Delivery of biannual ultrasound surveillance for individuals with cirrhosis and cured hepatitis C in the UK

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Figure S1. Breakdown of study cohort by geographic region (N=1908)

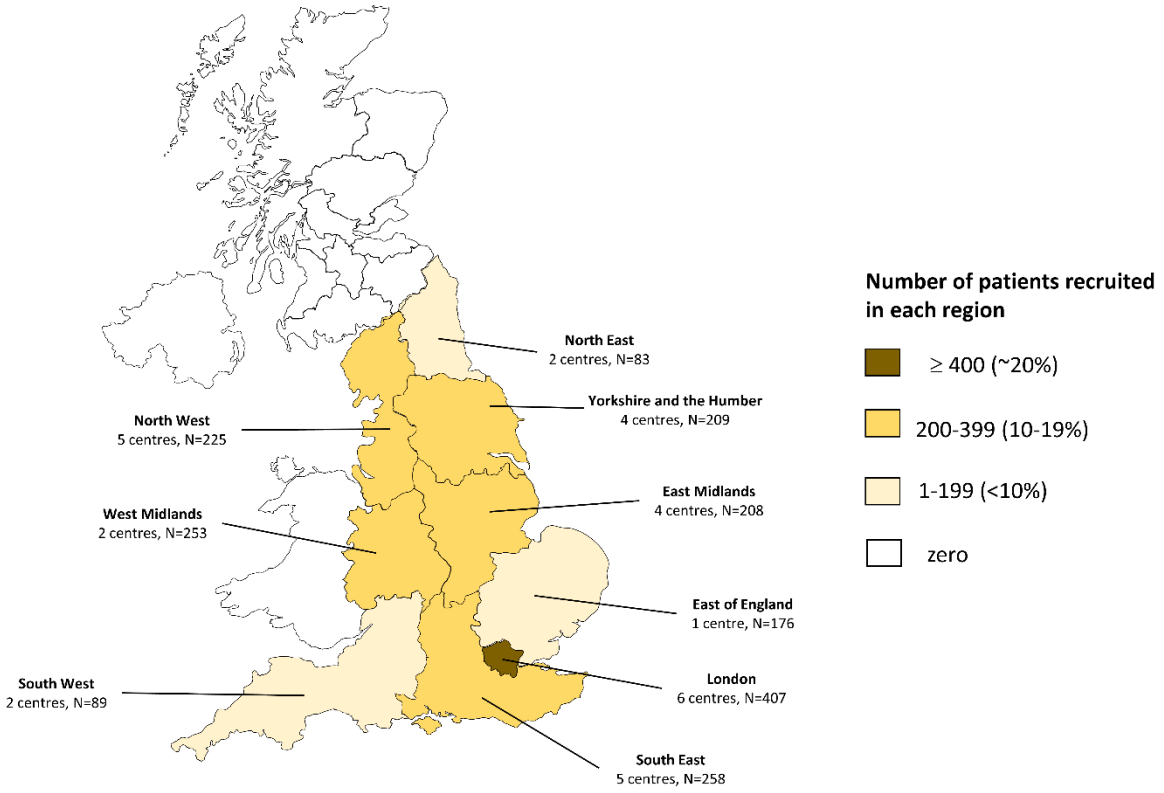


Figure S2. Proportion of cohort with biannual ultrasound uptake in sensitivity analyses.

