endoscopy ward)	0.137	0.140	0.142	0.145	0.148	1.02
Procedure (medical staff)	7.116	7.258	7.404	7.552	7.703	1.02
Procedure (assistent staff)	5.187	5.291	5.397	5.505	5.615	1.02
Total costs	**22.820**	**22.961**	**23.271**	**23.587**	**23.908**	

Costs per exam
Full cost pricing of diagnostic liver sonographies was based on a total median exam time of 12.4 minutes as identified for liver sonography. The full costs were calculated on basis of n = 6250 sonographies per year at a capacity utilization of 75%. Factor, inflation rate.

Opportunistic expenses for sonographic HCC screening

Opportunistic costs result from patients lost income and lost productivity during HCC screening. The income calculation is based on the assumption, that cHB patients are typically fully integrated in the employment market. This particularly holds true for cHB patients without disease activity and no impairment of liver function, as observed in our cohort (Table 1).

German federal office income statistics were applied and adjusted to the median age of male patients (32.7 years, IQR 31.1–35.2 years) and female patients (49.9 years, IQR 38.9–56.4 years) from the cHB cohort [13]. According to available data (year 2014) an average gross income of 19.13 €/hour for men and 17.08 €/hour for women was extrapolated. The resulting income loss was 17.5 €/exam for male patients and 15.6 €/exam for female patients for the year of assessment. Finally, German unemployment rates of 4.1% for men and 3.3% for women as well as an annual wage increase of 2% were taken into account (Table 4).

Table 4
Opportunistic wage expenses by patient involvement

PAGE-B eligible cHB cohort (PAGE-B score ≤ 9 points)					
	2018	**2019**	**2020**	**2021**	**2022**
Patients (n)	**94**	**91**	**87**	**83**	**81**
Male patients (n)	27	27	25	25	23
Employed male patients (n)	26	26	25	25	23
Average gross income / hour	19.1	19.5	19.9	20.3	20.7
Average gross income / minute	0.32	0.33	0.33	0.34	0.35
including ancillary labor costs/ minute	0.39	0.40	0.40	0.41	0.42
Opportunistic wage expenses / exam	17.5	17.9	18.2	18.6	18.9
Total costs (male patients)	*453.1*	*462.2*	*435.0*	*443.7*	*414.7*
Female patients (n)	67	64	62	58	58
Employed female patients (n)	65	62	60	56	56
Average gross income / hour	17.1	17.4	17.8	18.1	18.5
Average gross income / minute	0.28	0.29	0.30	0.30	0.31
including ancillary labor costs/ minute	0.35	0.35	0.36	0.37	0.38
Opportunistic wage expenses / exam	15.6	15.9	16.3	16.6	16.9
Total costs (female patients)	*1012.6*	*985.0*	*972.2*	*925.3*	*943.8*
Total costs	**1465.7**	**1447.2**	**1407.2**	**1369.0**	**1358.5**

Opportunistic, age and gender adjusted costs of sonographic HCC screening during a median turnaround time of 45 minutes in PAGE-B eligible cHB patients with low HCC risk. All patients attended the infectious and liver disease out-patient clinic during the year 2018. Unemployment rates of 4.1% for men and 3.3% for women were considered. An annual income increase of 2% was applied.

Gross domestic product (GDP) per working hour was also considered, as wages do not directly reflect overall productivity. Therefore, the average GDP of 35.56 €/hour, from the year 2017, was adjusted to the total turnaround time (45 min), resulting in a GDP loss of 26.7 €/ exam [14].