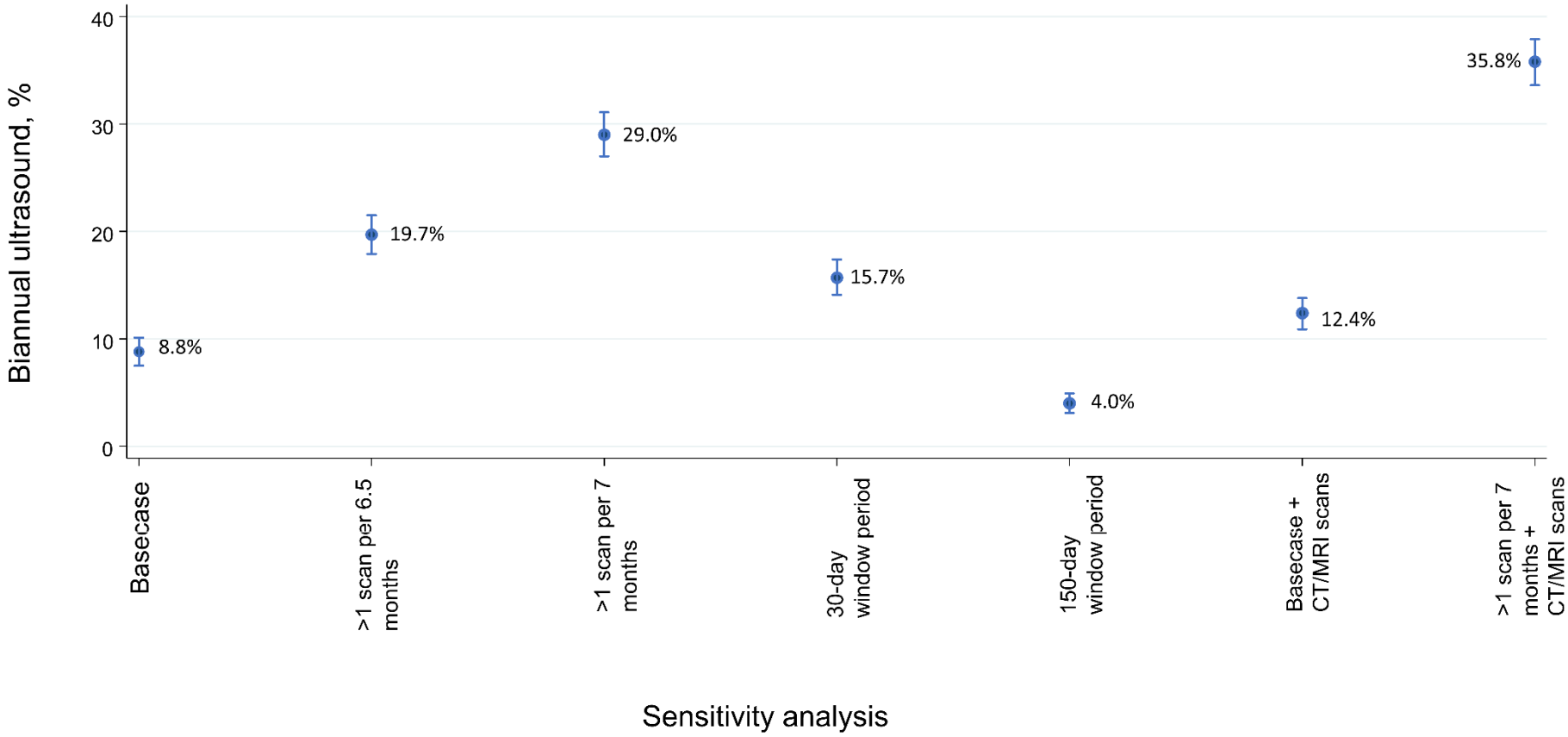
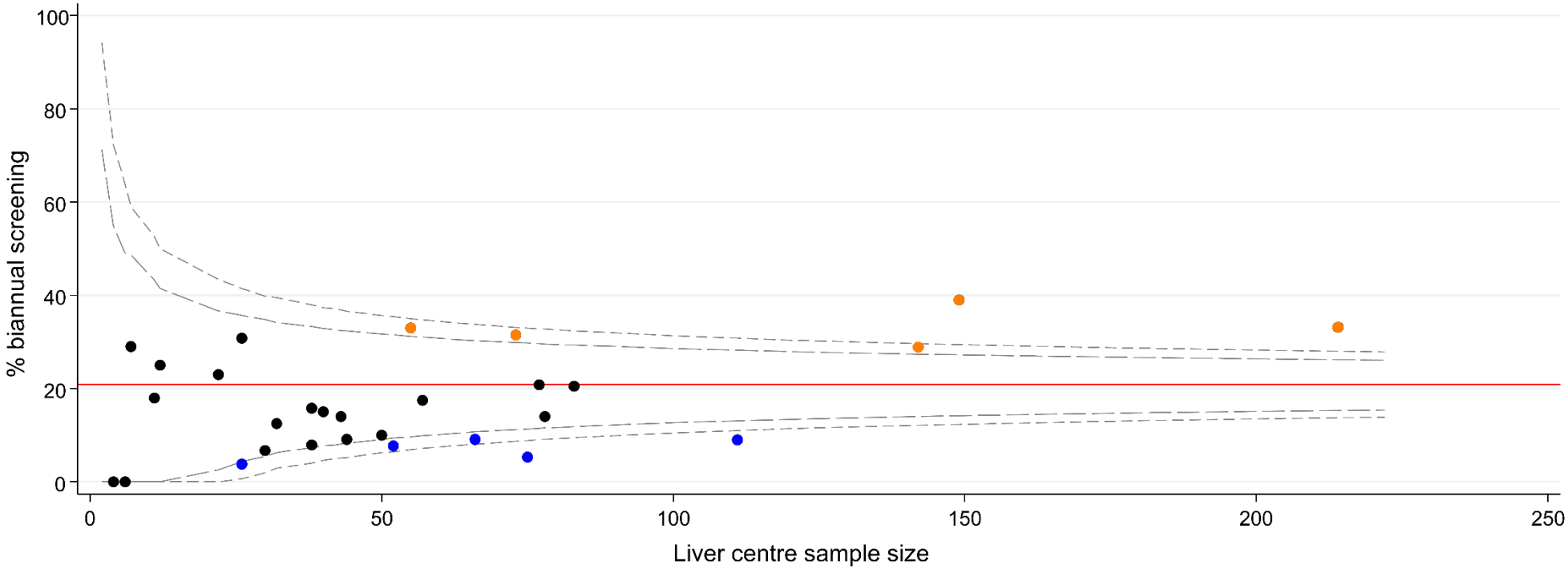


Figure S3. Funnel plots indicating the proportion of patients receiving biannual surveillance in the first 3 years after SVR, by liver centre.



Liver centres are represented by circular data points. Blue data points represents centres with atypically low uptake, given their sample size. Orange data points represents centres with atypically high uptake, given their sample size. The red horizontal line is the average uptake for all the data points represented in the plot. The grey dashed line refers to the 95% and 99% control limits, calculated using the exact method. Data points for two centres (centre “S” and “K”) were omitted from this plot. Please see appendix A for further details.

Figure S4. Time interval between consecutive ultrasound events

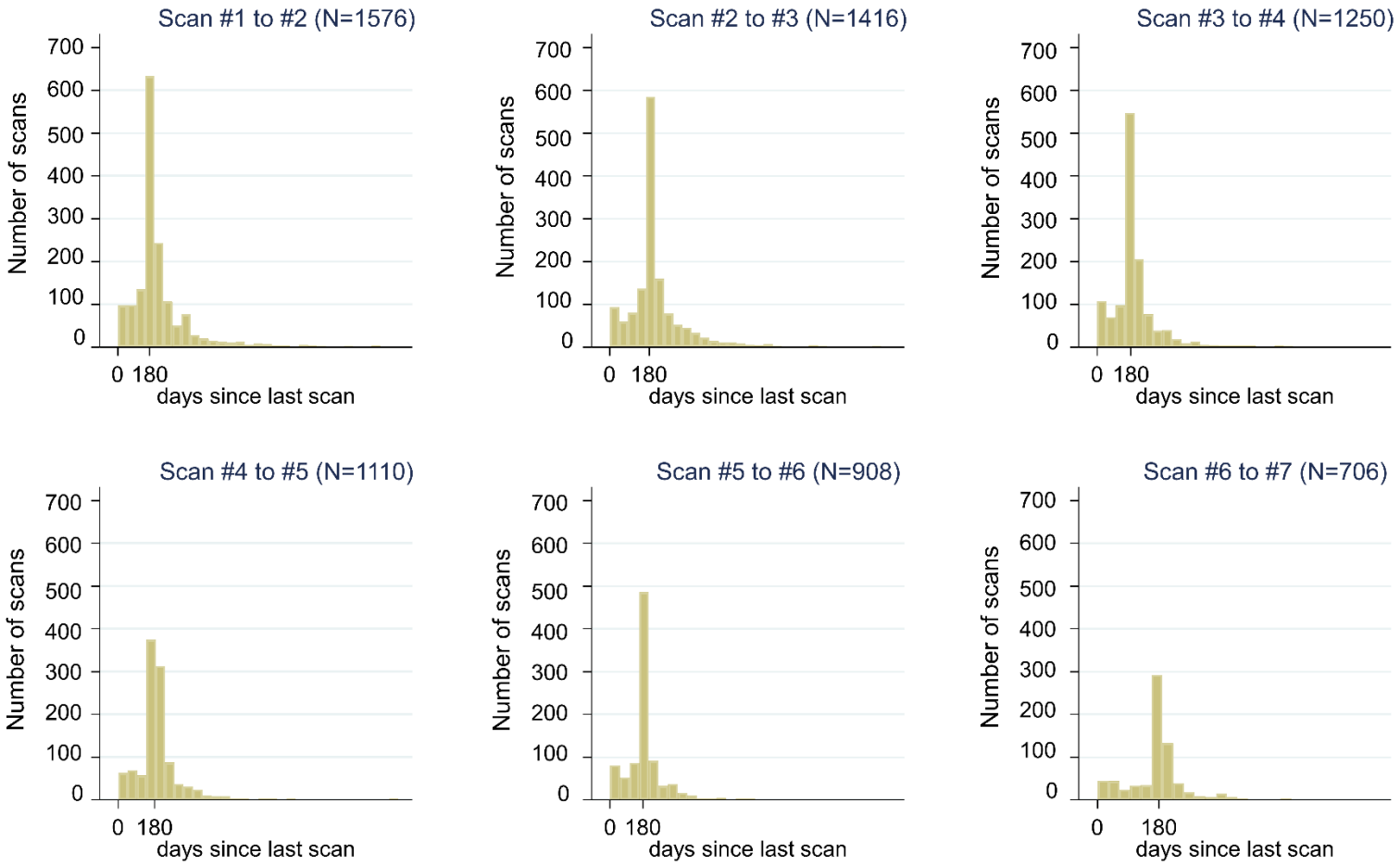


Figure S5. Imaging procedures in relation to time since HCC diagnosis