Cost reduction by PAGE-B score adapted HCC screening

The annual cost reduction at our institution was calculated on the basis of the expenses for liver sonography and the number of cHB patients with a low risk PAGE-B score (≤ 9 points) receiving NA treatment. This assessment led to a cost reduction of 2,145 € for HCC screening during the year 2018

(Table 5). Given that only age is a time dependent variable of the PAGE-B score, whereas gender and thrombocyte count remaining unchanged, we extrapolated the number of annual HCC screens until a PAGE-B score of 10 points was reached. Based on these assumptions a median of n = 12 (IQR 6–12) postponed sonographies per person was calculated for our cohort, which makes a total of n = 1410 sonography screenings in total. A more restrictive calculation for a maximum 5-year follow-up, identified a total of n = 436 postponed HCC screenings. This resulted in a total cost reduction of 10,488 € for a 5-year period (Table 5).

Table 5
Annual cost reduction for PAGE-B tailored liver sonography

	Total costs reduction for cHB patients (PAGE-B score ≤ 9 points)					
	2018	**2019**	**2020**	**2021**	**2022**	**Factor**
Patients (n)	94	91	87	83	81	
Consumables costs						
Paper cover	7.52	7.37	7.13	6.81	6.72	1.01
Paper towels	7.52	7.37	7.13	6.81	6.72	1.01
Desinfection towel	4.70	4.64	4.44	4.32	4.21	1.01
Sonography gel	0.94	0.91	0.87	0.83	0.81	1.01
Disposable gloves	6.58	6.46	6.18	5.98	5.91	1.01
Print out (Paper/Toner)	0.94	0.91	0.87	0.83	0.81	1.01
Fixed costs						
Sonography instrument	352.94	352.94	352.94	352.94	352.94	1.00
Instrument Service	70.19	70.19	70.19	70.19	70.19	1.00
Computer hardware	12.55	0.00	0.00	0.00	0.00	1.00
Printer hardware	2.88	0.00	0.00	0.00	0.00	1.00
SAP workplace license	38.18	38.18	38.18	38.18	38.18	1.00
Viewpoint workplace license	10.03	10.03	10.03	10.03	10.03	1.00
Facility fee	214.82	216.97	219.14	221.33	223.54	1.01
Facility services	198.85	200.84	202.85	204.88	206.93	1.01
Energy supply	15.78	16.09	16.42	16.75	17.08	1.02
Water supply	11.66	11.78	11.89	12.01	12.13	1.01
Personnel costs						
Administration						
out-patient clinic	19.65	19.38	18.97	18.43	18.31	1.02
endoscopy ward	12.88	12.74	12.35	12.04	11.99	1.02
Diagnostic procedure						
medical staff	668.90	660.48	644.15	626.82	623.94	1.02

	Total costs reduction for cHB patients (PAGE-B score ≤ 9 points)					
assistant staff	487.58	481.48	469.54	456.92	454.82	1.02
Total costs	**2,145.08**	**2,118.76**	**2,093.26**	**2,066.05**	**2,065.26**	

Annual full cost pricing was based on a total median exam time of 12.4 minutes as identified for liver sonography a capacity utilization of 75%. The full costs were calculated on the basis of patients, who did not require sonography HCC screening according to a low PAGE-B risk score of ≤ 9 points. Factor, inflation rate.

Nationwide cost reduction by PAGE-B adapted HCC screening was derived from population-based source data (**additional** Table 2), reporting cHB prevalence rates of 0.3% up to 0.7% in Germany [15–18]. Treatment criteria according to management guidelines were considered, as only patients under second-generation NA therapy are eligible for PAGE-B scoring [3]. Due to the limited population-based data on cHB and liver fibrosis in Germany, only a relevant HBV viral load (> 2000 IU/ml) in 14.7% and an elevated ALT activity in 43.8–59.4% were considered among HBsAg-positive patients [16, 19]. These data resulted in an estimated number of 15,493 (6.4%) up to 49,026 (8.7%) HBsAg-positive patients with antiviral therapy indication in Germany [16, 19]. Corresponding annual NA therapy costs for a total of 7,475,132 treatment days resulted in coherent patient numbers (n = 20,480) in Germany [20]. Eventually the proportion of a low risk PAGE-B score (≤ 9 points) was derived from two trials and from our cHB population, resulting in 24.7% [8], 38.6% [9] and 44.1% (Table 1), respectively. This range eventually results in a total number of 3,827–21,620 NA treated cHB patients with low HCC risk in Germany.