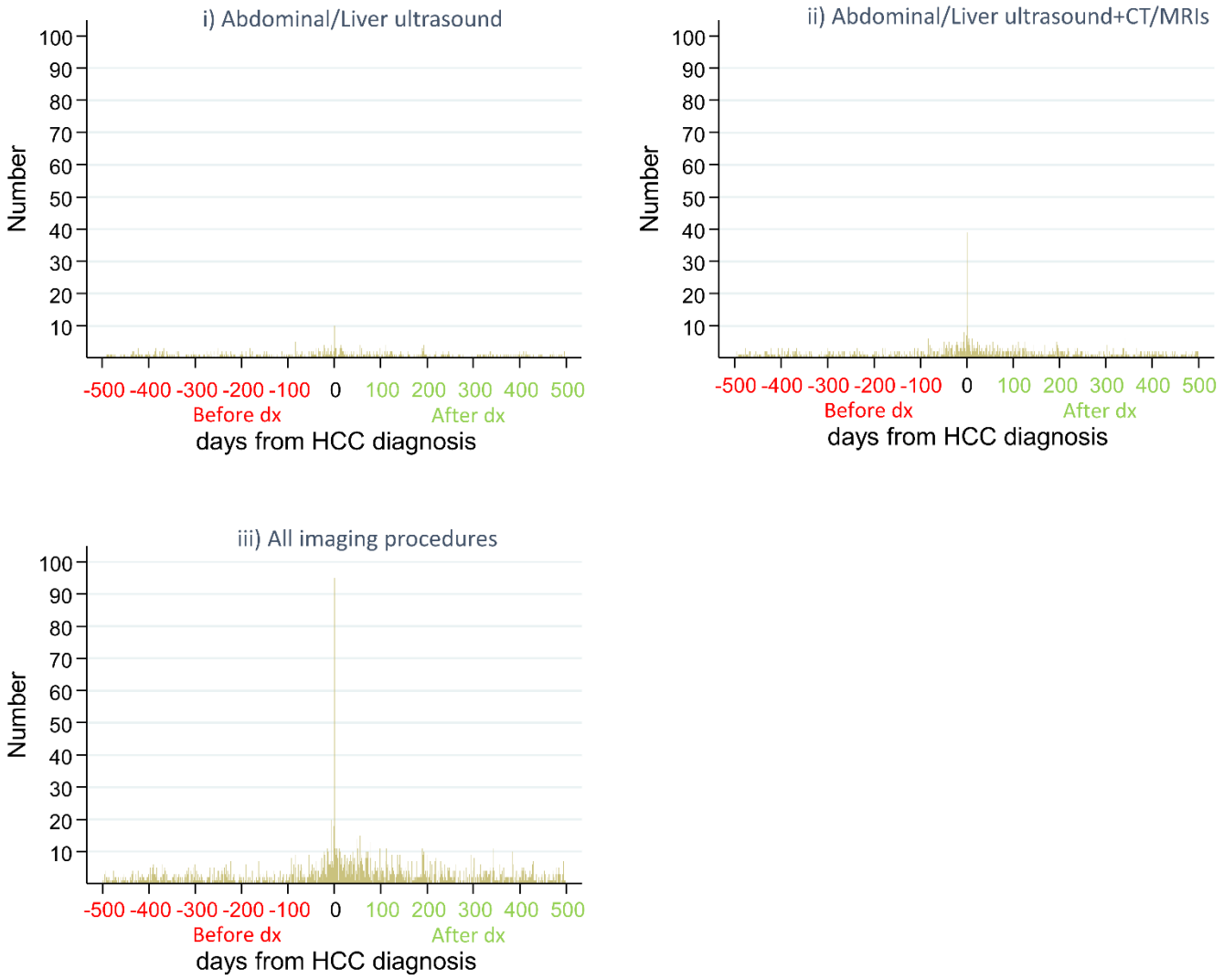
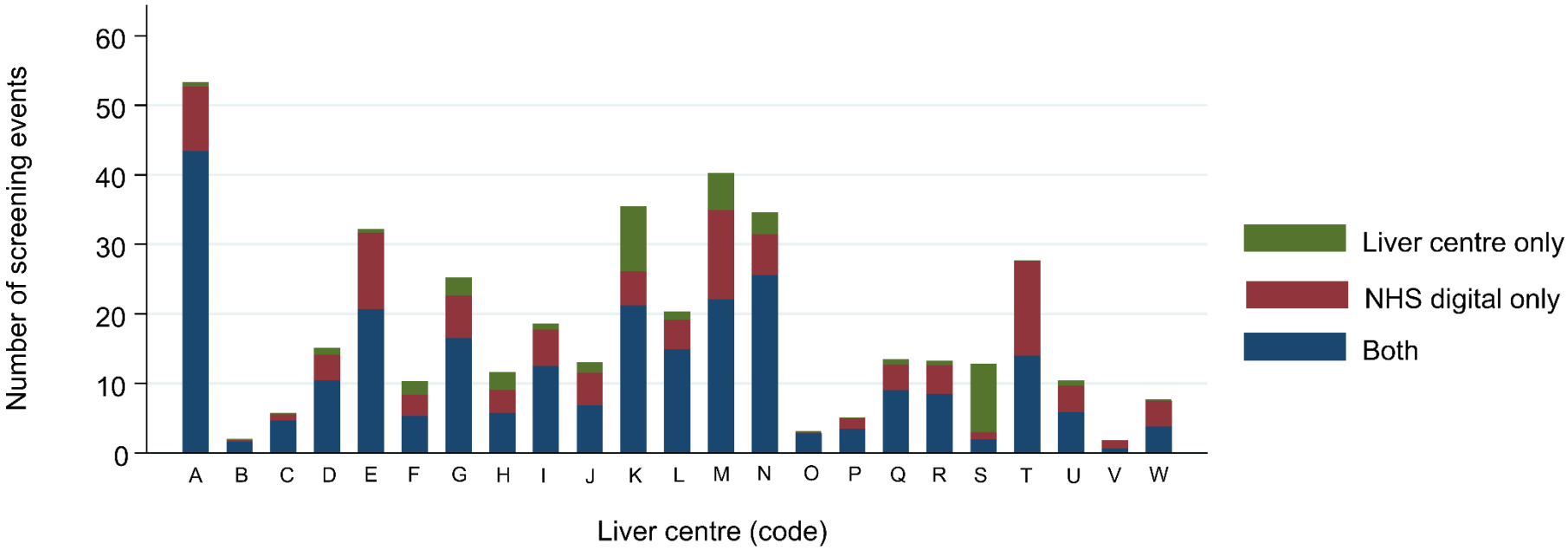
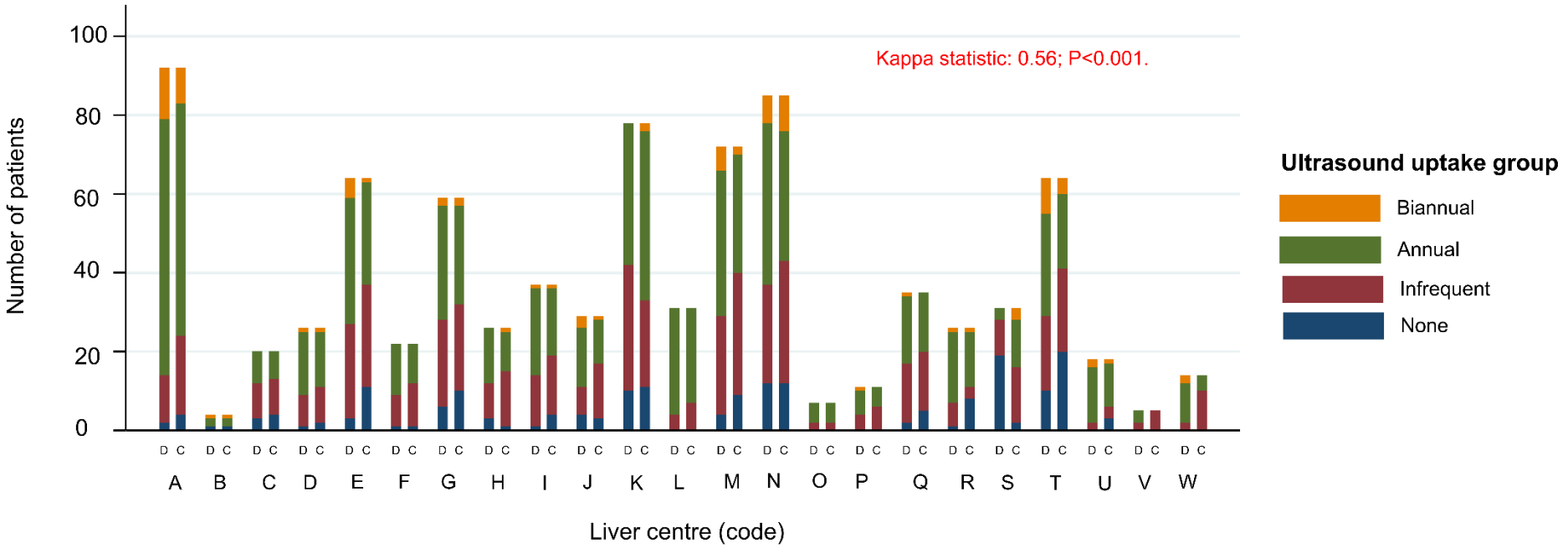


Figure S6. Source of ultrasound events, by liver centre.



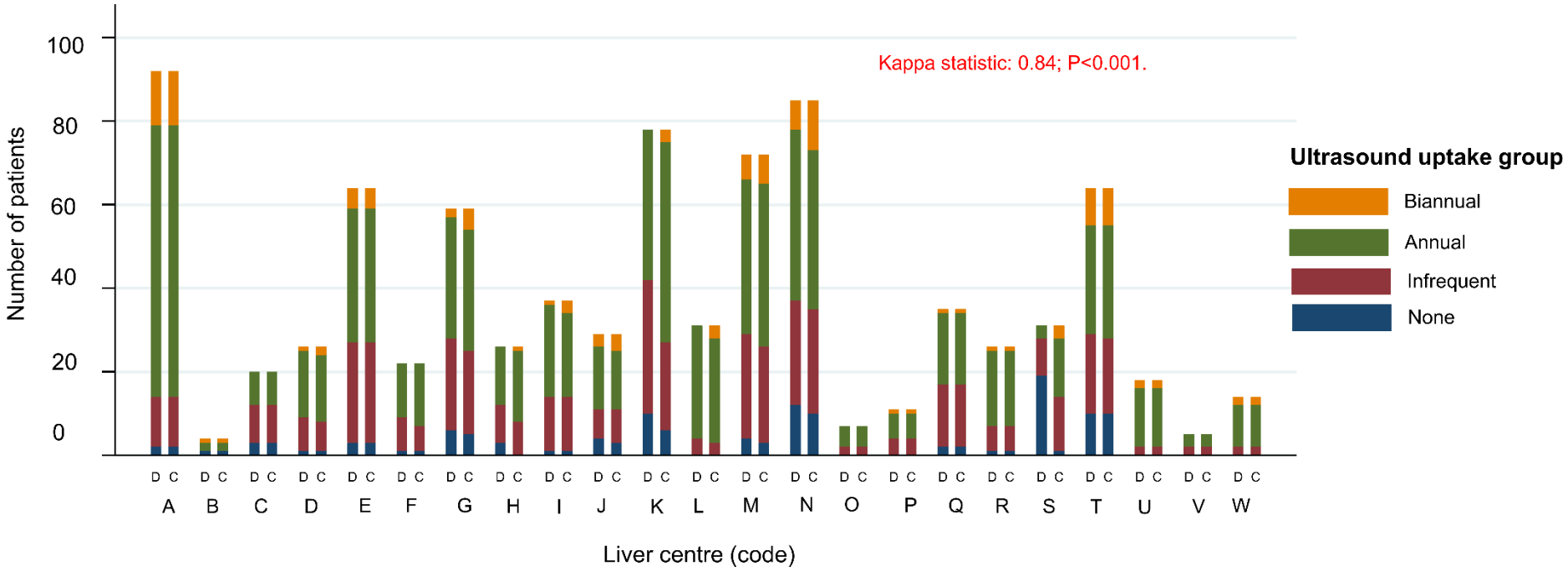
Data applies to validation subgroup only (n=856)

Figure S7. Agreement in ultrasound uptake group between NHS digital (D) versus liver centre (C) data.



Data applies to validation subgroup only (n=856). Higher values of the Kappa statistic indicate better agreement: a value of <0.4. 0.4-0.7 and >0.7 are typically interpreted as poor, moderate and good agreement, respectively

Figure S8. Agreement in ultrasound uptake group between NHS digital (D) versus amalgamation of liver centre and NHSD data (C).



Data applies to validation subgroup only (n=856). Higher values of the Kappa statistic indicate better agreement: a value of <0.4. 0.4-0.7 and >0.7 are typically interpreted as poor, moderate and good agreement, respectively

Table S1. ICD and OPCS4 codes used to defined relevant outcome events and exposure variables

Outcome	Registry	Code type	Code	Code description
Abdominal/liver ultrasound	Diagnostic imaging dataset	Snomed CT	431362005	Doppler ultrasonography of liver and portal system
			105377009	US scan of liver
			45036003	Ultrasonography of abdomen
			444900008	Ultrasonography of abdomen with contrast
			105377009	Ultrasonography of liver
			443630007	ultrasonography of liver with contrast
			9.90271E+14	ultrasonography surveillance of liver for hepatocellular carcinoma
	HES outpatient dataset	OPCS4	U082	Ultrasound of abdomen
HCC diagnosis	HES admitted patient care; mortality register; cancer register	ICD 10	C22.0	Liver cell carcinoma
Liver transplantation	HES admitted patient care	OPCS4	J01	Transplantation of liver
Curative HCC treatment	HES admitted patient care dataset	OPCS4	J124	Percutaneous radiofrequency ablation of lesion of liver
			J01	Transplantation of liver
			J127	Percutaneous microwave ablation of lesion of liver
			J023	Resection of segment of liver
			J033	Thermal ablation of single lesion of liver
			J021	Right hemihepatectomy NEC
			J024	Wedge excision of liver
			J125	Percutaneous thermal ablation of lesion of liver NEC
			J031	Excision of lesion of liver NEC
			J083	Endoscopic microwave ablation of lesion of liver using laparascope
			Y114*	Radiofrequency controlled thermal destruction of organ NOC
			Y084*	Laser destruction of lesion of organ NOC
			J034	Thermal ablation of multiple lesions of liver
			J022	Left hemihepatectomy NEC
			J032	Destruction of lesion of liver NEC
			J028	Other specified partial excision of liver
			J027	Extended left hemihepatectomy
Alcohol-related hospital admission	HES admitted patient care dataset	ICD 10	E24.4	Alcohol induced pseudo cushing's syndrome
			E51.2	Wernicke's encephalopathy
			F10	Mental and behavioural disorders due to use of alcohol
			G31.2	degeneration of nervous system due to alcohol
			G62.1	Alcoholic polyneuropathy
			G72.1	Alcoholic myopathy
			I42.6	Alcoholic cardiomyopathy
			K29.2	alcoholic gastritis
			K86.0	Alcohol induced chronic pancreatitis
			P04.3	fetus and newborn affected by maternal use of alcohol
			Q86.0	fetal alcohol syndrome
			R78.0	excessive blood level of alcohol
			T51.0	Toxic effect of alcohol
			X45, X65, Y15	alcohol poisoning
			Y90	high blood alcohol level
			Y91	evidence of alcohol involvement determined by level intoxication
Drug-related hospital admission	HES admitted patient care dataset	ICD 10	F11-F19	mental and behavioural disorders due to psychoactive substance use
			T40	poisoning by narcotics and psychodysleptic