The estimated population-based costs reduction for HCC screening in Germany was 185,830–1,049,815 € per year, based on the full costs for liver sonography and the loss of GDP (Table 6). Extrapolation for a 5-year period, which covers an average of 4.63 postponed sonographies per patient, resulted in a cost reduction (incl. GDP) of 861,934 up to 4,869,346 € for the German population.

Table 6
Screening costs for hepatitis B patients (PAGE-B ≤ 9 pts.) in Germany

Sonography costs (Euro)	**N_{min}**	**N_{max}**	**Costs/Exam**	**$Cost_{min}$**	**$Cost_{max}$**
	3,827	21,620	22.8	87,257	492,936
Opportunistic wage costs (Euro)	**N_{min}**	**N_{max}**	**Costs/Exam**	**$Cost_{min}$**	**$Cost_{max}$**
Male patients (28.7%)	1,098	6,205	—	—	—
Female patients (71.3%)	2,729	15,415	—	—	—
Employed male patients (-4.1%)	1,053	5,951	17.5	18,433	104,134
Employed female patients (-3.3%)	2,639	14,906	15.6	41,162	232,539
Total wage costs	—	—	—	59,595	336,674
Sonography costs incl. wage loss	**—**	**—**	**—**	**146,851**	**829,610**
Opportunistic GDP loss (Euro)	**N_{min}**	**N_{max}**	**Costs/Exam**	**$Cost_{min}$**	**$Cost_{max}$**
Employed male patients (-4.1%)	1,053	5,951	26.7	28,124	158,879
Employed female patients (-3.3%)	2,639	14,906	26.7	70,451	398,000
Total GDP loss				98,574	556,879
Sonography costs incl. GDP loss	**—**	**—**	**—**	**185,830**	**1,049,815**

Full cost pricing for liver sonography was based on the median total exam time (12.4 minutes). Opportunistic costs for diagnostic sonography was based on the median turnaround time (45 minutes). The total costs were calculated on basis of the estimated cHB prevalence in Germany with antiviral treatment indication (n = 15,493 – 49,026), which was adjusted by the rate of patients (24.7%-44.1%) with a PAGE-B score ≤ 9 points. Wage costs and gross domestic productivity (GDP) were also adjusted by the unemployment rates of 4.1% for men and 3.3% for women. Pts., points.

Discussion

The PAGE-B score was successfully introduced to tailor HCC surveillance in our cHB patient cohort. This included cautious selection of cHB monoinfected patients receiving NA therapy for one year, who are eligible to apply the PAGE-B score. The low risk subgroup defined by the PAGE-B score ≤ 9 points hereby showed no residual HCC risk, as previously identified by different clinical trials [8, 9]. Following this approach at our institution the PAGE-B score reduced annual sonography unit costs by 15.51% for HCC screening of cHB patients. This equals a cost reduction of 1.91% for our annual sonography expenses. In comparison, population-based estimates suggested to postpone HCC screening in 1.59% up to 3.85% of cHB patients in Germany. Given that our referral center for liver diseases reached a high NA therapy uptake of 97% (n = 258/266) in cHB patients, the general rate of PAGE-B eligible cHB patients receiving

NA treatment could be comparably lower. Particularly, as European and American trials have reported an average NA treatment uptake of only 41% in cHB patients with therapy indication [21].