Table S1 continued

Abdominal/liver MRI or CT	Diagnostic imaging	Snomed CT	169070004	CT of abdomen
			183881000000104	CT of abdomen and pelvis
			183971000000109	CT of chest and abdomen
			183981000000106	CT of chest, abdomen and pelvis
			241549007	CT of liver
			183991000000108	CT of neck, thorax, abdomen and pelvis
			438305004	Computed tomography dual phase study of liver (procedure)
			356261000000101	Computed tomography dual phase study of liver (procedure) (356261000000101)
			438305004	Computed tomography dual phase study of liver (procedure) (438305004)
			1110571000000110	Computed tomography four phase scan of liver with contrast (procedure)
			1110571000000110	Computed tomography four phase scan of liver with contrast (procedure) (1110571000000107)
			169070004	Computed tomography of abdomen (procedure)
			169070004	Computed tomography of abdomen (procedure) (169070004)
			419394006	Computed tomography of abdomen and pelvis (procedure)
			419394006	Computed tomography of abdomen and pelvis (procedure) (419394006)
			432370003	Computed tomography of abdomen and pelvis with contrast (procedure)
			432370003	Computed tomography of abdomen and pelvis with contrast (procedure) (432370003)
			418891003	Computed tomography of chest and abdomen (procedure)
			418891003	Computed tomography of chest and abdomen (procedure) (418891003)
			418023006	Computed tomography of chest, abdomen and pelvis (procedure)
			418023006	Computed tomography of chest, abdomen and pelvis (procedure) (418023006)
			440331001	Computed tomography of head, neck, thorax, abdomen and pelvis (procedure)
			440331001	Computed tomography of head, neck, thorax, abdomen and pelvis (procedure) (440331001)
			444630003	Computed tomography of head, neck, thorax, abdomen and pelvis with contrast (procedure)
			444630003	Computed tomography of head, neck, thorax, abdomen and pelvis with contrast (procedure) (444630003)
			241549007	Computed tomography of liver (procedure)
			241549007	Computed tomography of liver (procedure) (241549007)
			432905004	Computed tomography of liver and portal vein (procedure)
			429862006	Computed tomography of liver with contrast (procedure)
			429862006	Computed tomography of liver with contrast (procedure) (429862006)
			430439002	Computed tomography of neck, thorax and abdomen (procedure)
			433270008	Computed tomography of neck, thorax and abdomen with contrast (procedure)
			434438003	Computed tomography of neck, thorax, abdomen and pelvis with contrast (procedure)
			434438003	Computed tomography of neck, thorax, abdomen and pelvis with contrast (procedure) (434438003)
			429864007	Computed tomography of thorax and abdomen with contrast (procedure)
			429864007	Computed tomography of thorax and abdomen with contrast (procedure) (429864007)
			433761009	Computed tomography of thorax, abdomen and pelvis with contrast (procedure)
			433761009	Computed tomography of thorax, abdomen and pelvis with contrast (procedure) (433761009)
			912331000000104	Computed tomography triple phase study of abdomen and pelvis with contrast (procedure)
			438591004	Computed tomography triple phase study of liver (procedure)
			438591004	Computed tomography triple phase study of liver (procedure) (438591004)
			910561000000103	Diffusion weighted magnetic resonance imaging of liver (procedure)
			241621009	MRI of abdomen
			241622002	MRI of liver
			241621009	Magnetic resonance imaging of abdomen (procedure)
			241621009	Magnetic resonance imaging of abdomen (procedure) (241621009)
			432369004	Magnetic resonance imaging of abdomen with contrast (procedure)
			432369004	Magnetic resonance imaging of abdomen with contrast (procedure) (432369004)
			241622002	Magnetic resonance imaging of liver (procedure)
			241622002	Magnetic resonance imaging of liver (procedure) (241622002)
			432633002	Magnetic resonance imaging of liver and biliary tract with contrast (procedure)
			432633002	Magnetic resonance imaging of liver and biliary tract with contrast (procedure) (432633002)
			432551009	Magnetic resonance imaging of liver and spleen (procedure)
			432551009	Magnetic resonance imaging of liver and spleen (procedure) (432551009)
			431839003	Magnetic resonance imaging of liver with contrast (procedure)
			431839003	Magnetic resonance imaging of liver with contrast (procedure) (431839003)
			1099161000000110	Single photon emission computed tomography with computed tomography hepatobiliary study (procedure)
			443638000	Single photon emission computed tomography with computed tomography of liver and spleen (procedure)
			859191000000107	Single photon emission computed tomography with computed tomography of liver using technetium 99m macroaggregated albumin (procedure)
	HES outpatient dataset	OPCS4	U081	Computed tomography of abdomen
			U085	Magnetic resonance imaging of abdomen

At the time of analysis, all data registries were complete until 31st March 2020, with the exception of the mortality register which was complete until 31st March 2021. N.B. codes listed with an asterix are not specific to HCC, and thus were only included if present in combination with an ICD code for C22.0 (liver cell carcinoma).

Table S2. Factors associated with biannual screening uptake in base case and sensitivity analyses

Characteristic		Base case (1 scan per 6 months)		Sensitivity analysis 1 (30 day window period)		Sensitivity analysis 2 (150 day window period)		Sensitivity analysis 3 (1 scan per 6.5 months)		Sensitivity analysis 4 (1 scan per 7 months)		Sensitivity analysis 5 (+CT/MRI scans)		Sensitivity analysis 6 (1 scan per 7 months + CT/MRI scans)	
		aOR	P	aOR	P	aOR	P	aOR	P	aOR	P	aOR	P	aOR	P
Age, per 10 year increase		1.41 (1.17-1.71)	<0.001	1.28 (1.10-1.48)	0.01	1.32 (1.02-1.72)	0.04	1.47 (1.28-1.69)	<0.001	1.39 (1.23-1.57)	<0.001	1.32 (1.12-1.55)	0.001	1.44 (1.28-1.61)	<0.001
Gender	Female	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-
	Male	1.08 (0.74-1.57)	0.70	0.83 (0.63-1.11)	0.22	1.66 (0.92-3.03)	0.10	1.13 (0.86-1.49)	0.36	1.06 (0.83-1.35)	0.63	0.98 (0.71-1.35)	0.90	1.11 (0.88-1.49)	0.38
Ethnicity	White	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-
	Non-white	1.09 (0.73-1.64)	0.67	1.09 (0.79-1.50)	0.62	0.93 (0.51-1.71)	0.82	1.26 (0.94-1.69)	0.12	1.26 (0.97-1.64)	0.08	1.30 (0.92-1.85)	0.14	1.47 (1.14-1.90)	0.003
Decompensated cirrhosis	No	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-
	Yes	1.64 (1.10-2.43)	0.02	1.51 (1.10-2.08)	0.01	1.04 (0.57-1.90)	0.90	1.11 (0.82-1.51)	0.50	0.88 (0.67-1.17)	0.38	1.81 (1.29-2.55)	0.001	1.13 (0.87-1.46)	0.001
Alcohol hospital admission	No	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-
	Past	0.51 (0.26-1.00)	0.05	0.58 (0.36-0.95)	0.03	0.76 (0.33-1.77)	0.52	0.61 (0.38-0.96)	0.03	0.54 (0.36-0.80)	0.002	0.68 (0.40-1.16)	0.16	0.53 (0.37-0.76)	0.001
	Recent	0.81 (0.44-1.50)	0.51	1.01 (0.64-1.60)	0.95	0.75 (0.30-1.84)	0.22	1.11 (0.72-1.70)	0.63	0.94 (0.64-1.39)	0.76	0.83 (0.50-1.40)	0.48	0.80 (0.55-1.15)	0.22
Substance misuse hospital admission	No	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-
	Past	1.05 (0.66-1.67)	0.84	1.11 (0.78-1.59)	0.56	0.99 (0.51-1.93)	0.99	0.75 (0.53-1.06)	0.11	0.67 (0.49-0.90)	0.01	0.92 (0.60-1.39)	0.68	0.76 (0.57-1.00)	0.05
	Recent	0.69 (0.42-1.12)	0.13	0.73 (0.51-1.06)	0.10	0.87 (0.45-1.68)	0.67	0.66 (0.47-0.92)	0.02	0.61 (0.45-0.82)	0.001	0.70 (0.46-1.05)	0.08	0.62 (0.47-0.82)	0.001
Follow up at transplant clinic	No	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-	REF (1.00)	-
	Yes	3.41 (2.40-4.83)	<0.001	3.10 (2.38-4.04)	<0.001	4.88 (2.83-8.41)	<0.001	2.97 (2.33-3.78)	<0.001	3.10 (2.51-3.83)	<0.001	2.59 (1.93-3.46)	<0.001	2.79 (2.29-3.42)	<0.001
Follow-up duration, per 1 year increase		0.72 (0.63-0.82)	<0.001	0.81 (0.74-0.90)	<0.001	0.69 (0.57-0.83)	<0.001	0.92 (0.84-1.00)	0.06	0.97 (0.90-1.04)	0.38	0.65 (0.58-0.73)	<0.001	0.92 (0.85-0.99)	0.024

Table S3. Factors associated with biannual screening uptake with adjustment for baseline HCC risk (via aMAP score)

Characteristic		Without aMAP adjustment		With aMAP adjustment	
		aOR	P	aOR	P
Follow up at transplant clinic	**No**	**REF (1.00)**	**-**	**REF (1.00)**	**-**
	Yes	**3.51 (2.48-4.97)**	**<0.001**	**3.61 (2.42-5.39)**	**<0.001**
aMAP risk score		**NA**	**NA**	**1.06 (1.03-1.09)**	**<0.001**
Ethnicity	White	REF (1.00)	-	REF (1.00)	-
	Non-white	0.95 (0.63-1.42)	0.24	0.85 (0.54-1.33)	0.48
Alcohol hospital admission	No	REF (1.00)	-	REF (1.00)	-
	Past	0.51 (0.27-1.00)	0.05	0.42 (0.18-0.96)	0.04
	Recent	0.88 (0.49-1.58)	0.67	0.82 (0.43-1.58)	0.55
Substance misuse hospital admission	No	REF (1.00)	-	REF (1.00)	-
	Past	0.94 (0.59-1.49)	0.79	0.89 (0.52-1.54)	0.68
	Recent	0.65 (0.40-1.05)	0.08	0.56 (0.32-0.97)	0.04
Follow-up duration, per 1 year increase		0.69 (0.60-0.78)	<0.001	0.75 (0.64-0.88)	<0.001

Statisitcally significant associations are highlighted in grey.