The presented full cost calculation identified lower expenses for diagnostic sonography compared to published costs of 31.43–51.47 € per exam [22]. These differences result from a shorter exam time (12.4 min) quantified at our institution, compared to the exam time (~ 20 min) assumed by the other authors [23, 24]. A time-related effect particularly holds true, as full costs for diagnostic sonography adjusted to 20 min were 37.18 € per exam, which was in line with a resent German cost calculation [22]. However, the exam time of previous studies was either derived from a limited number of sonographies (n = 30) [24] or was assessed by a practitioner questionnaire, which did not include any standardized time acquisition [23]. Therefore, robust data are provided by the presented approach, which employed a reliable time tracking system during the project, avoiding any time lag between the monitored activity and documentation. More so, the study focused on HCC screening in the ambulatory setting, which potentially reduced the average exam time, as shorter exam times for out-patients (18.9 min) compared to hospitalized patients (21.7 min) were observed during sonography [23].

The presented consumable costs were based on a published cost point composition, which covers all aspects of sonography screening [22]. Our assumptions did not include variable instrument expenses between 50,000 € and 125,000 €, depending on the configuration of ultrasonography unit. Instrument expenses may therefore alter costs for a single liver ultrasound to 21.22 € (-7.02%) and 24.45 € (+ 7.15%). Marginal differences compared to published full cost calculations were also observed for the personnel costs, as medical training at our institution has some effect on personnel related expenses. Despite these observational limitations we provide a precise cost assessment, which is in line with previous cost calculations and could be generalized for the HCC screening in Germany.

The total population-based costs for sonographic HCC screening were based on the full costs for liver sonography and productivity loss in patients. Estimates of lost productivity (GDP) (26.7 €/exam) or lost earnings (15.6–17.5 €/exam) hereby dependent on the cross section of the analyzed population [25, 26]. Current German population surveys and census were applied for this project, which do not entirely represent the composition of cHB patients [13, 27]. Hence, data were adjusted for age and gender, as younger female patients assigned to low PAGE-B risk group have a lower income and productivity compared to the average population [13, 14]. Due to limited data, the rate of foreign cHB patients for example and their specific human capital could not be considered. A microcensus showed that among households with a low income (< 500 €/ month) the rate of persons with migration background is 66.2% for example [28]. Given that an immigration status was present in 35.6 up to 60% of HBsAg-positive persons, this has some impact on the estimated human income loss [16, 19].

Conclusions

Following our analyses, we conclude that PAGE-B risk score adapted HCC screening of cHB patients is efficient to reduce costs. Particularly, automated calculation of the PAGE-B score and its readily available

components make it a nearly cost neutral tool to reduce sonography expenses. PAGE-B score-based screening allocation to patients deserving HCC surveillance also protects limited personnel resources. Tailored screening could, therefore, focus on high risk populations, still facing suboptimal uptake of HCC surveillance of 28–65% [29, 30]. Resource sparing risk assessment therefore combines cost reduction as well improvement of healthcare allocation, particularly in context of personnel intensive HCC surveillance.

Abbreviations

cHB chronic hepatitis B

HCC hepatocellular carcinoma

NA nucleos(t)ide analogues

PAGE-B platelet-age-gender–HBV risk score

HBsAg HBs-antigen

ETV Entecavir

TDF Tenofovir disoproxil fumarate

TAF Tenofovir alafenamid fumarate

n number

€ Euro

IQR interquartile range

ALT alanine aminotransferase

AST aspartate aminotransferase

g gram

kPa kiloPascal

U units

l liter

ml milliliter

min minute

GDP gross domestic productivity

Declarations

Ethics approval statement and consent to participate:

The trial was conducted according to the principles of the Declaration of Helsinki. Approval was provided by the local ethic committee (Landesärztekammer, Rhineland-Palatinate, Germany, file number 2019-14206) and data safety officer. A waiver for patient consent was provided by the ethics committee as outlined above.

Consent for Publication: Not applicable

Availability of data The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Competing interest: The authors declare no financial and non-financial conflict of interest regarding the content of this manuscript.

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Authors' contributions MFS: study concept, data analysis, writing the manuscript

CF, WMK: sonographic data acquisition

SK, AW: data management, clinical data acquisition

KJL and PRG: study approval, manuscript revision

All authors have read and approved the manuscript.

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