N.B. age, gender and decompensated disease are omitted from these models as they are captured through aMAP

N.B. the aMAP score is a proxy for HCC risk. Higher scores indicate a higher risk of HCC

Table S4. Characteristics of study population at baseline for full cohort and validation subgroup

Characteristic		Full cohort (N=1908) n (col %)	Validation subgroup (N=856) n (col %)
baseline			
Age, mean (sd)		55.0 (sd:9.3)	55.7 (sd:9.2)
Gender	Female	506 (26.5)	229 (26.8)
	Male	1402 (73.5)	627 (73.3)
Ethnicity	White	1542 (80.8)	712 (83.2)
	non-White	366 (19.2)	144 (16.8)
Decompensated cirrhosis, n(col%)	No	1529 (80.1)	670 (78.3)
	Yes	379 (19.9)	186 (21.7)
Follow up at transplant clinic	No	1105 (57.9)	564 (65.9)
	Yes	803 (42.1)	292 (34.1)
Alcohol hospital admission, n(col%)	No	1450 (76.0)	616 (72.0)
	Past	227 (11.9)	114 (13.3)
	Recent	231 (12.1)	126 (14.7)
Substance misuse hospital admission, n(col%)	No	1102 (57.8)	460 (53.7)
	Past	348 (18.2)	141 (16.5)
	Recent	458 (24.0)	255 (29.8)
IFN free therapy	No	472 (24.7)	74 (8.6)
	Yes	1436 (75.2)	782 (91.4)
Year SVR achievment, median (IQR)		2015 (IQR: 2014-2016)	2015 (IQR: 2015-2016)
aMAP score at SVR, median (IQR)		61.3 (IQR:55.9-65.9)	60.9 (IQR:55.8-65.6)
Median duration of follow-up (years)		3.8 (IQR:3.3-4.9)	3.5 (IQR:3.0-4.0)

APPENDIX A: VALIDATION OF NHS DIGITAL DATA

1.0 Methods:

Internal and external validation approaches was performed to assess the validity of NHS digital data to measure uptake of abdominal/liver ultrasound (US) events in cirrhosis patients.

1.1 Internal validity

First, the average time interval between consecutive US scans was calculated to assess consistency with the screening interval recommended in clinical guidelines.

Second, we assessed the timing of imaging examinations in patients who developed HCC.

1.2 Agreement with data collected from individual centres

Moreover, for a subset of patients, we collected information on liver/abdominal US scans directly from liver centres. On behalf of the HCVRUK, we contacted centres directly to request the dates of US examinations performed after SVR achievement for patients in this study population. Centres then retrieved these dates manually by interrogating local patient information systems by clinicians and/or data entry personnel. Not all centres responded to this request however, and thus data were only available for a subset of the total study population. Dates of US scans from NHS digital were then amalgamated with those collected from individual liver centres. Scans occurring on the same date were regarded as duplicates. Contiguous scans occurring within 90 days of one another were collapsed into a single screening episode, as described previously. We then assessed agreement between US dates supplied by individual liver centres versus those ascertained through NHS digital data. We did this both visually (bar charts) and quantitatively (Kappa statistic). In general, higher values of kappa indicate better agreement; a value of <0.4, 0.4-0.7 and >0.7 are typically interpreted as poor, moderate and good agreement, respectively.

We also assessed the agreement between biannual US uptake inferred from NHS digital data versus biannual uptake inferred by amalgamating dates from NHS digital + individual centres.

2.0 RESULTS

2.1 Internal validity

The median time interval between successive US scans (i.e. US events) was 182-189 days. (Figure S4).

Imaging procedures were clustered around the date of HCC diagnosis (Figure S5). This was most pronounced for CT/MRI scans and for all imaging procedures. The most common non-liver imaging procedure within 10 days of HCC diagnosis was a plain chest X-ray. This implies frequent HCC detection following pulmonary metastasis, consistent with Katyal S, et al. Radiology. 2000;216:698-703.

2.2 Agreement with data collected from individual centres

2.2.1 Combining scans provided by liver centres with scans from NHS digital

We collected dates of US events directly from individual centres for a subgroup of 856/1908 (44.8%) patients. The characteristics of this subgroup are shown in Table S4. In total, 4131 US events were identified after pooling the data collected from individual centres with data from NHS digital. The provenance of these events were: 433 (10%) reported by liver centres alone; 1079 (26%) reported by NHS digital data only; and 2619 (63%) reported by both the liver centre and the NHS digital data. However, these proportions did vary by clinic. In clinic “A” for instance, only 6/533 (1%) events were sourced from the clinic alone, whereas for clinic “S”, 98/128 (77%) events were reported by the clinic alone. Clinic “K” also exhibited a high proportion of events sourced from clinic data alone (Figure S6).

2.2.2 Quantifying agreement:

The proportion with biannual US uptake was 4.6%, 6.4% and 9.1% when inferred from individual centre data only, NHS digital data only, and an amalgamation of the two, respectively.

With respect to biannual US uptake, the overall agreement between NHS digital data Vs individual centre data was moderate (kappa statistic 0.56; $P<0.001$) (Figure S7).

With respect to biannual US uptake, the overall agreement between NHS digital data Vs NHS digital + individual centre data was good (Kappa statistic: 0.84; P<0.001). (Figure S8)

3.0 Interpretation

Overall, NHS digital data showed good validity for measuring US uptake in patients with cirrhosis. However, some blind spots for patients attending specific liver centres. In clinic “K” for example, biannual uptake was 0% based on NHS digital alone versus 4% when based on NHS digital + individual centre data. Subsequent local investigation of clinic “K” showed that the ultrasound scans missed by NHS digital were all performed by one specific non-NHS provider. The most likely explanation therefore is that this specific provider was not contributing data to the DID, even though the services carried out were commissioned by the NHS. The data for clinic “S” also appeared to be unreliable. Despite these gaps in the NHS digital data, the additional data from liver centres did not change the broad picture on screening uptake. For example, in the validation cohort, the proportion of patients with biannual uptake increased only modestly after adding centre data into the mix (i.e. from 6.4% when based on NHS digital data only, to 9.1% when based on NHS digital data + data from individual centres). Moreover, the agreement between biannual US uptake when inferred from NHS digital Vs. NHS digital + centre data was very strong with a Kappa statistic >0.80. This justifies our reliance on the NHS digital alone in our main analysis.